129. The Synthesis of 4-Decarboxy-4-phosphono-*O*-2-isooxacephems, -isopenams and -isooxacephems Containing Phosphorus at the 3-Position

by **Gholam Hosein Hakimelahi**[1]) and **George Just**

Department of Chemistry, McGill University Montreal, Quebec, Canada H3A 2K6

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Summary

Two new types of iso-oxacephems have been synthesized in which a phosphonate group replaces either the carboxyl group or C(3). The latter compound exists as a stable trialkoxyphosphonium ylide.

Potassium thioacetate and O_2 in DMF are transformed in an autocatalytic, probably sulfur-catalyzed process to CH_3COOK and sulfur; the latter two reagents are sufficient to transform the methanesulfonate **7** to the isopenam **15**.

As part of a programme to prepare new types of nuclear analogues of cephalosporin and penicillin, we synthesized β-lactams **6**, **8** and **17**. The method used to prepare the monocyclic precursors **4** derives from that developed by *Doyle et al.* [1] and by ourselves [2].

As starting material, we used *t*-butyl α-amino-α-diethylphosphonoacetate (**1a**) [3], and the corresponding dimethyl phosphonate **1b**, prepared similarly to **1a** [3]. The sequence **1** → **5** was identical for **1a** and **1b**. The cinnamylidene derivative of **1a** [3] was converted to the β-lactam **2a** (70%) [1] [4]. The expected *cis*-configuration of **2** was confirmed by ^{1}H-NMR. (D_6-benzene), which showed a characteristic coupling constant of ≈ 5 Hz for the β-lactam protons [5] [6]. Reduction of the azide group with hydrogen sulfide/triethylamine [7], followed by acylation of the crude amine with phenylacetyl chloride in pyridine, gave the amide **3a** (*ca.* 90%). Ozonolysis of **3a** [2], followed by treatment with dimethyl sulfide and reduction of the corresponding aldehyde with $NaBH_4$-impregnated alumina [8] in methylene chloride, yielded alcohol **4a** (83%). Treatment of alcohol **4a** with trifluoroacetic acid/methylene chloride gave δ-lactone **5a** (70%) as evidenced by IR., NMR. (absence of a *t*-butyl group) and mass spectrometric and microanalytical data. Treatment of **5a** with ethereal diazomethane in the presence of boron trifluoride etherate gave the ketene acetal **6a** (20%). This transformation was accompanied by a shift of the β-lactam frequency from 1770 to 1791 cm^{-1}, the disappearance of the δ-lactone band at 1745 cm^{-1} and the appearance at 1732 cm^{-1} of a C=C stretching frequency typical of double bonds substituted with electron-with-

[1]) Author to whom correspondence should be addressed.

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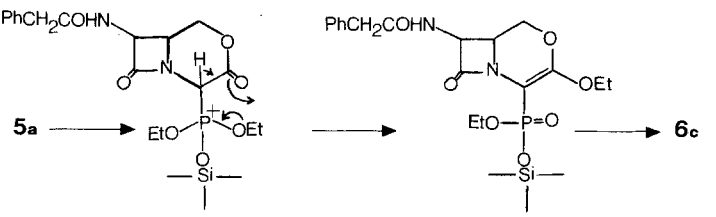
drawing groups [9]. The very different appearance of the ^{1}H-NMR. spectra of **5a** and **6a** probably precludes the possibility that **5a** exists in its enol form **6a** (R″ = H). Removal of an ethyl group of the phosphonate **6a** to give **6b** was effected by trimethylsilyl chloride/sodium iodide, followed by aqueous hydrolysis [10]. Steric crowding precluded the removal of the second ethyl group. Under more forcing conditions, **6b** decomposed to a series of unidentified products.

Since we could not remove both ethyl groups of the diethyl phosphonate function of **6a**, we attempted to hydrolyze **5a** to the corresponding phosphonic acid using trimethylsilyl chloride/sodium iodide [10], but we obtained the monoethyl phosphonate **6c** as main product in 70% yield. A possible path for its formation is depicted below.

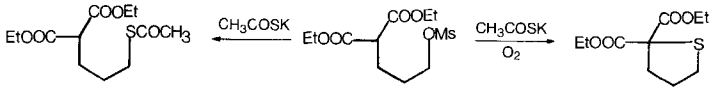


Because of the low yield of the methylation **5a** → **6a**, the sequence **1** → **5** was repeated using dimethyl phosphonate **1b**. Cyclization of **4b** gave a mixture of **5b** and **6d** which was separated by chromatography. Compound **5b** could be cleanly converted to **6d** using trimethylsilyl chloride in acetonitrile, and, in practice, the mixture of **5b** and **6d** was directly submitted to the latter conditions. Compound **6d** was further characterized by methylation with diazomethane to the dimethyl phosphonate **6e**.

We next attempted to form the cyclic phosphonate **9**. β-Lactam **4a** was methanesulfonated, and the methanesulfonate **7** treated with sodium iodide in boiling acetonitrile. Instead of the product **9a** expected from an *Arbusov*-type reaction, the trialkoxyphosphonium ylide **8a** was obtained. It is a relatively stable compound which could be converted to the corresponding free acid **10** by means of trifluoroacetic acid in methylene chloride. The free acid was obtained as its trifluoroacetate salt in impure form only. Reaction with ethereal diazomethane-solution gave **8b** in low yield, the structure of which was assigned only by comparison of IR. and mass spectra. Whereas the *t*-butyl ester **8a** seemed to be a single compound, the mass spectrum of the methyl derivative indicated a mixture of ylide **8b** and perhaps phosphonate **9b**.

Ylides similar to **8** have been recently reported [11]. Further work to define the chemistry of compounds such as **8** is in progress.

We next prepared isopenam **15**. Recently [12] we reported that potassium thioacetate and oxygen in diemthylformamide (DMF) or dimethyl sulfoxide (DMSO) transformed methanesulfonate **12** to tetrahydrothiophene **13**, and that none of the expected thioacetate **11** was obtained. This type of transformation being practical for the preparation of isopenam of type **15**, the methanesulfonate **7** was treated with potassium thioacetate by the method already reported for the preparation of **13** [12]. Instead of the cyclized product **15**, the acetylthiomethyl-β-lactam **14** was



11 **12** **13**

obtained quantitatively. Therefore we repeated our original reaction (**12** → **13**) with different batches of CH_3COSK; surprisingly, we did isolate the thioacetate **11**, the tetrahydrothiophene **13**, or a mixture of both.

Analysis by ^{1}H-NMR.[2]) of the various batches of CH_3COSK revealed that bottles opened a few years ago contained substantial amounts of CH_3COOK, the other contaminant being sulfur. Reaction of the methanesulfonate **12** with S/CH_3COOK in DMF or S/t-BuOK in THF gave a high yield of the tetrahydrothiophene **13**, suggesting the following sequence:

$$CH_3COSK + O_2(S) \xrightarrow{DMF} CH_3COOK + S$$

$$CH_3COOK + S + \mathbf{12} \xrightarrow{DMF} \mathbf{13} + MsOK + CH_3COOH$$

In order to obtain a better understanding of the processes involved, a solution of recrystallized CH_3COSK (76 mg, 0.67 mmol) in DMF (3 ml) or D_7-DMF was stirred with oxygen in a 'catalytic hydrogenator' at atmospheric pressure. There was a slow but steady uptake of oxygen for 5 h (total uptake over 5 h period, 1.7 ml, $\approx$0.2 equiv.; *Fig.*), at which point the solution turned faintly yellow. ^{1}H-NMR. indicated that, at that stage, no CH_3COOK had been formed, and that all the CH_3COSK or a substance having the same or very similar NMR. signal was present. This was followed by a very rapid uptake of O_2, the color of the solution turning from yellow to red-brown. NMR. analysis indicated that the uptake of oxygen over this region paralleled the conversion of CH_3COSK to CH_3COOK, and substantial amounts of sulfur precipitated. After a total uptake of 11.75 $\pm$ 0.25 ml (1.5 equiv.) of oxygen, the reaction stopped.

The reaction is clearly autocatalytic. Addition of CH_3COOK did not alter the rate of the reaction. However, addition of 25 mol % of S to CH_3COSK/DMF in the presence of oxygen gave an intense blue colour, which immediately turned to yellow, with concomitant rapid uptake of oxygen. When only 0.25 mol % of S was added, the same blue color developed immediately, followed by rapid discoloration, but there was virtually no effect on the reaction rate. However, at 1 mol % S content, sulfur catalysis was noticeable.

The reaction seemed to be moisture sensitive. Addition of 5% (*v*/*v*) of water brought the reaction to a virtual standstill ($\approx$ 30% of expected oxygen uptake after 15 h). In pure water, there was no reaction. When DMF was dried by distillation over BaO followed by storage over molecular sieves, the reaction took 4 h rather than 6.5 h to go to completion.

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[2]) Potassium thioacetate: NMR. (D_7-DMF): 1.92; (D_6-DMSO) 2.21 and (D_2O) 2.42 ppm. Potassium acetate: NMR. (D_7-DMF): 1.46; (D_6-DMSO) 1.73 and (D_2O) 1.98 ppm.

In an attempt to mimic the reaction of CH_3COSK and air, giving CH_3COOK and sulfur over a period of months or years, pure CH_3COSK was heated to its melting point (225–228°) in the presence of air. Sulfur sublimed, and CH_3COOK was formed quantitatively after 15–20 min. In conclusion, solid CH_3COSK is transformed very slowly to CH_3COOK and S in air at r.t. and rapidly at its melting temperature. CH_3COSK, when contaminated with S, undergoes in DMF in the presence of air a rapid conversion to CH_3COOK and S.

Having established a good procedure for cyclization, we treated the methanesulfonate **7** with 1.2 equiv. of *t*-BuOK and 1.4 equiv. of S_8 in THF at −20° for 45 min, and obtained *cis*-substituted-β-lactam **15** as a (1:1)-mixture of two diastereoisomers in nearly quantitative yield (the reaction of **7** with S_8 in DMF at 25° in the presence of CH_3COOK also gave isopenam **15** after 20 h in good yield). Reaction of **15** with trifluoroacetic acid gave the acid **16a** which was characterized by its methylation to **16b**. Decarboxylation of **16a** was achieved by means of $NaHCO_3$/HCl (50%). All attempts to hydrolyze the ester function of the isopenams **17** failed, and resulted in the destruction of the β-lactam ring.

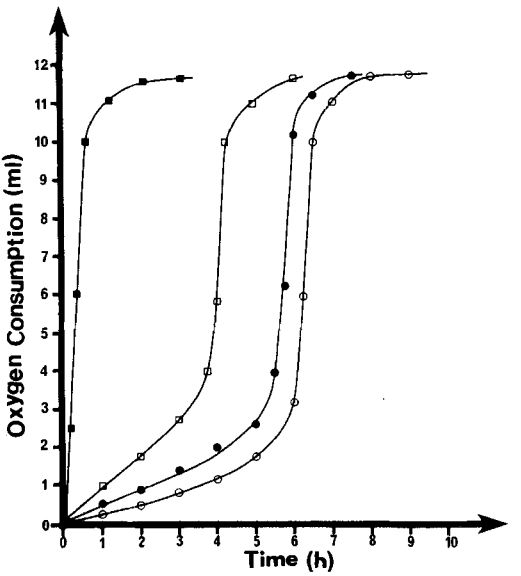


Figure. *Conversion of CH_3COSK to CH_3COOK in the presence of oxygen in DMF at 25° and 760 Torr:* ○, CH_3COSK (0.67 mmol); ●, containing 1 mol% S_8; □, 6 mol% S_8; ■, 25 mol% S_8

Experimental Part

General procedures: see [2].

Preparation of t-butyl 2-(3-azido-2-oxo-4-styryl-1-azetidinyl)-2-diethylphosphonatoacetate (**2a**). To a solution of *t*-butyl 2-amino-2-diethylphosphonatoacetate (**1a**, 2.67 g, 0.01 mol) in 40 ml dry CH_2Cl_2 was added cinnamaldehyde (1.6 g, 0.012 mol), and magnesium sulfate (10 g). After stirring at r.t. for 3 h the mixture was filtered. Triethylamine (1.01 g, 0.01 mol) was added, followed by dropwise addition of azidoacetyl chloride (1.20 g, 0.01 mol) at r.t. After stirring for 1 h, the solution was washed with water, dried and evaporated to give the crude β-lactam which was purified by column chromatography

on silica gel. Elution with CH_2Cl_2 gave 3.6 g (78%) of the oily azido β-lactam **2a** as a mixture of 2 diastereoisomers. – IR. (CH_2Cl_2): 2100 (N_3), 1765 (β-lactam), 1745 (ester). – NMR. ($CDCl_3$): 1.15–1.60 (*m*, 15 H, 2 CH_3 and CMe_3); 3.90–4.40 (*m*, 4 H, 2 CH_2); 4.80 (*d*, J = 22 Hz, 1 H, CH); 4.90 (*m*, 2 H, H–C(3,4)); 6.10–6.90 (*m*, 2 H, CH=CH); 7.20–7.50 (*m*, 5 H, Ph). – Chemical ionization (CI.). – MS.: 465 ($M^+ + 1$), 381 ($M^+ - N_3CH{=}C{=}O$), 408 ($M^+ + 1 - C(CH_3)_3$).

$C_{21}H_{29}N_4O_6P$ (464.21) Calc. C 54.31 H 6.25 N 12.06% Found C 54.25 H 6.19 N 12.01%

Preparation of azido-β-lactam **2b**. In identical manner as for **2a**. – IR. (CH_2Cl_2): 2100 (N_3), 1765 (β-lactam), 1745 (ester). – NMR. ($CDCl_3$): 1.51 (2 *s*, 9 H, $C(CH_3)_3$); 3.59–3.98 (*m*, 6 H, 2 OMe); 4.80 (*d*, J = 22 Hz, 1 H, CH); 4.98 (*m*, 2 H, H–C(3,4)); 6.11–6.97 (*m*, 2 H, CH=CH); 7.35 (*m*, 5 H, Ph). – CI.: 437 ($M^+ + 1$), 380 ($M^+ + 1 - C(CH_3)_3$).

Preparation of azido-β-lactam **2c**. In identical manner as for **2a**. – NMR. (C_6D_6): 0.35–0.81 (*m*, 9 H, 3 CH_3); 3.17–4.00 (*m*, 7 H, 3 CH_2 and CHC=C); 4.30 (*d*, J = 5 Hz, 1 H, CHN_3); 4.72, 4.73 (2 *d*, J = 22 Hz, 1 H, PCH); 6.20–6.40 (*m*, 2 H, CH=CH); 6.80–7.30 (*m*, 5 H, Ph).

Preparation of t-*butyl 2-(2-oxo-3-phenylacetamido-4-styryl-1-azetidinyl)-2-diethylphosphonatoacetate* (**3a**) *and* t-*butyl 2-(2-oxo-3-phenylacetamido-4-styryl-1-azetidinyl)-2-diemthylphosphonatoacetate* (**3b**). Triethylamine (0.6 g, 0.006 mol) was added to a solution of a diastereoisomeric mixture of **2a** (2.32 g, 0.005 mol) in 50 ml dry CH_2Cl_2 at 0° and H_2S was bubbled in for 35 min. The solution was allowed to stand for 2 h at r.t. Nitrogen was bubbled in for 30 min. Then was added (1.3 g, 0.015 mol) pyridine, followed by dropwise addition of 0.9 g (0.006 mol) phenylacetyl chloride in 20 ml CH_2Cl_2. The solution was stirred for 2 h at 25°, then was washed with 10% HCl, 10% of $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to give the impure amide **3** which was chromatographed on silica gel. CH_2Cl_2 eluted impurities, and $CHCl_3$/EtOAc (1:1) gave 2.51 g (90%) of β-lactam **3a**, a mixture of diastereoisomers, as an oil. – IR. (CH_2Cl_2): 3410 (NH), 1770 (β-lactam), 1740 (ester), 1685 (amide). – NMR. ($CDCl_3$): 1.01–1.41 (*m*, 6 H, 2 CH_3); 1.52 (2 *s*, 9 H, $C(CH_3)_3$); 3.40 (*s*, 2 H, CH_2Ph); 3.91–4.42 (*m*, 4 H, 2 CH_2O); 4.61–5.22 (*m*, 2 H, PCH and C*H*–CH=CH); 5.37–5.61 (*m*, 1 H, C*H*–NH); 5.81–6.80 (*m*, 2 H, CH=CH); 7.02 (*s*, 5 H, Ph); 7.31 (*s*, 5 H, Ph–C=C); 7.40 (br., 1 H, NH). – MS.: 263 (M^+–Ph–CH=CH–CH=CH–NHCOCH$_2$Ph). – CI.-MS.: 557 ($M^+ + 1$), 501 ($M^+ + 1 - CH_2{=}C(CH_3)_2$), 457 ($M^+ + 1 - CH_2{=}CH(CH_3)_2{-}CO_2$), 382 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$).

$C_{29}H_{37}N_2O_7P$ (556.21) Calc. C 62.58 H 6.65 N 5.03% Found C 62.49 H 6.57 N 4.99%

The β-lactam **3b** was obtained by the same method as described for **3a**, and was purified on silica gel with ethyl acetate (80%). – IR. (CH_2Cl_2): 3410 (NH), 1770 (β-lactam), 1740 (ester), 1684 (amide). – NMR. ($CDCl_3$): 1.49 (2 *s*, 9 H, $C(CH_3)_3$); 3.48 (br. *s*, 2 H, CH_2Ph); 3.69–3.99 (2 *d*, J = 12 Hz, 6 H, $OPOMe_2$); 4.62–5.30 (*m*, 2 H, PCH and C*H*–CH=CH–); 5.39–5.62 (*m*, 1 H, C*H*–NH); 5.88–6.89 (*m*, 2 H, CH=CH); 7.02 (*s*, 5 H, Ph); 7.35 (*s*, 5 H, Ph–C=C); 7.8 (*d*, 1 H, NH). – CI.-MS.: 529 ($M^+ + 1$), 354 ($M^+ + 1 - PhCH_2COHN{-}CH{=}C{=}O$).

Preparation of t-*butyl 2-(4-hydroxymethyl-2-oxo-3-phenylacetamido-1-azetidinyl)-2-diethylphosphonoacetate* (**4a**) *and* t-*butyl 2-(4-hydroxymethyl-2-oxo-3-phenylacetamido-1-azetidinyl)-2-dimethylphosphonoacetate* (**4b**). β-Lactam **3a** (2 g, 3.59 mmol) in 50 ml dry CH_2Cl_2 was saturated with N_2 at −78°. Then a mixture of O_3/N_2 was bubbled in until KI/starch paper showed excess ozone (15 min), which was removed by passing a stream of N_2 for 10 min. Dimethyl sulfide (1.12 g, 5 equiv.) was added and the temperature of the solution was allowed to rise to 25° over 1 h, following which 4 g $MgSO_4$ were added. After 5 min, $NaBH_4/Al_2O_3$ 1:10 [8] was added while stirring. After 1 h, the solution was filtered and evaporated to give the crude product. Chromatography on silica gel with CH_2Cl_2 followed by $CHCl_3$ removed benzyl alcohol. Compound **4a**, 1.5 g (83%) was eluted with EtOAc. – IR. (CH_2Cl_2): 3300–3400 (OH, NH), 1760 (β-lactam), 1735 (ester), 1670 (amide). – NMR. ($CDCl_3$): 1.20–1.59 (*m*, 15 H, 2 CH_3 and $C(CH_3)_3$); 3.60 (*s*, 2 H, C*H*$_2$Ph); 3.80–4.42 (*m*, 8 H, 2 CH_2O and $CHCH_2OH$); 4.95 and 4.84 (2 *d*, J = 23 Hz, 1 H, CHP); 5.41–5.80 (*d*×*d*, J = 5 and 10 Hz, 1 H, C*H*–NH); 7.01 (*d*, 1 H, NH); 7.38 (*s*, 5 H, Ph). – CI.-MS.: 485 ($M^+ + 1$), 385 ($M^+ + 1 - CO_2{-}CH_2{=}C(CH_3)_2$), 367 ($M^+ + 1 - CO_2{-}CH{=}C(CH_3)_2{-}H_2O$), 293 ($M^+ - PhCH_2CONHCH{=}CHCH_2OH$).

$C_{22}H_{33}N_2O_8P$ (484.18) Calc. C 54.54 H 6.81 N 5.78% Found C 54.49 H 6.71 N 5.81%

Preparation of the β-lactam **4b**. In identical manner as **4a** (see above). – IR. (CH_2Cl_2): 3300–3410 (OH, NH), 1760 (β-lactam), 1735 (ester), 1672 (amide). – NMR. ($CDCl_3$): 1.51 (*s*, 9 H, $C(CH_3)_3$); 3.59 (*s*, 2 H, CH_2P); 3.80–4.41 (*m*, 10 H, 2 OCH_3 and $CHCH_2OH$); 4.95 and 5.01 (2 *d*, J = 23 Hz,

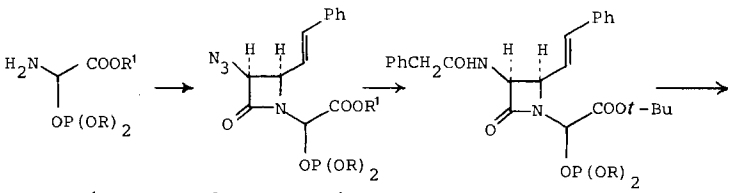
1 H, CHP); 5.40–5.79 ($d \times d$, $J = 5$ and 10 Hz, 1 H, CH–N); 7.25 (*s*, 6 H, Ph and NH). – CI.-MS.: 457 ($M^+ + 1$), 282 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$).

$C_{20}H_{29}N_2O_8P$ (455.97) Calc. C 52.63 H 6.35 N 6.14% Found C 52.61 H 6.33 N 6.20%

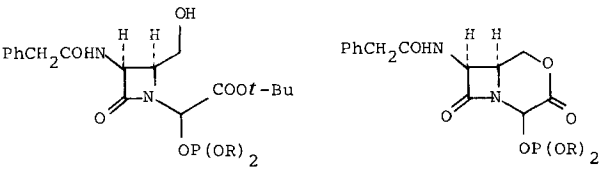
Preparation of 4-diethylphosphonato-3-oxo-7β-phenylacetamido-O-2-isocepham (**5a**). A mixture of trifluoroacetic acid/CH_2Cl_2 4:6 (8 ml) was added dropwise at 0–5° in 4 min to β-lactam **4a** (0.484 g, 1 mmol) in 2 ml dry CH_2Cl_2. The mixture was stirred at r.t. for 20 h, then evaporated, and the crude product chromatographed on silica gel using CH_2Cl_2 and $CHCl_3$ to remove the impurities. The lactone **5a** (0.287 g) was eluted with AcOEt. – IR. (CH_2Cl_2): 3400 (NH), 1770 (β-lactam), 1745 (lactone), 1680 (amide). – NMR. ($CDCl_3$): 1.10–1.48 (*m*, 6 H, $2\,CH_2CH_3$); 3.58 (*s*, 2 H, CH_2Ph); 3.60–3.81 (*m*, 2 H, CH_2O); 3.87–4.42 (*m*, 5 H, $2\,CH_2CH_3$ and $CH{-}CH_2$); 5.05 (2 *d*, $J = 22$ Hz, 1 H, CHP); 5.55 ($d \times d$, $J = 5$ and 10 Hz, 1 H, $CH{-}NH$); 7.31 (*s*, 6 H, Ph and NH). – CI.-MS.: 236 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$); 218 ($M^+ - PhCH_2CONHCH{=}C{=}O{-}OH$); 293 ($M^+ + 1 - PhCH{=}C{=}O$).

$C_{18}H_{23}N_2O_7P$ (410.17) Calc. C 52.68 H 5.61 N 6.82% Found C 52.59 H 5.71 N 6.71%

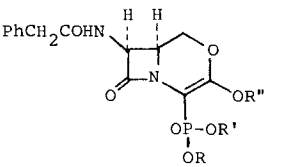
Preparation of 4-diethylphosphonato-3-methoxy-7β-phenylacetamido-3,4-didehydro-O-2-isocepham (**6a**). BF_3-etherate (3 equiv.) in 20 ml ether was added to lactone **5a** (0.25 g, 0.6 mmol) in 4 ml dry CH_2Cl_2. A solution of CH_2N_2 (5 equiv.) in ether was added dropwise until the yellow color persisted. The solution was stirred for 30 min, then washed with water, dried and evaporated to give the crude product, which was chromatographed on silica gel using CH_2Cl_2 and $CHCl_3$ to remove impurities. Elution with AcOEt gave **6a**, 0.52 g (20%). – IR. (CH_2Cl_2): 3410 (NH), 1791 (β-lactam), 1732 (C=C), 1685 (amide). – NMR. ($CDCl_3$): 1.35 (*t*, $J = 6$ Hz, 6 H, $2\,CH_3$); 3.60 (*s*, 2 H, CH_2Ph);



1a R = Et, R^1 = *t*-Bu **2a** R = Et, R^1 = *t*-Bu
1b R = Me, R^1 = *t*-Bu **2b** R = Me, R^1 = *t*-Bu **3a** R = Et
1c R = Et, R^1 = Et **2c** R = Et, R^1 = Et **3b** R = Me



4a R = Et **5a** R = Et
4b R = Me **5b** R = Me



6a R = R′ = Et, R″ = Me
6b R = Et, R′ = H, R″ = Me **6d** R = H, R′ = R″ = Me
6c R = Et, R′ = H, R″ = Et **6e** R = R′ = R″ = Me

3.80 (*s*, 3 H, OCH_3); 3.71–3.95 (*m*, 2 H, $CHCH_2O$); 3.96–4.60 (*m*, 6 H, CH_2CH_3 and 2 CH); 6.91 (*d*, 1 H, NH); 7.38 (*s*, 5 H, Ph). – CI.-MS.: 425 ($M^+ + 1$), 217 ($M^+ + 1 - O(CH_3O)C{=}CPO(OCH_2CH_3)_2$).

*Preparation of 4-monoethylphosphonato-3-methoxy-7β-phenylacetamido-3,4-didehydro-*O*-2-isocepham* (**6b**). Trimethylsilyl chloride (0.218 g, 2 mmol) and anhydrous NaI (0.310 g, 2 mmol) were added to **6a** (0.2 g, 0.47 mmol) in 8 ml acetonitrile and the mixture was stirred at 40° for 45 min, then evaporated and water was added. The product was extracted with EtOAc, the solution dried ($MgSO_4$), filtered, and the volume was reduced to about 10 ml by evaporation, following which ether was added slowly to give **6b**, 0.07 g (36%) as crystals, m.p. 82–85°. – IR. (Nujol): 3100–3700 (OH, NH), 1785 (β-lactam), 1735 (C=C), 1668 (amide). – NMR. ($DMSO/D_2O$): 1.29 (*t*, $J = 8$ Hz, 3 H, CH_2CH_3); 3.56 (*s*, 2 H, CH_2Ph): 3.58–3.75 (*m*, 5 H, H–C(1) and OCH_3); 4.00–4.30 (*m*, 2 H, CH_2OP); 4.31–4.56 (*m*, 2 H, H–C)7,8)); 7.30 (*s*, 5 H, Ph); 8.61 (*d* × *d*, $J = 6$ Hz, 1 H, NH). – CI.-MS.: 397 ($M^+ + 1$), 222 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$).

Preparation of β-lactam **6c**. Trimethylsilyl chloride (0.218 g, 2 mmol) and anhydrous NaI (0.310 g, 2 mmol) were added to **5a** (0.25 g, 0.6 mmol) in 10 ml dry acetonitrile and the mixture was stirred at 40° for 1 h, then evaporated. Water was added and the product was extracted with AcOEt. The solution was dried and evaporated to give a dark brown residue, which was chromatographed on silica gel. Impurities were eluted with CH_2Cl_2 and $CHCl_3$ and **6c** with AcOEt, 0.17 g, foam (73%). – IR. (Nujol): 3100–3700 (OH, NH), 1785 (β-lactam), 1735 (C=C), 1670 (amide). – NMR. (D_6-acetone/D_2O): 1.20–1.41 (*m*, 6 H, $2\,CH_3$); 3.60–3.81 (*m*, 4 H, CH_2Ph and 2 H–C(1)); 3.85–4.61 (*m*, 6 H, $2\,OCH_2CH_3$ and H–C(7,8)); 6.15 (*d* × *d*, $J = 6$ Hz, 1 H, NH); 7.32 (*m*, 5 H, Ph). – CI.-MS.: 236 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$), 218 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O - H_2O$), 100%), 233 ($M^+ + 1 - O(OC_2H_5)C{=}CPO(OH)OC_2H_5-$), 303 ($M^+ + 1 - PO(OH)OC_2H_5$).

$C_{18}H_{23}N_2O_7P$ (410.17) Calc. C 52.68 H 5.61 N 6.82% Found C 52.70 H 5.59 N 6.84%

Preparation of β-lactams **5b**, **6d** *and* **6e**. A mixture of trifluoroacetic acid/CH_2Cl_2 4:6 (10 ml) was added dropwise at 0–5° in 5 min to β-lactam **4b** (0.456 g, 1 mmol) in 2 ml dry CH_2Cl_2. The mixture was stirred at r.t. for 20 h, then evaporated to dryness. CCl_4 (10 ml) was added and evaporated under vacuum to remove remaining trifluoroacetic acid. The residue was a mixture of **5b** and **6d** 1:1. – IR. (Nujol): 3100–3550 (OH, NH), 1785 (β-lactam in **6d**), 1770 (β-lactam in **5b**), 1745 (lactone), 1732 (C=C), 1660–1685 (amide). The above mixture (0.3 g) was dissolved in 10 ml acetonitrile. Trimethylsilyl chloride (0.6 g) was added, and the solution was stirred at r.t. for 5 h. The silylated derivative of **6d** was precipitated as a white crystalline compound which was filtered off and washed with ether to give **6d** as a mixture of 2 diastereoisomers. Crystallization with $CHCl_3$ gave 90% **6d**, m.p. 90–93°. – IR. (Nujol): 3100–3600 (NH, OH), 1785 (β-lactam), 1735 (C=C), 1660 (amide). – NMR. (D_6-DMSO/$CDCl_3$, 200 MHz): 3.55 (2 *s*, 2 H, CH_2Ph); 3.56–3.70 (*m*, 2 H, 2 H–C(1)); 3.71, 3.80 (2 *s*, 3 H, OCH_3); 3.72 and 3.74 (2 *d*, $J = 11$ Hz, 3 H, $PO(OCH_3)$); 4.11–4.61 (*m*, 2 H, H–C(7,8)); 7.31 (*s*, 5 H, Ph); 8.61 and 8.75 (2 *d*, $J = 6$ Hz, 1 H, NH, exchangeable with D_2O); 8.80–9.05 (br., 1 H, OH, exchangeable with D_2O).

$C_{16}H_{19}N_2O_7P$ (382.16) Calc. C 50.26 H 4.97 N 7.32% Found C 50.01 H 4.90 N 7.21%

Compound **6d** was treated in MeOH with CH_2N_2 to give **6e** as a foam in quantitative yield. – IR. (CH_2Cl_2): 3400 (NH), 1791 (β-lactam), 1735 (C=C), 1680 (amide). – NMR. ($CDCl_3$, 200 MHz): 3.60 (*s*, 2 H, CH_2Ph); 3.61–3.82 (*m*, 11 H, $3\,OCH_3$ and OCH_2); 4.12–4.62 (*m*, 2 H, H–C(7,8)); 6.91 (*d*, 1 H, NH); 7.35 (*s*, 5 H, Ph). – CI.-MS.: 397 ($M^+ + 1$).

Preparation of t-*butyl 2-(2-oxo-4-mesyloxymethyl-3-phenylacetamido-1-azetidinyl)-2-diethylphosphonatoacetate* (**7**). Pyridine (0.237 g, 3 mmol) was added to 4-hydroxymethyl azetidinone **4a** (0.242 g, 0.5 mmol) in 20 ml dry CH_2Cl_2. Then methanesulfonyl chloride (0.342 g, 3 mmol) in 10 ml dry CH_2Cl_2 was added dropwise at 0°. The solution was stirred at r.t. for 24 h, then washed with water, dried, and evaporated to give **7**, which was purified on silica gel using CH_2Cl_2 and $CHCl_3$ to remove impurities. Elution with AcOEt gave 0.24 g (80%) product as an oil. – IR. (CH_2Cl_2): 3405 (NH), 1770 (β-lactam), 1740 (ester), 1680 (amide). – NMR. ($CDCl_3$): 1.21–1.60 (*m*, 15 H, $2\,CH_3$ and $C(CH_3)_3$); 2.80 (*s*, 3 H, CH_3SO_2); 3.51 (*s*, 2 H, CH_2Ph); 3.90–4.59 (*m*, 7 H, $2\,OCH_2$ and $CHCH_2OMs$); 4.87 (*d*, $J = 23$ Hz, 1 H, CHP); 5.41 (*d* × *d*, $J = 5$ and 8 Hz, 1 H, CHNH); 7.39 (*s*, 5 H, Ph); 7.71 (*d*, $J = 8$ Hz, 1 H, NH). – CI.-MS.: 467 ($M^+ + 1 - OMs$), 409 ($M^+ - OMs - C(CH_3)_3$).

*Preparation of 3-diethoxy-4-ethoxycarbonyl-7β-phenylacetamido-3-phospha-3,4-didehydro-*O*-2-isocepham* (**8a**). Sodium iodide (0.15 g, 1 mmol) was added to **7** (0.1 g, 0.17 mmol) in 20 ml dry aceto-

nitrile and the solution stirred at 60° for 12 h. TLC. showed the complete disappearance of **7** and appearance of a product much more polar than the starting material. The solution was evaporated and water was added. Extraction with AcOEt and chromatography on silica gel with AcOEt/methanol 7:3 gave compound **8a** in quantitative yield. – IR. (CH_2Cl_2): 3400 (NH), 1770 (β-lactam), 1740 (ester), 1675 (amide). – NMR. ($CDCl_3$): 1.11–1.60 (*m*, 15 H, 2 CH_2CH_3 and $C(CH_3)_3$); 3.43–3.71 (*m*, 4 H, CH_2Ph and 2 H–C(1)); 3.90–4.62 (*m*, 5 H, 2 CH_2CH_3 and H–C(8)); 4.71–5.10 (br., 1 H, H–C(7)); 7.38 (*s*, 6 H, Ph and NH). – CI.-MS.: 467 ($M^+ + 1$), 411 ($M^+ + 1 - CH_2{=}C(CH_3)_2$), 383 ($M^+ + 1 - CH_2{=}C(CH_3)_2 - CH_2{=}CH_2$), 330 ($M^+ + 1 - PO(OEt)_2$), 331 ($M^+ + 2 - PO(OEt)_2$), 275 ($M^+ + 2 - PO(OEt)_2 - CH_2{=}C(CH_3)_2$), 218 ($M^+ - PhCH_2CONHCH{=}C{=}O - OC(CH_3)_3$), 200 ($218 - H_2O$).

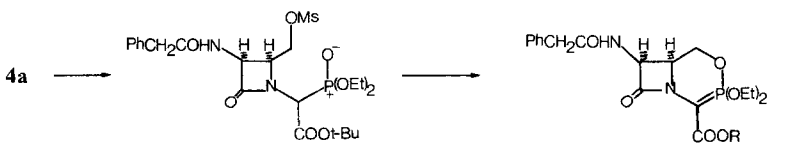
$C_{22}H_{31}N_2O_7P$ (466.17) Calc. C 56.65 H 6.65 N 6.08% Found C 56.36 H 6.39 N 6.20%

Preparation of 3-diethoxy-4-carboxy-7β-phenylacetamido-3-phospha-3,4-didehydro-O-2-isocepham (**10**). A solution of **8a** (0.1 g, 0.21 mmol) in 8 ml CF_3COOH/CH_2Cl_2 4:6 was stirred at r.t. for 7 h and evaporated to dryness. The residue was dissolved in 5 ml CH_2Cl_2. Dropwise addition of dry ether gave 0.07 g (76%) acid **10**, m.p. 110–114°. – IR. (Nujol): 3100–3500 (NH, COOH), 1760 (β-lactam), 1690–1670 (acid, amide). – NMR. ($DMSO/CDCl_3$): 1.35 (*t*, $J = 8$ Hz, 6 H, 2 OCH_2CH_3); 3.41–3.71 (*m*, 4 H, CH_2Ph and 2 H–C(1)); 3.90–4.61 (*m*, 5 H, CH_2OP and H–C(8)); 4.70–5.31 (*m*, 2 H, H–C(7) and H–C(4)); 7.41 (*s*, 5 H, Ph and NH); 7.51–7.92 (br., 1 H, COOH). – CI.-MS.: 367 ($M^+ + 1 - CO_2 - CF_3COOH$), 218 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O - H_2O - CF_3COOH$), 200 ($218 - H_2O$).

Treatment of acid **10** with CH_2N_2 gave a mixture presumably of the corresponding methyl ester **8b** and the cyclic phosphonate **9b**. – IR. (CH_2Cl_2): 3400 (NH), 1770 (β-lactam), 1750 (ester). 1675 (amide). – CI.: 425 ($M^+ + 1$) for **8b** and 397 ($M^+ + 1$) for **9b**.

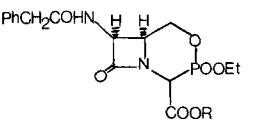
Preparation of 3-(t-butoxycarbonyl)-3-diethylphosphonato-6β-phenylacetamido-isopenam (**15**). To a solution of **7** (0.562 g, 1 mmol) in 3 ml dry THF was added sulfur (1.4 mmol) then *t*-BuOK (0.134 g, 1.2 mmol) at −20° under N_2. The mixture was stirred for 45 min at 25°. Water (20 ml) was added and the aqueous solution was extracted with ether. The ethereal layer was dried, filtered and evaporated to give crude **15** as a mixture of 2 diastereoisomers (1:1). Isopenam **15** was purified by column chromatography on silica gel. Elution with CH_2Cl_2 removed impurities and 10% of one of the diastereoisomers was eluted with $CHCl_3$. AcOEt eluted 80% of the 2 diastereoisomers of **15**. – IR. (CH_2Cl_2): 3405 (NH), 1785 (β-lactam), 1739 (ester), 1685 (amide). – NMR. ($CDCl_3$): 0.98–1.31 (*m*, 15 H, 2 CH_3 and $C(CH_3)_3$); 2.73–3.11 (*m*, 2 H, 2 H–C(1)); 3.61 (br. *s*, 2 H, CH_2Ph); 3.91–4.70 (*m*, 5 H, 2 OCH_2CH_3 and H–C(7)); 5.10 and 5.18 (2 *d* × *d*, 1 H, H–C(6)); 6.80–7.00 (br., 1 H, NH); 7.22 (*s*, 5 H, Ph). – NMR. of the single diastereoisomer **15** resulted in a sharpening of the signals and showed the *cis*-position of the H-atoms (*d* × *d*, $J = 4.5$ and 8 Hz, 1 H, CHN). – CI.-MS.: 499 ($M^+ + 1$).

$C_{22}H_{31}N_2O_7PS$	Calc.	C 53.01	H 6.22	N 5.62	S 6.42%
(498.16)	Found	„ 53.12	„ 6.32	„ 5.60	„ 6.43%

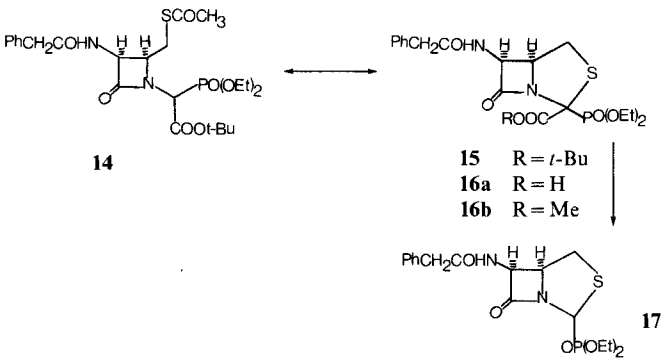


7

8a R = *t*-Bu
8b R = Me
10 R = H



9a R = *t*-Bu
9b R = Me



Preparation of 3-carboxy-3-diethylphosphonato-6β-phenylacetamido-(**16a**) *and of -3-diethylphosphonato-3-methoxycarbonyl-6β-phenylacetamido-isopenam* (**16b**). A (1:1)-mixture of CH_2Cl_2/CF_3COOH (5 ml) was added dropwise at 0° under N_2 over a period of 5 min to **15** (0.498 g, 1 mmol) in 0.3 ml dry CH_2Cl_2. The solution was stirred at r.t. for 8 h, then evaporated to dryness and CCl_4 was added and re-evaporated to remove the remaining trifluoroacetic acid. AcOEt/ether 1:10 were added to give **16a** as a crystalline compound (30%), m.p. 96–99°. – IR. (Nujol): 3300–3500 (NH, COOH), 1770 (β-lactam), 1710 (acid), 1665 (amide). – NMR. ($CDCl_3$/one drop DMSO): 1.08–1.12 (*m*, 6 H, 2 CH_3); 2.71–3.15 (*m*, 2 H, 2 H–C(1)); 3.51 (br. *s*, 2 H, CH_2Ph); 3.91–4.58 (*m*, 5 H, 2 OCH_2CH_3 and H–C(7)); 5.01–5.23 (*m*, 1 H, H–C(6)); 6.91–7.00 (br., 1 H, NH); 7.21 (*s*, 5 H, Ph); 7.22–7.45 (br., 1 H, COOH). – CI.-MS.: 399 ($M^+ + 1 - CO_2$, S-cluster), 224 ($M^+ + 1 - CO_2 - PhCH_2CONHCH{=}C{=}O$).

Treatment of **16a** with CH_2N_2 in $CHCl_3$/ether 1:1 gave the corresponding methyl ester **16b** in quantitative yield as a foam. – IR. (CH_2Cl_2): 3400 (NH), 1785 (β-lactam), 1739 (ester), 1685 (amide). – NMR. ($CDCl_3$): 0.99–1.33 (*m*, 6 H, 2 CH_3); 2.72–3.11 (*m*, 2 H, 2 H–C(1)); 3.61 (br. *s*, 2 H, CH_2Ph); 3.71 (*d*, 3 H, OCH_3); 3.90–4.71 (*m*, 5 H, 2 OCH_2CH_3 and H–C(7)); 4.99–5.31 (*m*, 1 H, H–C(6)); 6.91 (br., 1 H, NH); 7.22 (*s*, 5 H, Ph). – CI.-MS.: 457 ($M^+ + 1$, S-cluster); 282 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$).

Preparation of 3-diethylphosphonato-6β-phenylacetamido-isopenam (**17**). A solution of 5% aqueous $NaHCO_3$-solution (4 ml) was added to **16a** (0.443 g, 1 mmol) in 1 ml DMF and stirred for 10 min. The solution was neutralized with hydrochloric acid to pH ≈4, and was extracted 3 times with AcOEt. The organic layer was separated, dried and evaporated to give crude **17** which was purified on silica gel and eluted with $CHCl_3$ to give **17** (50%) as an oily mixture of 2 diastereoisomers. – IR. (CH_2Cl_2): 3400 (NH), 1775 (β-lactam), 1680 (amide). – NMR. ($CDCl_3$): 1.20 (*t*, 6 H, 2 CH_3); 2.81–3.21 (*m*, 2 H, 2 H–C(1)); 3.51 (*s*, 2 H, CH_2Ph); 3.91–4.38 (*m*, 5 H, 2 OCH_2CH_3 and H–C(7)); 4.51 and 4.68 (2 *d*, J = 22 Hz, 1 H, H–C(3)); 5.01–5.31 (*d*×*d*, J = 5 and 9.5 Hz, 1 H, H–C(6)); 6.81 (*d*, 1 H, NH); 7.31 (*s*, 5 H, Ph). – CI.-MS.: 399 ($M^+ + 1$, S-cluster), 224 ($M^+ + 1 - PhCH_2CONHCH{=}C{=}O$).

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. *55*, 484 (1977).
[2] *G. H. Hakimelahi & G. Just*, Can. J. Chem. *57*, 1932 (1979).
[3] *G. H. Hakimelahi & G. Just*, Synth. Commun. *10*, 429 (1980).
[4] *A. K. Bose, G. Spiegelman & M. S. Manhas*, J. Am. Chem. Soc. *90*, 4506 (1968).
[5] *H. B. Kagan, J. J. Basselier & J. L. Luche*, Tetrahedron Lett. *1964*, 941.
[6] *P. J. Decazes, J. L. Luche & H. B. Kagan*, Tetrahedron Lett. *1970*, 3661.
[7] *T. W. Doyle, B. Belleau, B. Y. Luh, C. F. Ferrari & M. P. Cunningham*, Can. J. Chem. *55*, 468 (1977).
[8] *E. Santaniello, F. Ponti & A. Manzocchi*, Synthesis *1978*, 891.
[9] *R. M. Silverstein & G. C. Bassler*, 'Spectrometric Identification of Organic Compounds', John Wiley and Sons, Inc., p. 81, 1968.
[10] *T. Morita, Y. Okamoto & H. Sakurai*, Tetrahedron Lett. *1978*, 2523.
[11] *R. Burgada, Y. Leroux & Y. O. El Khoshnieh*, Tetrahedron Lett. *1980*, 925.
[12] *G. H. Hakimelahi & G. Just*, Tetrahedron Lett. *1980*, 2119.