β-Lactams. XI. Synthesis of *N*-phosphorylated mono- and bicyclic β-lactams[1]

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Starting from appropriately substituted monocyclic β-lactam, *N*-phosphorylated mono- and bicyclic β-lactams have been synthesized.

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Des β-lactames mono- et bicycliques *N*-phosphorylés ont été synthétisés à partir de β-lactames monocycliques.

Some time ago (2, 3), we postulated that the ring strain of penicillins and cephalosporins, which seems to be responsible for the high frequency of β-lactam ir absorption and hence also for their chemical and biological reactivity, may be replaced by electronic activation, and that properly activated monocyclic β-lactams should possess antibacterial activity. As part of this continuing program, we described the synthesis of bicyclic β-lactam **5**, in which the β-lactam nitrogen is directly attached to a phosphate. Because of the importance of the recently described *N*-sulfated monobactams (4), we also describe the synthesis of *N*-phosphorylated monobactams **21***b* and **24***b* using methodology developed for the preparation of **5**.

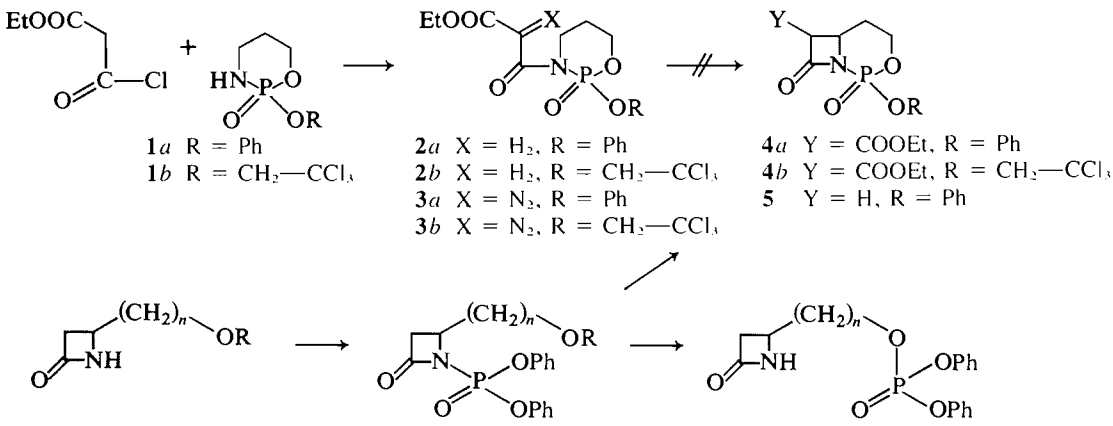
Phenyl cyclophosphoramidate **1***a* was treated with ethyl malonyl chloride (5) to give **2***a* in excellent yield (6). Amide **2***a* underwent base catalyzed diazo exchange with *p*-toluenesulfonyl azide (7) to afford **3***a*. We next attempted to form the β-lactam **4***a* by a carbene insertion reaction, a method pioneered by Corey and Felix (8) and extensively applied by Lowe and co-workers (9) to the synthesis of a variety of bicyclic β-lactams. Irradiation of the α-diazo-amide **3***a* at 0°C in carbon tetrachloride using a Rayonet photochemical reactor, with maximum output at 350 mμ, led to a complicated reaction mixture. The infrared spectrum did not show any diazo or β-lactam absorptions at 2200 or ~1750 cm^{-1}, respectively. Using flash chromatography, one of the less polar spots isolated proved to be phenol. Since phenol absorbs in the ultraviolet spectrum at 210 mμ and 270 mμ, we suspected that it might interfere with the carbene insertion reaction under the photolysis condition. We therefore decided to replace the phenoxy moiety by a trichloroethyl group. This protecting group can be removed in the presence of a β-lactam (10), and should not absorb light.

Addition of 3-amino-1-propanol and triethylamine to trichloroethyl dichlorophosphate, prepared *in situ* by reaction of trichloroethyl alcohol and triethylamine with phosphorus oxychloride, afforded the cyclophosphoramidate **1***b*, in 93% yield, after flash chromatography. It was coupled, as before, with ethyl malonyl chloride to give amide **2***b*. The diazo compound **3***b* was obtained in a manner analogous to that of its corresponding phenyl derivative **3***a*.

Irradiation as described before, or treatment with copper in toluene or rhodium acetate in methylene chloride (11), gave a mixture of products which were not identified.

In a second, more successful series of reactions, alcohol **7***a* (12) was transformed to its tetrahydropyranyl ether **7***b* (13). Reaction of **7***b* with *n*-butyllithium at −78°C in dry tetrahydrofuran, followed by addition of diphenylchlorophosphate, gave the reactive diphenylphosphoramidate **9** in 80% yield. Deprotection with pyridinium *p*-toluenesulfonate (13) gave alcohol **11**, clearly characterized by its nmr spectrum.

Reaction of diphenylphosphoramidate **11** with anhydrous cesium fluoride[2] in *tert*-butanol gave the cyclized β-lactam **5**, in 20% yield, along with phenol and β-lactam **13**, as the sole side products that could be isolated. Attempts to improve the yield of the reaction and to eliminate the side product **13** were



1*a* R = Ph
1*b* R = CH_2—CCl_3

2*a* X = H_2, R = Ph
2*b* X = H_2, R = CH_2—CCl_3
3*a* X = N_2, R = Ph
3*b* X = N_2, R = CH_2—CCl_3

4*a* Y = COOEt, R = Ph
4*b* Y = COOEt, R = CH_2—CCl_3
5 Y = H, R = Ph

6 *n* = 1, *a* R = H, *b* R = THP
7 *n* = 2, *a* R = H, *b* R = THP

8 *n* = 1, R = THP
9 *n* = 2, R = THP
10 *n* = 1, R = H
11 *n* = 2, R = H

12 *n* = 1
13 *n* = 2

[1]Abstracted in part from ref. 1.
[2]Reference 14; also unpublished results of Dr. Ogilvie's laboratory, McGill University.

in vain. This suggested that perhaps the β-lactam nitrogen was in part acting as the leaving group, during treatment with CsF, instead of the phenoxide anion.

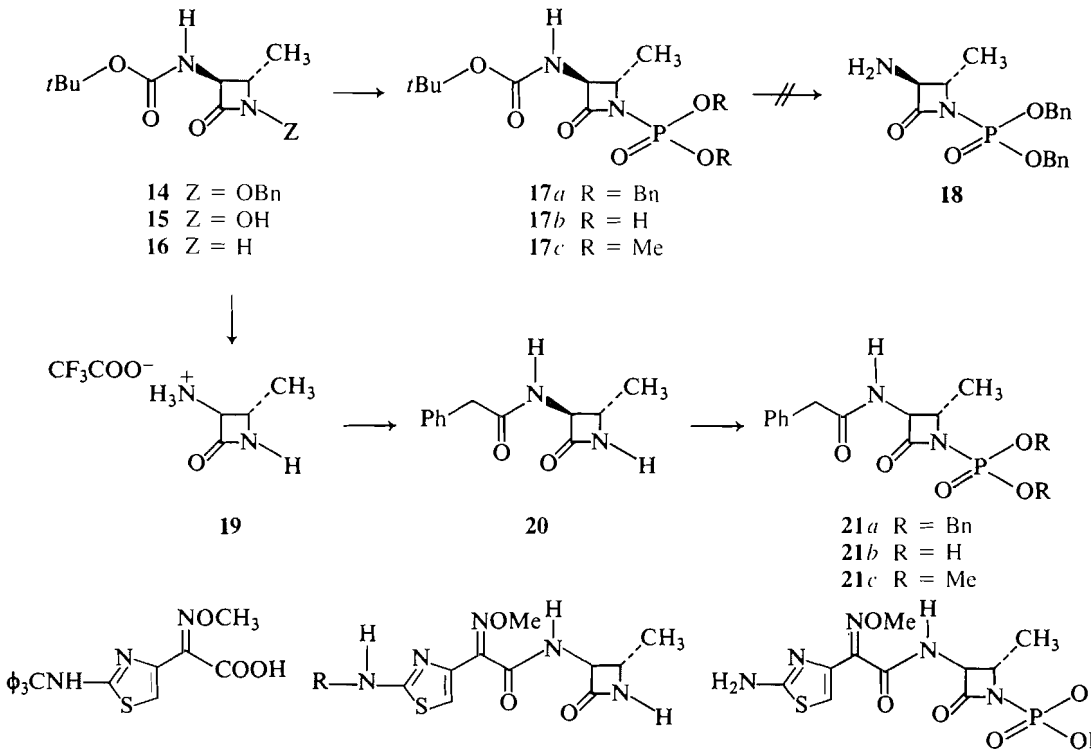
Both structures **5** and **13** were proven by 200 MHz ^{1}H nmr spectra and by mass spectrometry, which showed m/e's due to loss of ketone. In addition, monocyclic β-lactam **13** was prepared by reaction of alcohol **7***a* with diphenylchlorophosphate. Attempts to hydrolyze this material to the free phosphoric acid failed.

When this sequence was repeated using alcohol **6***a* (**6***a* → **6***b* → **8** → **10** → **11** → **12**), obtained by sodium borohydride reduction of 4-carbobenzyloxyazetidinone kindly provided by Dr. Christensen, Merck Laboratories, no bicyclic lower homolog corresponding to **5** was obtained, and only monocyclic diphenylphosphate **12** was isolated. The latter was identical to **12**, prepared from alcohol **6***a* and diphenylchlorophosphate.

The formation of monocyclic β-lactam, although conceptually simple, was fraught with experimental difficulties due to the acid-lability of the N—P bond. β-Lactam **16**, prepared by adaptation of known procedures (15) via the sequence **14** → **15** → **16**, was phosphorylated with dibenzylchlorophosphate in a manner similar to that described before. Catalytic hydrogenolysis of dibenzylphosphate **17***a* in methanol over Pd/C at 1 atm gave after 1 h the phosphoric acid **17***b* which was characterized by conversion to its dimethylester **17***c* using diazomethane. Deblocking of the *t*-BOC group of **17***a* under a variety of acidic conditions did not lead to the expected amine **18**. Instead, either N—P bond cleavage (trifluoroacetic acid (16)), or opening of the β-lactam ring (*p*-toluenesulfonic acid, ethyl acetate (17)) was observed.

Therefore, **16** was hydrolyzed in trifluoroacetic acid (16) at 0°C to the ammonium salt **19**. Reaction of **19** with phenylacetyl chloride (18) gave β-lactam amide **20**. Formation of a mono anion by means of butyllithium at −78°C, followed by addition of dibenzylchlorophosphate, gave phosphorylated β-lactam **21***a*. Catalytic debenzylation using 10% Pd/C in methanol gave the phosphoric acid **21***b* which could be characterized, as was acid **17***b*, by conversion to its methyl ester **21***c*.

Similarly, compound **19** was transformed in phosphoric acid **25***b* in the following manner. First, reaction of **19** with the



appropriate acid **22** (19) was carried out in THF/CH_2Cl_2, using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (20) as coupling agent. Deblocking of the trityl group by formic acid in a methanolic solution led, after 1 h refluxing, to β-lactam **24** in 83% yield. The dibenzylphosphate **25***a*, isolated by phosphorylation of **24** as described before, was hydrogenolyzed under two different conditions, both requiring long reaction times. Thus, under the first set of conditions, previously used (10% Pd/C, hydrogen at 1 atm, methanol), debenzylation gave, after 10 h, the phosphoric acid **25***b* which could be isolated as free acid or as its triethylamine salt **25***d*. Under the second set of conditions (hydrogen at 1 atm, 1 equiv. of $KHCO_3$ in THF−ethanol−water (ref. 21)), hydrogenolysis provided after 6 h the corresponding monopotassium salt **25***e*.

All compounds reported gave good, interpretable nmr and mass spectra except for **25***a*, **25***b*, and **25***c*, where mass spectra could not be interpreted.

None of the *N*-phosphates tested had notable antibacterial activity when compared to Squibb's monobactam SQ 26.776 or piperacillin.

In view of the extensive work of the Squibb group on phosphorylated monobactams (monophosphams) recently described

(22), we do not plan to do any further work in the monophospham area.

Experimental

Thin-layer chromatography was performed on Merck Silica Gel 60 aluminum-backed plates. Flash chromatography was done with Woelm Silica (32–63 μ) using predistilled solvents. Melting points were determined on a Gallenkamp block and are uncorrected. Optical rotations were measured in a 1 dm cell on a Perkin–Elmer 141 polarimeter. Nuclear magnetic resonance spectra were recorded on Varian T-60, T-60A, and XL-200 spectrometers. Infrared (ir) spectra were run on a Perkin–Elmer 297 spectrophotometer. Mass spectra were taken on HP5984A or LKB 9000 spectrometers.

Phenyl cyclophosphoramidate **1**a

To 3-amino-1-propanol (1 g, 13.3 mmol) in dry methylene chloride (20 mL) was added pyridine (3.16 g, 40 mmol) and phenyldichlorophosphate (2.8 g, 13.3 mmol) at 0°C. The mixture was stirred at room temperature for 18 h. The solution was washed with water (2 × 15 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (ethyl acetate) to afford 2.24 g (79%) of **1***a* as a colorless oil. Infrared (film) ν_{max}: 3250 (NH, amide), 1590, 1485, 1260, 1210 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.2–2.4 (m, 2H, CH_2), 2.8–3.7 (m, 2H, CH_2N), 4.1–4.7 (m, 3H, NH, CH_2O), 7.32 (s, 5H, C_6H_5); ms (70 eV, 69°C), *m/e* (‰): 213 (643, $M^{+\cdot}$), 120 (382, $M^{+\cdot} - C_6H_5O^{\cdot}$).

Amide **2**a

To a solution of **1***a* (1.44 g, 6.76 mmol) in THF (10 mL), ethyl malonyl chloride (1.02 g, 6.78 mmol) in THF (5 mL) was added. The reaction was followed by means of tlc. When starting material disappeared (~15 h), the solvent was evaporated. The residue was introduced into a flash chromatography column to afford 1.85 g (84%) of **2***a* as a colorless oil. Infrared (film) ν_{max}: 1740 (C=O, ester), 1690 (C=O, amide) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.24 (t, 3H, CH_3), 1.6–2.5 (m, 2H, $NCH_2CH_2CH_2O$), 3.0–3.6 (m, 1H, CHN), 3.83, 3.90 (2s, 2H, CH_2CO), 4.11 (q, 2H, CH_3CH_2), 4.1–4.9 (m, 3H, CH_2O, CHN), 7.30 (s, 5H, C_6H_5); ms (20 eV, 20°C), *m/e* (‰): 327 (20, $M^{+\cdot}$), 234 (1000, $M^{+\cdot} - C_6H_5O^{\cdot}$).

Diazo-amide **3**a

To a solution of **2***a* (1.85 g, 5.66 mmol) in acetonitrile (20 mL) containing triethylamine (0.63 g, 6.24 mmol) was added *p*-toluenesulfonyl azide (1.18 g, 5.98 mmol) at 0°C. The mixture was stirred for 40 h at room temperature. The solvent was evaporated below 30°C and replaced by methylene chloride (40 mL). After being washed with 0.4 *N* potassium hydroxide, water, dried ($MgSO_4$), and evaporated, the residue was purified by flash chromatography (petroleum ether – ethyl acetate, 1:1) to afford 1.70 g (85%) of **3***a* as a yellow oil. Infrared (film) ν_{max}: 2135 (N_2), 1730 (C=O, ester), 1690, 1650, 1590, 1490 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.30 (t, 3H, CH_3), 1.6–2.5 (m, 2H, CH_2), 3.2–3.8 (m, 1H, NCH), 4.30 (q, 2H, CH_3CH_2), 4.0–4.7 (m, 3H, NCH, $NCH_2CH_2CH_2O$), 7.23 (s, 5H, C_6H_5); ms (20 eV, 60°C), *m/e* (‰): 353 (32, $M^{+\cdot}$), 325 (245, $M^{+\cdot} - N_2$), 260 (77, $M^{+\cdot} - C_6H_5O^{\cdot}$), 253 (341), 94 (1000).

Trichloroethyl cyclophosphoramidate **1**a

A solution of 2,2,2-trichloroethyl alcohol (0.49 g, 3.28 mmol) and triethylamine (0.33 g, 3.27 mmol) in anhydrous tetrahydrofuran (3 mL) was added dropwise at −78°C into phosphorus oxychloride (0.5 g, 3.27 mmol) in THF (5 mL) under nitrogen atmosphere. After stirring 0.5 h, the temperature slowly increased to room temperature within 1 h and the mixture was cooled again to −78°C. To the cooled mixture, a solution of 3-amino-1-propanol (0.245 g, 3.26 mmol) and triethylamine (0.693 g, 6.86 mmol) in THF (3 mL) was added. The mixture was allowed to warm to room temperature and stirred for another 4 h. The tetrahydrofuran was evaporated. The residue was added to methylene chloride (50 mL) and water (40 mL). The organic layer was washed with 1% HCl (30 mL), dried ($MgSO_4$), and evaporated. The crude product was purifed by flash chromatography (ethyl acetate) to obtain 0.81 g (93%) of **1***b* as a light yellow oil. Infrared (film) ν_{max}: 3250 (NH), 1420, 1335, 1260, 1100 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.5–2.5 (m, 2H, $NCH_2CH_2CH_2O$), 3.0–3.7 (m, 2H, NCH_2), 4.1–4.8 (m, 3H, $NHOCH_2$), 4.50 (d, 2H, CH_2CCl_3, J = 7 Hz); ms (70 eV, 20°C), *m/e* (‰): 273 (4, $M^{+\cdot}$ + 6, Cl_3^{37}), 271 (18, $M^{+\cdot}$ + 4, $Cl_1^{35}Cl_2^{37}$), 269 (55, $M^{+\cdot}$ + 2, $Cl_2^{35}Cl_1^{37}$), 267 (57, $M^{+\cdot}$, Cl_3^{35}), 120 (1000, $M^{+\cdot} - OCH_2CCl_3^{\cdot}$).

Amide **2**b

This compound was obtained from **1***b* via the procedure for the preparation of **2***a*, in 90% yield after flash chromatography (petroleum ether – EtOAc, 1.5:1). Infrared (film) ν_{max}: 1735 (C=O, ester), 1690 (C=O, amide), 1330, 1300 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.30 (t, 3H, CH_3), 1.7–2.3 (m, 2H, $NCH_2CH_2CH_2O$), 3.1–3.7 (m, 1H, NCH), 3.8–4.8 (mb, 3H, OCH_2, NCH), 3.90, 4.04 (2s, 2H, CH_2), 4.20 (q, 2H, CH_3CH_2), 4.70 (d, 2H, OCH_2CCl_3, J = 7 Hz); ms (70 eV, 37°C), *m/e* (‰): 385 (15, $M^{+\cdot}$ + 4, $Cl_1^{35}Cl_2^{37}$), 383 (36, $M^{+\cdot}$ + 2, $Cl_2^{35}Cl_1^{37}$), 381 (38, $M^{+\cdot}$, Cl_3^{35}), 234 (194, $M^{+\cdot} - OCH_2CCl_3^{\cdot}$).

Diazo-amide **3**b

Compound **3***b* was obtained from **2***b* via the procedure for the preparation of **3***a*, in 80% yield after flash chromatography (petroleum ether – EtOAc, 1.5:1). Infrared (film) ν_{max}: 2115 (N_2), 1720 (C=O, ester), 1650 (C=O, amide, 1330 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.30 (t, 3H, CH_3), 1.6–2.3 (m, 2H, $NCH_2CH_2CH_2O$), 3.1–3.8 (m, 1H, NCH), 3.8–4.8 (m, 5H, NCH, CH_2O, OCH_2CH_3), 4.80 (d, 2H, OCH_2CCl_3, J = 7 Hz); ms (70 eV, 51°C), *m/e* (‰): 272 (14, $M^{+\cdot} - EtOOCCN_2CO^{\cdot}$ + 6, Cl_3^{37}), 270 (44, $M^{+\cdot} - EtOOCCN_2CO^{\cdot}$ + 4, $Cl_1^{35}Cl_2^{37}$), 268 (81, $M^{+\cdot} - EtOOCCN_2CO^{\cdot}$ + 2, $Cl_2^{35}Cl_2^{37}$), 266 (14, $M^{+\cdot} - EtOOCCN_2CO^{\cdot}$, Cl_3^{35}).

β-*Lactam* **7**b

A solution of β-lactam **7***a* (4.39 mg, 3.82 mmol) and dihydropyran (482 mg, 5.73 mmol) in dry methylene chloride (10 mL) containing pyridinium *p*-toluenesulfonate (PPTS) (96 mg, 0.382 mmol) was stirred for 8 h at room temperature. The solution was diluted with ether and washed with half-saturated brine to remove the catalyst. After drying and evaporation of the solvent, flash chromatography (ethyl acetate) gave 410 mg (54%) THP ether **7***b*. Infrared (film) ν_{max}: 3300 (NH), 1760 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.4–2.1 (m, 8H, CH_2CH_2O, $CHCH_2CH_2CH_2$), 2.49 (ddd, 1H, CHHCO, J_{gem} = 13 Hz, J_{trans} = 2.2 Hz, J_{NH} = 1.1 Hz), 3.10 (ddd, 1H, CHHCO, J_{gem} = 13 Hz, J_{cis} = 4.2 Hz, J_{NH} = 1.1 Hz), 3.3–4.1 (m, 5H, CHNH, $2CH_2O$), 4.6 (bm, 1H, $CH_2OCHOCH_2$), 6.3–6.7 (bs, 1H, NH); ms (70 eV, 20°C), *m/e* (‰): 199 (99, $M^{+\cdot}$), 99 (103, $M^{+\cdot} - HOCH(CH_2)_4O^{\cdot}$), 85 (1000, THP^+).

β-*Lactam* **9**

Under a nitrogen atmosphere, a solution of β-lactam **7***b* (253 mg, 1.27 mmol) in dry THF (5 mL) was cooled to −78°C and treated with n-BuLi (1 equiv.) in THF. After being stirred for 10 min, diphenyl chlorophosphate (342 mg, 1.27 mmol) was added dropwise, and stirring, at −78°C, was continued for a period of 30 min. The reaction mixture was warmed to room temperature by itself. After adding methylene chloride (20 mL), the organic layer was washed with water (2 × 15 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (petroleum ether – ethyl acetate; 1:1.5) to afford 438 mg of β-lactam **9** in 80% yield. Infrared (film) ν_{max}: 1790 (C=O, β-lactam) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.2–2.1 (m, 8H, CH_2CH_2O, $CH_2CH_2CH_2$), 2.6–3.0 (m, 2H, CH_2CO), 3.1–4.0 (m, 5H, CHN, CH_2O, CH_2O), 4.2 (b, 1H, CH), 7.00 (s, 10H, $2C_6H_5$).

β-*Lactam* **6**b

Compound **6***b* was obtained from β-lactam **6***a*, via the procedure for the preparation of **7***b*, in 80% yield after flash chromatography (EtOAc). Infrared (film) ν_{max}: 3280 (NH), 1750 (C=O, β-lactam) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.2–2.0 (m, 6H, $OCH(CH_2)_3$), 2.51 (app.bd, 1H, COCHH, J_{gem} = 14 Hz), 2.96 (2ddd, 1H, COCHH, J_{gem} = 14, J_{cis} = 4 Hz, J_{NH} = 1.5 z), 3.2–4.0 (m, 4H, OCH_2, OCH_2), 4.48 (bs, 1H, OCH), 6.7–7.0 (bs, 1H, NH); ms (70 eV, 19°C), *m/e* (‰): 185 (21 $M^{+\cdot}$), 85 (1000, THP^+).

β-*Lactam* **8**

This compound was obtained from **6***b*, via the same procedure as for the preparation of **9**, in 85% yield used for the next reaction without purification. Infrared (film) ν_{max}: 1795 (β-lactam), 1595, 1490 (aromatic C=C), 1290 (P=O) cm $^{-1}$; ^{1}Hmr ($CDCl_3$) δ: 1.1–2.0 (m, 6H, $CH_2CH_2CH_2$), 2.9–3.2 (m, 2H, CH_2CO), 3.2–4.0 (m, 5H, $2OCH_2$, NCH), 4.2–4.5 (m, 1H, OCH), 7.12 (s, 10H, $2C_6H_5$); ms (70 eV, 76°C), *m/e* (‰): 417 (54, $M^{+\cdot}$), 333 (47, $M^{+\cdot}$ – DHP), 275 (287 ($M^{+\cdot}$ – $CH_2CHCH_2OTHP^{\cdot}$), 94 (936, $C_6H_5OH^{+\cdot}$), 77 (1000).

β-*Lactam* **10**

Compound **10** was obtained from **8** via the procedure for the preparation of **11**, in 60% yield after flash chromatography (petroleum ether – EtOAc, 1:2.5). Infrared (film) ν_{max}: 3600–3200 (OH), 1790 (C=O, β-lactam), 1590, 1485 (aromatic C=C), 1280 (P=O) cm $^{-1}$; ^{1}Hmr ($CDCl_3$) δ: 2.5–3.4 (m, 2H, CH_2CO), 3.2–3.5 (b, 1H, OH, exchangeable with D_2O), 3.5–3.7 (m, 2H, CH_2OH), 4.0–4.1 (m, 1H, CHN), 7.27 (s, 10H, $2C_6H_5$); ms (70 eV, 26°C), *m/e* (‰): 333 (165, $M^{+\cdot}$), 275 (820, $M^{+\cdot}$ – CH_2CHCH_2OH), 233 (280 $(O)P(OC_6H_5)_2^+$), 94 (664, $C_6H_5OH^{+\cdot}$), 77 (1000).

β-*Lactam* **11**

A solution of THP ether **9** (180 mg, 0.42 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (20 mg, 0.08 mmol) in absolute ethanol (5 mL) was stirred at 55°C (oil bath temperature) for 5 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed (EtOAc – petroleum ether, 2:1) to afford 124 mg (85%) of β-lactam **11**. Infrared (film) ν_{max}: 3450 (OH), 1790 (C=O, β-lactam) cm $^{-1}$; ^{1}Hmr 200 MHz ($CDCl_3$ and D_2O) δ: 1.6–2.0 (m, 2H, CH_2CH_2OH), 2.79 (ddd, 1H, COC*H*H, J_{gem} = 16 Hz, $J_{cis} = J_{PH} \simeq 3$ Hz), 3.22 (ddd, 1H, COC*H*H, J_{gem} = 16 Hz, $J_{trans} = J_{PH} \simeq 6$ Hz), 3.4–3.8 (m, 2H, CH_2OH), 4.0–4.2 (m, 1H, NCH), 7.38 (m, 10H, $2C_6H_5$); ms (70 eV, 56°C), *m/e* (‰): 347 (101, $M^{+\cdot}$), 276 (961, $M^{+\cdot}$ – CH_2=CH–$(CH_2)_2OH$ + 1), 254 (117, $M^{+\cdot}$ – $OC_6H_5^{\cdot}$), 77 (1000).

Bicyclic β-*lactam* **5**

To a solution of **11** (150 mg, 0.43 mmol) in *t*-BuOH (2 mL) was added CsF (66 mg, 0.43 mmol). After stirring at room temperature for 2 h, the solvent was evaporated. Ethyl acetate was added. The mixture was washed with brine, dried, and evaporated to afford 22 mg (20%) of β-lactam **5**, after flash chromatography (petroleum ether – EtOAc, 1:2); mp 103°C; ir (CH_2Cl_2) ν_{max}: 1760 (C=O, β-lactam), 1590, 1490, 1190 cm $^{-1}$; ^{1}Hmr (acetone-d_6) δ: 1.8–2.2 (m, 2H, CH_2), 2.90 (app.dd, 2H, CH_2CO), 3.8–5.0 (m, 3H, CH, CH_2O), 6.9–7.5 (m, 5H, C_6H_5); ^{1}Hmr 200 MHz (acetone-d_6 and D_2O) δ: 1.8–2.2 (m, 2H, CH_2), 2.8–3.0 (m, 2H, CH_2O), 3.9–4.1 (m, 1H, CH), 4.3–4.7 (m, 2H, CH_2O), 6.9–7.5 (m, 5H, C_6H_5); ms (70 eV, 82°C), *m/e* (‰): 254 (372, $M^{+\cdot}$ + 1), 212 (1000, $M^{+\cdot}$ – CH_2=C=O).

β-*Lactam* **13**

To a solution of alcohol **7***a* (150 mg, 1.3 mmol) and pyridine (162 mg, 1.43 mmol) in CH_2Cl_2 (10 mL) was added dropwise diphenyl chlorophosphate (349 g, 1.3 mmol). After stirring for 2 h the solution was washed with water (3 × 5 mL) and brine (8 mL), dried ($MgSO_4$), and evaporated to give 392 mg (87%) of β-lactam **13** after flash chromatography. Infrared (film) ν_{max}: 1765 (C=O, β-lactam), 1590, 1490 (C=C, aromatic) cm $^{-1}$; ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.8–2.2 (m, 2H, CH_2), 2.60 (ddd, 1H, COC*H*H, J_{gem} = 15 Hz, J_{trans} = 2 Hz), 3.05 (ddd, 1H, COCH*H*, J_{gem} = 15 Hz, J_{cis} = 5 Hz, J_{NH} = 2 Hz), 3.6–3.8 (m, 1H, CH), 4.2–4.6 (m, 2H, CH_2O), 6.3 (bs, 1H, NH), 7.1–7.5 (m, 10H, $2C_6H_5$); ms (70 eV, 55°C), *m/e* (‰): 347 (46, $M^{+\cdot}$), 305 (437, $M^{+\cdot}$ – CH_2=C=O), 304 (203, $M^{+\cdot}$ – OCNH).

Alcohol **6**a

To a solution of 4-carbobenzyloxyazetidinone (0.205 g, 1 mmol) in methanol (10 mL) was added sodium borohydride (114 mg, 3 mmol) in portions. After stirring at room temperature for 18 h, concentrated HCl was added dropwise to neutralize to pH 5. The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was purified by flash chromatography (EtOAc – methanol, 10:1) to afford 0.05 g (50%) of alcohol **6***a*. Infrared (film) ν_{max}: 3400–3000 (NH, OH), 1730 (C=O, β-lactam) cm $^{-1}$; ^{1}Hmr (acetone-d_6) δ: 2.6 (dd, 1H, COC*H*H, J_{gem} = 15 Hz, J_{trans} = 2Hz), 2.9 (m, 1H, COCH*H*, J_{gem} = 15 Hz, J_{cis} = 5 Hz, J_{NH} = 1.5 Hz), 3.5–3.9 (m, 3H, CH_2O, CH), 4.2 (bs, 1H, OH), 7.3 (bs, 1H, NH); gc–ms (TMS derivative), *m/e* (‰): 245 (24, $M^{+\cdot}$, di-TMS derivative).

β-*Lactam* **12**

Diphenyl chlorophosphate (0.31 mL, 1.48 mmol) was added dropwise to a solution of alcohol **6***a* (149 mg, 1.48 mmol) and triethylamine (0.21 mL) in anhydrous tetrahydrofuran (5 mL). After stirring for 0.5 h methylene chloride (20 mL) was added to the reaction mixture. The organic layer was washed with water (2 × 15 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by flash chromatography (EtOAc) to afford 438 mg (89%) of β-lactam **12**. Infrared (film) ν_{max}: 3260 (NH), 1780 (C=O, β-lactam), 1590, 1490 (aromatic C=C), 1290 (P=O) cm $^{-1}$; ^{1}Hmr ($CDCl_3$) δ: 2.51 (ddd, 1H, C*H*HCO, J_{gem} = 15 Hz, J_{trans} = 3 Hz, J_{NH} = 1.5 Hz), 2.83 (ddd, 1H, C*H*HCO, J_{gem} = 15 Hz, J_{cis} = 4 Hz, J_{NH} = 1.5 Hz), 3.5–3.8 (m, 1H, CHN), 3.9–4.3 (m, 2H, CH_2O), 6.6 (bs, 1H, NH), 7.00 (s, 10H, $2C_6H_5$); ms (70 eV, 55°C), *m/e* (‰): 333 (34, $M^{+\cdot}$), 291 (1000, $M^{+\cdot}$ – CH_2=C=O), 94 (861, $C_6H_5OH^{+\cdot}$), 77 (820, $C_6H_5^{+\cdot}$).

*4-Methyl-3-[(*tert*-butoxycarbonyl)amino]-1-hydroxyazetidinone* **15** (ref. 15*b*)

Compound **14** (1.53 g, 5 mmol) was dissolved in 140 mL of methanol and hydrogenated at 1 atm of H_2 in the presence of 10% Pd/C (140 mg); filtration and evaporation gave **15** as a white solid; mp 143–145°C (recrystallized from ether–hexanes); $[\alpha]_D^{20}$ −30.8° (*c* 1.05, CH_3OH); ir (Nujol) ν_{max}: 3350 (NH), 1775 (CO, β-lactam), 1685 (CO, *t*-BOC) cm $^{-1}$; ^{1}Hmr (CD_3OD) δ: 1.4 (d, 3H, CH_3, J = 6.5 Hz), 1.46 (s, 9H, *t*-Bu), 3.76 (9d, 1H, CHMe, J = 6.5, 1.5 Hz), 4.0 (br m, 1H, C*H*NH), 4.8 (br s, 2H).

*4-Methyl-3-[(*tert*-butoxycarbonyl)amino]azetidinone* **16** (ref. 15*b*)

Compound **15** (1.92 g, 8.9 mmol) was dissolved in 18 mL of CH_3OH and added to 73 mL of H_2O at pH 7. While the mixture was stirred under N_2 and the pH maintained at 7 by dropwise addition of 3 *N* NaOH solution, 36 mL (4 equiv.) of a 15% aqueous solution of $TiCl_3$ (BDH) was added dropwise. After the addition was completed, stirring was continued for 3 h. The aqueous mixture was then adjusted to pH 8 and extracted with three 30-mL portions of ethyl acetate. The combined ethyl acetate was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was recrystallized from ethyl acetate – hexanes to give 0.77 g (3.85 mmol, 43%) of **16**; mp 123–125°C; $[\alpha]_D^{20}$ −60.5° (*c* 1.1, CH_3OH); ir ($CHCl_3$) ν_{max}: 3440 and 3320 (NH), 1760 (CO β-lactam), 1710 (CO, *t*-BOC) cm $^{-1}$; ^{1}Hmr ($CDCl_3$) δ: 1.4 (d, 3H, CH_3, J = 6.5 Hz), 1.45 (s, 9H, *t*-Bu), 3.68 (qd, 1H, C*H*Me, J = 6.5, 1.5 Hz), 4.16 (dd, 1H, C*H*NH, J = 7.0, 1.5 Hz), 5.85 (d, 1H, NH amide, J = 7.0 Hz), 7.0 (br s, 1H, NH β-lactam).

*4-Methyl-3-[(*tert*-butoxycarbonyl)amino]-1-dibenzylphosphoryl-2-azetidinone* **17**a

Under a nitrogen atmosphere, a solution of β-lactam **16** (150 mg, 0.75 mmol) in dry THF (15 mL) was cooled at −78°C and treated with n-BuLi (1.1 equiv.). The reaction mixture was stirred for 20 min and a solution of dibenzyl chlorophosphate (266 mg, 0.9 mmol) in THF (2 mL) was added dropwise; stirring at −78°C was continued for 1 h. The solution was allowed to warm up to −10°C. The solvent was removed and, after adding ethyl acetate, the organic layer was washed twice with brine, dried on $MgSO_4$, and evaporated. The residue was purified by flash chromatography (ethyl acetate – hexanes, 45:55) to afford 208 mg of β-lactam **17***a* in 60% yield; $[\alpha]_D^{20}$ −3.9° (*c* 1.35, CH_3OH); ir ($CDCl_3$) ν_{max}: 3300 (NH), 1785 (CO β-lactam), 1710 (CO *t*-BOC), 1270 (P=O) cm $^{-1}$; ^{1}Hmr ($CDCl_3$) δ: 1.33–1.43 (s + d, 12H, *t*-Bu + CH_3), 3.70–4.20 (m, 3H, CH—CH, NH), 5.0–5.2 (2d, 4H, $2CH_2$, $J_{P—OCH_2}$ = 9 Hz), 7.3 (s, 10H, $2C_6H_5$); ms (70 eV, 80°C), *m/e* (‰), 304 (110, $M^{+\cdot}$ – *t*-BOCNHCHCO + 1,

$M^{+\cdot}$ − *t*-BOCNHCHCHCH$_3$ + 1), 157 (70, *t*-BOCNHCHCO$^+$, *t*-BOCNHCHCHCH$_3^+$), 107 (40, $C_6H_5CH_2O^+$), 101 (350, *t*-BuOCO$^+$), 91 (880, $C_6H_5CH_2^+$), 57 (1000, *t*-Bu$^+$, $\overline{CH_2—CO—NH^{+\cdot}}$, $\overline{CH_2—CHMe—NH^{+\cdot}}$).

*4-Methyl-3-[(*tert*-butoxycarbonyl)amino]-1-phosphoryl-2-azetidinone* **17**b

Dibenzylphosphoramidate **17***a* (40 mg, 0.087 mmol) was dissolved in methanol (5 mL) and hydrogenated for 1 h at 1 atm of H_2 in the presence of 10% Pd/C (5 mg). After filtration and evaporation, the residue was washed with chloroform (3 × 1 mL) to afford 22 mg of amidophosphoric acid **17***b* in 90% yield; pH (CH_3OH solution) 2.5−3; ir ($CHCl_3$) ν_{max}: 3450−2600 (OH), 3350 (NH), 1760 (CO β-lactam), 1705 (CO *t*-BOC), 1250 (P=O) cm^{-1}; ^{1}Hmr 200 MHz (D_2O) δ: 1.33 (s, 9H, *t*-Bu), 1.43 (d, 3H, CH_3, J = 6.5 Hz), 3.7−5.0 (m, 5H); ms (70 eV), *m/e* (‰): 497 (120, $M^{+\cdot}$ + 1 + 3TMS), 397 (120), 395 (740, $M^{+\cdot}$ − *t*-BuOCO + 3TMS), 340 (370, $M^{+\cdot}$ − *t*-BOCNHCHCO + 1 + 3TMS, $M^{+\cdot}$ − *t*-BOCNHCHCHCH$_3$ + 1 + 3TMS), 323 (150, $M^{+\cdot}$ − *t*-BuO + 3TMS), 101 (20, *t*-BuOCO$^+$), 73 (1000, *t*-BuO$^+$), 57 (340, *t*-Bu$^+$, $\overline{CH_2—CO—NH^{+\cdot}}$, $\overline{CH_2—CHMe—NH^{+\cdot}}$).

*4-Methyl-3-[(*tert*-butoxycarbonyl)amino]-1-dimethylphosphoryl-2-azetidinone* **17**c

To a suspension of β-lactam phosphoric acid **17***c* (8.5 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0°C a solution of diazomethane (2.5 equiv.) in ether. The reaction mixture was warmed to room temperature by itself. After evaporation of the solvent 10 mg of dimethylphosphoramidate **17***c* were obtained in a quantitative yield; ir ($CHCl_3$) ν_{max}: 3450 (NH), 1780 (CO β-lactam), 1715 (CO *t*-BOC), 1270−1180 (P=O) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.3−1.45 (s + d, 12H, *t*-Bu + CH_3), 3.6−4.4 (m, 2H, CH—CH), 3.8−4.0 (2d, 4H, 2 OCH_3, $J_{P—OCH_3}$ = 12 Hz), 5.2 (br d, 1H, NH); ms (70 eV), *m/e* (‰): 235 (60 $M^{+\cdot}$ − *t*-BuO), 157 (20, *t*-BOCNHCHCO$^+$, *t*-BOCNHCHCHCH$_3^+$), 152 (460, $M^{+\cdot}$ − *t*-BOCNHCHCO + 1, $M^{+\cdot}$ − *t*-BOCNHCHCHCH$_3$ + 1), 109 (80, $\overline{PO(OMe)_2^{+\cdot}}$), 101 (245, *t*-BuOCO$^+$), 57 (1000, *t*-Bu$^+$, $\overline{CH_2—CO—NH^{+\cdot}}$, $\overline{CH_2—CHMe—NH^{+\cdot}}$).

β-*Lactam* **19**

β-Lactam **16** (200 mg, 1 mmol) was dissolved in trifluoroacetic acid (1 mL) at 0°C. After stirring for 10 min, the acid was removed by evaporation and the residue washed with carbon tetrachloride (3 × 1 mL); ir (film) ν_{max}: 3450−2680 (NH, OH), 1770 (CO β-lactam), 1670 (CO) cm^{-1}; ^{1}Hmr (CD_3COCD_3) δ: 1.5 (d, 3H, CH_3, J = 6.5 Hz), 3.8−4.4 (m, 3H, C*H*Me, NH_2), 5.05 (d, 1H, C*H*NH, J = 1.5 Hz).

4-Methyl-3-phenylacetamido-2-azetidinone **20**

To a solution of β-lactam **19** (214 mg, 1 mmol) and pyridine (237 mg, 3 mmol) in dry methylene chloride (20 mL) was added, dropwise under nitrogen, phenylacetyl chloride (232 mg, 1.5 mmol) in 5 mL methylene chloride. After the addition was complete the solution was stirred for 3 h, washed with pH 4.5 buffer (KH_2PO_4) and water, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (ethyl acetate) to afford a colorless solid (50 mg) in 23% yield; mp 138−140°C; $[\alpha]_D^{20}$ −36.0° (*c* 0.65, CH_3OH); ir ($CHCl_3$) ν_{max}: 3420 and 3300 (NH), 1760 (C=O β-lactam), 1670 (C=O amide), 1600 (C=C) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.5 (d, 1H, CH_3, J = 6.5 Hz), 3.4−3.7 (m, 3H, CH_2, C*H*Me), 4.5 (dd, 1H, C*H*NH, J = 6.0, 2.0 Hz), 6.5 (br s, 1H, NH β-lactam), 6.8 (d, 1H, NH amide, J = 6.0 Hz), 7.3 (s, 5H, C_6H_5); ms (70 eV), *m/e* (‰): 175 (380, $C_6H_5CH_2CONHCHCO^+$, $\overline{C_6H_5CH_2CONHCHCHMe^+}$), 91 (670, $C_6H_5CH_2^+$), 57 (1000, $\overline{CH_2—CO—NH^{+\cdot}}$, $\overline{CH_2—CHMe—NH^{+\cdot}}$).

4-Methyl-3-phenylacetamido-1-dibenzylphosphoryl-2-azetidinone ***21***a was prepared from β-lactam **20** as described for **17***a*, in 30% yield after flash chromatography (EtOAc−hexanes, 60:40); ir ($CHCl_3$) ν_{max}: 3400 (NH), 1780 (CO β-lactam), 1670 (CO amide), 1270−1180 (P=O) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.5 (d, 3H, CH_3, J = 6.5 Hz), 3.65 (s, 2H, CH_2), 3.75−4.1 (m, 1H, C*H*Me), 4.2−4.4 (dd, 1H, C*H*NH, J = 7.0, 2.0 Hz), 5.1−5.3 (2d, 4H, $2CH_2$, J = 9 Hz), 6.1 (d, 1H, NH, J = 7.0 Hz), 7.4 (s, 15H, $3C_6H_5$); ms (70 eV), *m/e* (‰): 478 (150, $M^{+\cdot}$), 304 (140, $M^{+\cdot}$ − $C_6H_5CH_2CONHCHCO$ + 1, $M^{+\cdot}$ − $C_6H_5CONHCHCHMe$ + 1), 281 (490), 175 (490, $C_6H_5CH_2CONHCO^+$, $\overline{C_6H_5CH_2CONHCHCHMe^+}$), 91 (1000, $C_6H_5CH_2^+$), 57 (170, $\overline{CH_2—CONH^{+\cdot}}$, $\overline{CH_2CHMe—NH^{+\cdot}}$).

4-Methyl-3-phenylacetamido-1-phosphoryl-2-azetidinone ***21***b was prepared from β-lactam **21***a* as described for **17***b*. Yield: 85%; pH (CH_3OH solution) 3.5; ir (Nujol) ν_{max}: 3450−3000 (OH, NH), 1750 (C=O β-lactam), 1650 (C=O amide), 1200 (P=O) cm^{-1}; ^{1}Hmr (CD_3OD) δ: 1.5 (d, 3H, CH_3, J = 6.5 Hz), 3.6 (s, 2H, CH_2), 3.7−4.6 (m, 3H, CH—CH, NH), 7.3 (s, 5H, C_6H_5).

4-Methyl-3-phenylacetamido-1-dimethylphosphoryl-2-azetidinone **21**c was prepared from β-lactam **21***b* as described for **17***c*; ms (70 eV), *m/e* (‰): 327 (5, $M^{+\cdot}$ + 1), 175 (10, $C_6H_5CH_2CONHCHCO^+$, $C_6H_5CH_2CONHCHCHMe^+$), 152 (1000, $M^{+\cdot}$ − $C_6H_5CH_2CONHCHCO$ + 1, $M^{+\cdot}$ − $C_6H_5CH_2CONHCHCHMe$ + 1), 109 (20, $\overline{PO(OCH_3)_2^+}$), 91 (380, $C_6H_5CH_2^+$), 57 (70, $\overline{CH_2CONH^{+\cdot}}$, $\overline{CH_2—CHMe—NH^{+\cdot}}$).

β-*Lactam* **23**

To a solution of β-lactam **19** (1.07 g, 5 mmol) in 150 mL of dry THF−CH_2Cl_2 (1:2) was added triethylamine (0.60 g, 6 mmol) at 0°C and under nitrogen. The reaction mixture was stirred for 1 h and allowed to warm to room temperature. Then two solutions, trityl acid **22** (2.66 g, 6 mmol) in 30 mL dry CH_2Cl_2 and EEDQ (1.48, 6 mmol) in 20 mL dry CH_2Cl_2, were successively added dropwise. After stirring for a period of 15 h, the solvent was removed and ethyl acetate added. The organic layer was washed with a 4% $NaHCO_3$ solution (2 × 20 mL) and brine, dried ($MgSO_4$), and evaporated. The crude material was purified by flash chromatography (EtOAc−hexanes 75:25) to afford 0.98 g of β-lactam **23** in 38% yield; mp 135−140°C; $[\alpha]_D^{20}$ −31.4° (*c* 1.35, CH_3OH); ir ($CHCl_3$) ν_{max}: 3420 and 3360 (NH), 1765 (CO β-lactam), 1680 (CO amide) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.5 (d, 3H, CH_3, J = 6.5 Hz), 4.0 (s, 3H, OCH_3), 3.5−4.0 (qd, 1H, C*H*Me, J = 6.5, 2.0 Hz), 4.4−4.6 (dd, 1H, C*H*NH, J = 6.0, 2.0 Hz), 6.2 (s, 1H, NH β-lactam), 6.6 (s, 1H, CH=), 7.1 (d, 1H, NH amide), 7.3 (s, 15H, $3C_6H_5$).

β-*Lactam* **24**

Trityl β-lactam **23** (485 mg, 0.92 mmol) in 75 mL of methanol − formic acid (4:1) was refluxed for 1 h. After evaporation of the solvent, the crude material was washed with carbon tetrachloride to give 227 mg (0.80 mmol, 86%) of amino β-lactam **24**; mp 125−130°C (dec.); $[\alpha]_D^{20}$ −70.5° (*c* 2.47, CH_3OH); ir ($CHCl_3$) ν_{max}: 3480, 3410, 3300 (NH), 1760 (CO β-lactam), 1670 (CO amide), 1600 (C=C) cm^{-1}; ^{1}Hmr (CD_3COCD_3) δ: 1.4 (d, 3H, CH_3, J = 6.5 Hz), 3.6−4.0 (m, 4H, OCH_3, C*H*Me), 4.5−4.7 (dd, 1H, CHNH, J = 8.0, 2.0 Hz), 6.72 (s, 1H, CH=), 6.92 (br s, 2H, NH_2), 7.5 (s, 1H, NH β-lactam), 8.4 (d, 1H, NH amide); ms (70 eV), *m/e* (‰): 283 (80, $M^{+\cdot}$), 252 (100, $M^{+\cdot}$ − OCH_3), 240 (150, $M^{+\cdot}$ − CONH, $M^{+\cdot}$ − MeCHNH), 126 (1000), 125 ($H_2N—C=N—C—C\equiv N$, 99 (S—CH)), (250), 83 (300), 57 (250).

N-*dibenzylphosphoryl* β-*lactam* ***25***a was prepared from compound **24** (227 mg, 0.8 mmol) following the procedure described for **17***a*. However, in the present case, the organic layer was washed with a 4% $NaHCO_3$ solution and brine. The crude compound was purified by flash chromatography (EtOAc) to afford 150 mg of β-lactam **25***a* in 35% yield; $[\alpha]_D^{20}$ −18.4° (*c* 1.05, CH_3OH); ir ($CHCl_3$) ν_{max}: 3480, 3380 (NH), 1780 (CO β-lactam), 1670 (CO amide), 1600 (C=C), 1190 (P=O) cm^{-1}; ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.43 (d, 3H, CH_3, J = 6 Hz), 3.89 (s, 3H, OCH_3), 4.15 (qd, 1H, C*H*Me, J = 6.0, 2.0 Hz), 4.62 (dd, 1H, C*H*NH, J = 7.0, 2.0 Hz), 5.11−5.17 (2d, 4H, $2CH_2$, $J_{P—OCH_2}$ = 8 Hz), 5.76 (s, 2H, NH_2), 6.66 (s, 1H, CH=), 7.22 (m, 10H, $2C_6H_5$), 8.11 (br d, 1H, NH, J = 7 Hz); ms (70 eV), *m/e* (‰): 187 (180), 167 (110), 149 (370), 107 (170), 100 (830), 97

(160), 91 (1000, $C_6H_5CH_2^+$), 83 (103), 79 (100), 69 (680), 57 (760), 55 (610), 45 (250).

N-*phosphoryl* β-*lactam* **25**b was prepared from **25***a* (47 mg, 0.086 mmol) according to the method given for **17***b*. After 10 h of reaction, filtration, and evaporation, the crude material was recrystallized in MeOH–EtOAc (1:3) to give phosphoric acid **25***b* in 80% yield; pH (MeOH solution) 5.5; $[\alpha]_D^{20}$ 26.3° (*c* 0.18, CH_3OH); ir (KBr) ν_{max}: 3600–2900 (NH, OH), 1745 (CO β-lactam), 1665 (CO amide), 1210 (P=O) cm^{-1}; ^{1}Hmr 200 MHz (CD_3OD) δ: 1.47 (d, 3H, CH_3, J = 6.5 Hz), 3.93 (s, 3H, OCH_3), 3.47–3.77 (m, 1H, C*H*Me), 4.2–4.4 (m, 1H, C*H*NH), 6.8 (s, 1H, CH=), 7.22–7.47 (m, 5H, NH_2, NH, 2OH); ms (70 eV), *m/e* (‰): 368 (40), 97 (110), 91 (200), 83 (180), 69 (370), 57 (450), 55 (410), 44 (1000).

N-*dimethyl phosphoryl* β-*lactam* **25**c was prepared from compound **25***b* as described for **17***c*; ms (70 eV), *m/e* (‰): 279 (60), 167 (120), 149 (280), 130 (120), 121 (110), 97 (160), 95 (120), 91 (110), 85 (150), 83 (220), 81 (250), 73 (360), 71 (330), 69 (655), 57 (780), 55 (680), 43 (1000).

Triethylamine salt **25**d was obtained by addition of triethylamine (5 mg, 0.05 mmol) to a solution of acid **25***b* (9 mg, 0.025 mmol) in 1 mL MeOH. After stirring for 5 min, the solvent was removed to afford 13 mg of β-lactam **25***d* in 92% yield; ir (KBr) ν_{max}: 3550–3300 (NH), 1745 (CO β-lactam), 1660 (CO amide), 1610 (C=C), 1245, 1205 (P=O) cm^{-1}; ^{1}Hmr (CD_3OD) δ: 1.3–1.5 (t + d, 9H, $2CH_2$—CH_3, CH_3, J = 7.5, 6.5 Hz), 3.1 (q, 4H, $2CH_2$—Me, J = 7.5 Hz), 3.5–4.6 (m, 5H, C*H*Me, C*H*NH, OCH_3), 6.85 (s, 1H, CH=), 7.3 (m, 5H, 3NH, NH_2).

Monopotassium salt **25**e

Dibenzylphosphoramidate **25***a* (5.4 mg, 0.01 mmol) was dissolved in 2 mL THF–EtOH (1:1) and 12 μL of a 1 *M* aqueous solution of $KHCO_3$ (0.012 mmol) was added. The mixture was hydrogenated for 6 h in the presence of 20% Pd(OH)/C (3 mg). After filtration and evaporation, the residue was washed with ethyl acetate to afford 3.8 mg (95%) of potassium salt **25***e*; ir (KBr) ν_{max}: 3600–2900 (OH, NH), 1745 (CO β-lactam), 1655 (CO amide), 1595 (C=C), 1250 (P=O) cm^{-1}.

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