

Synthesis of Phosphonobenzocarbaephems by Intramolecular Radical Cyclization of Haloaryl-Substituted β -Lactams

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A series of benzo-fused tricyclic β -lactams, most of them phosphonobenzocarbaephems, were prepared in a straightforward way starting from phosphonoazadienes. In this paper, the synthetic route including a Staudinger reaction

towards the β -lactams, followed by radical ring closing with tributyltin hydride and AIBN, which resulted in the envisaged tricyclic compounds, is reported.

Introduction

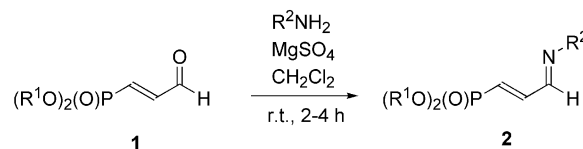
The synthesis of novel 2-azetidinone-based heterocycles is still intensively investigated since the discovery of penicillin in 1929. In the early years, the research was mainly focused on the improvement of the antibacterial properties of these compounds. The discovery of potent elastase-inhibiting properties for structurally modified cephalosporin antibiotics in 1986 led to the investigation of other than antibacterial properties of these β -lactams. Soon various other activities were discovered such as thrombin inhibition, human cytomegalovirus protease inhibition, cathepsin inhibition and many others.^[1] The antibacterial properties nevertheless remained important research topics. Due to the popularity of β -lactams as drugs against bacterial infections, numerous bacteria have developed resistance to these traditional drug therapies by the presence of β -lactamases. These enzymes break the β -lactam ring and inactivate the drug. Several strategies were evaluated to contravene this action, the alteration of the structure of the β -lactam-antibiotic to render it insensitive to the destroying effect being one of them. Another possible solution lies in the combination of the β -lactam and a compound inactivating the β -lactamase. These β -lactamase inhibitors can be completely distinct structures like clavulanic acid, or β -lactam derivatives working synergetically with the antibiotic. Known β -lactamase inactivators are, among others, benzocarbaephems and benzocarbaephems, the latter class being the most investigated one.^[2–4]

Several reactivity studies and research on the synthetic use of phosphonoazadienes^[5,6] have been conducted over the past years. These precursors have already proven their usefulness in the preparation of potentially active phosphonoaziridines,^[5a,5b] phosphorylated γ -lactams,^[5c] γ -phos-

phono- α -aminobisphosphonates^[6a] and bisphosphonoazadienes.^[6b] These good results prompted us to focus also on the preparation of β -lactams bearing a phosphonate substituent, using these as precursors for benzo-fused tricyclic β -lactams. Thus combining the biological activity of the phosphonate moiety and the benzocarbaephem structure. We investigated the (racemic) synthesis of phosphono-substituted tricyclic β -lactams, particularly benzocarbaephems, by intramolecular radical cyclization of the haloaryl-substituted β -lactams.

Results and Discussion

The starting compounds for the synthesis of the β -lactam precursors are dialkyl (*E*)-3-oxoprop-1-enylphosphonates **1**. These compounds can be prepared in a few steps, starting from epibromohydrin.^[6a,7] Imination of the phosphonoaldehydes **1** with 2-bromobenzylamine in the presence of MgSO_4 resulted in 4-phosphono-1-aza-1,3-dienes **2a** and **2d** in good yields. A few other amines (without haloaryl moiety, so not suited to enable radical ring-closing in the final step) were also evaluated to prove the general character of the route towards the monocyclic β -lactams (Scheme 1, Table 1).



Scheme 1.

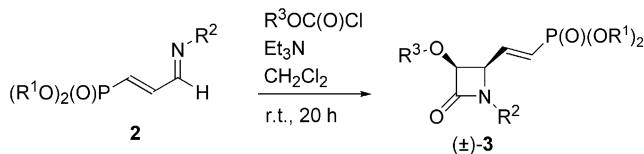
The *E*-imines **2** resulted in the corresponding phosphono- β -lactams **3** by the Staudinger reaction with the suitable acid chlorides and in the presence of Et_3N (Scheme 2, Table 2). In the case of the propargylimine **2e** however, a slight change in the reaction circumstances was needed. If

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Table 1. Synthesis of 4-phosphono-1-aza-1,3-dienes.

Entry	R ¹	R ²	Product	Yield (%)
1	Me	2-Br-Bn	2a	97
2	Me	<i>i</i> Pr	2b	83
3	Me	<i>p</i> -MeO-Ph	2c	99
4	Et	2-Br-Bn	2d	97
5	Et	propargyl	2e	97

the aldimine **2e** was dissolved in CH₂Cl₂ together with Et₃N before adding the acid chloride, an isomerization of the double bond occurred, leading to several end products. Therefore, the acid chloride was first stirred in the presence of Et₃N for 20 min to form the ketene, then followed by addition of the imine. In this way, isomerization could be avoided and only β-lactam **3h** was formed. The racemic β-lactams **3** were all obtained as single *cis*-diastereoisomers. Purification by column chromatography sometimes resulted in a drop of the yield, due to the large affinity of the compounds for the silica gel.



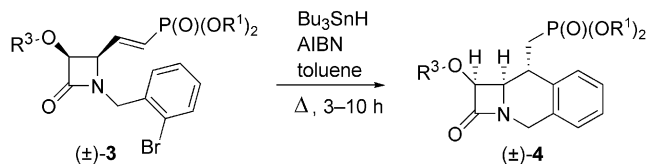
Scheme 2.

Table 2. Synthesis of phosphono β-lactams.

Entry	R ¹	R ²	R ³	Product	Yield (%)
1	Me	2-Br-Bn	Ph	3a	88 ^[a]
2	Me	2-Br-Bn	Bn	3b	70 ^[a]
3	Me	<i>i</i> Pr	Ph	3c	74 ^[a]
4	Me	<i>i</i> Pr	2-Br-Ph	3d	60 ^[a]
5	Me	<i>p</i> -MeO-Ph	Ph	3e	76 ^[a]
6	Et	2-Br-Bn	Ph	3f	62 ^[a]
7	Et	2-Br-Bn	Bn	3g	56 ^[a]
8	Et	propargyl	Ph	3h	66 ^[a]

[a] After purification by column chromatography.

Having obtained the monocyclic precursors bearing a haloaryl moiety (**3a,b,d,f,g**), the next step was the conversion into benzo-fused tricyclic β-lactams **4**. This key ring-closing step was performed through intramolecular aryl-radical cyclization. The β-lactams **3** were treated with tributyltin hydride and AIBN in dry toluene at reflux temperature. After 3–10 h the reaction was completed and the benzocarpacephems **4** were present in the reaction mixture as single diastereomers (Scheme 3, Table 3). To remove the organotin halides, several types of work-up and purification procedures were evaluated. It turned out to be extremely difficult to remove all the traces of this reagent, as is already well known in literature.^[8] The best results were obtained by washing the reaction with a solution of KF in water.^[9] In all of the cases, however, column chromatography was required and resulted, without exception, in a considerable drop of the yield.



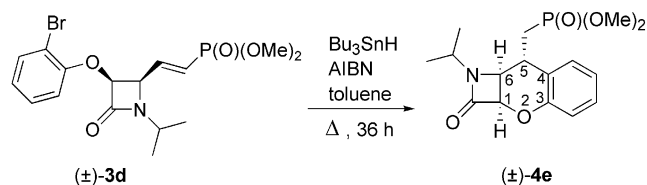
Scheme 3.

Table 3. Intramolecular aryl radical cyclization.

Entry	R ¹	R ²	R ³	Product	Yield (%)
1	Me	2-Br-Bn	Ph	4a	62 ^[a]
2	Me	2-Br-Bn	Bn	4b	66 ^[a]
3	Et	2-Br-Bn	Ph	4c	69 ^[a]
4	Et	2-Br-Bn	Bn	4d	71 ^[a]
5	Me	<i>i</i> Pr	2-Br-Ph	4e	82 ^[b] (80:20) (<i>anti/syn</i>)

[a] After purification by column chromatography. [b] Yield of crude product (mixture of isomers).

The radical cyclization of **3d** to **4e** was a special case in this series. The oxygen in the side chain is bearing the haloaryl moiety instead of the nitrogen atom of the β-lactam-ring. Treatment of this haloarene under similar conditions for the preparation of benzocarpacephems **4a–d** gave the fused tricyclic β-lactam **4e** (Scheme 4). This compound was formed as a mixture of diastereomers, namely epimers at the newly formed C5 stereocentre. The relative stereochemistry of this new chiral centre could be determined by the coupling constants of protons H5 and H6 and the ratio was defined by a combination of ³¹P NMR and ¹H NMR spectra of the crude reaction mixture (before purification). These findings are in accordance with similar results obtained by Alcaide et al.^[2] on derivatives without a phosphonate substituent. The *syn* isomer could not be isolated.



Scheme 4.

Conclusions

The racemic synthesis of phosphono-substituted benzocarpacephems was accomplished by starting from the corresponding β-lactams. The key reaction consisted of an intramolecular radical cyclization using Bu₃SnH and AIBN and also proved to be suitable for other fused tricyclic β-lactams bearing a phosphonate moiety. The possible anti-β-lactamase activity of these compounds is currently under investigation.

Experimental Section

Synthesis of 4-Phosphono-1-aza-1,3-dienes 2a–e: All phosphonylated α,β-unsaturated aldimines **2a–e** were prepared by mixing di(m)

ethyl (1*E*)-3-oxoprop-1-enylphosphonate (**1**) with 1 equiv. of amine and 0.5 equiv. of MgSO₄ in dry dichloromethane. After stirring for 2–4 h at room temperature with a CaCl₂ tube, the MgSO₄ was filtered off and the dichloromethane was evaporated in vacuo. The imines **2a–e** were isolated as yellowish oils in high purity and yield.

Dimethyl [(1*E*,3*E*)-3-(2-Bromobenzylimino)prop-1-en-1-yl]phosphonate (2a**):** Yellowish oil (0.95 g, 97%). ¹H NMR (300 MHz, CDCl₃): δ = 3.78 [d, ³J_{HP} = 11.0 Hz, 6 H, P(O)(OCH₃)₂], 4.83 (s, 2 H, NCH₂), 6.23 (dd, ²J_{HP} = 17.9, *J* = 17.3 Hz, 1 H, HC=CHP), 7.17 (ddd, *J* = 17.3, ³J_{HP} = 12.1, *J* = 8.5 Hz, 1 H, HC=CHP), 7.13–7.59 (m, 4 H, 4 × CH_{arom.}), 8.08 (dd, *J* = 8.5, *J* = 1.4 Hz, 1 H, HC=N) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 52.79 (²J_{CP} = 5.8 Hz, CH₃), 52.80 (²J_{CP} = 5.8 Hz, CH₃), 64.52 (CH₂), 123.81 (C_{quat.,arom.}), 126.66 (¹J_{CP} = 189.2 Hz, HC=CHP), 127.72 (CH_{arom.}), 128.94 (CH_{arom.}), 130.07 (CH_{arom.}), 132.77 (CH_{arom.}), 137.40 (C_{quat.,arom.}), 146.46 (²J_{CP} = 5.8 Hz, HC=CHP), 162.33 (³J_{CP} = 30.0 Hz, HC=N) ppm. ³¹P NMR (121 MHz, CDCl₃): δ = 19.35 ppm. IR: ν_{max.} = 1028 (br., P–O), 1251 (P=O) cm^{−1}. MS (ESI, pos. mode): *m/z* (%) = 332/334 (100/100) [M + H⁺].

Dimethyl [(1*E*,3*E*)-3-(Isopropylimino)prop-1-en-1-yl]phosphonate (2b**):** Yellowish oil (1.33 g, 83%) Already known.

Dimethyl [(1*E*,3*E*)-3-[(4-Methoxyphenyl)imino]prop-1-en-1-yl]phosphonate (2c**):** Yellowish oil (1.21 g, 99%). ¹H NMR (300 MHz, CDCl₃): δ = 3.80 [d, ³J_{HP} = 11.0 Hz, 6 H, 2 × P(O)OCH₃], 3.84 (s, 3 H, C_{quat.,arom.}OCH₃), 6.31 (dd, ²J_{HP} = 17.9, *J* = 17.3 Hz, 1 H, HC=CHP), 6.93 (d, *J* = 9.1 Hz, 2 H, 2 × CH_{arom.}), 7.23 (d, *J* = 9.1 Hz, 2 H, 2 × CH_{arom.}), 7.28 (ddd, ³J_{HP} = 20.4, *J* = 17.3, *J* = 8.8 Hz, 1 H, HC=CHP), 8.22 (dd, ³J_{HP} = 8.8, *J* = 1.7 Hz, 1 H, HC=N) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 52.80 [²J_{CP} = 5.8 Hz, 2 × P(O)OCH₃], 55.51 (C_{quat.,arom.}OCH₃), 114.51 (2 × CH_{arom.}), 122.74 (2 × CH_{arom.}), 126.31 (¹J_{CP} = 190.4 Hz, HC=CHP), 143.15 (C_{quat.,arom.}), 146.99 (²J_{CP} = 5.8 Hz, HC=CHP), 156.44 (³J_{CP} = 30.0 Hz, HC=N), 159.52 (C_{quat.,arom.}OCH₃) ppm. ³¹P NMR (121 MHz, CDCl₃): δ = 19.58 ppm. IR: ν_{max.} = 1031 (P–O), 1053 (P–O), 1250 (P=O), 1506, 1597 cm^{−1}. MS (ESI, pos. mode): *m/z* (%) = 270 (100) [M + H⁺].

Diethyl [(1*E*,3*E*)-3-(2-Bromobenzylimino)prop-1-en-1-yl]phosphonate (2d**):** Pale yellow oil (0.91 g, 97%). ¹H NMR (300 MHz, CDCl₃): δ = 1.35 [t, *J* = 7.2 Hz, 6 H, P(O)(OCH₂CH₃)₂], 4.14 [dq, ²J_{HP} = 7.7, *J* = 7.2 Hz, 4 H, P(O)(OCH₂CH₃)₂], 4.82 (s, 2 H, NCH₂), 6.26 (dd, ²J_{HP} = 17.6, *J* = 17.6 Hz, 1 H, HC=CHP), 7.08–7.24 (m, 2 H, HC=CHP, CH_{arom.}), 7.28–7.36 (m, 2 H, 2 × CH_{arom.}), 7.56–7.60 (m, 1 H, CH_{arom.}), 8.08 (dd, *J* = 8.8, *J* = 1.7 Hz, 1 H, HC=N) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 16.49 (³J_{CP} = 5.8 Hz, 2 × OCH₂CH₃), 62.42 (²J_{CP} = 5.8 Hz, 2 × OCH₂CH₃), 64.63 (NCH₂), 123.91 (C_{quat.,arom.}), 127.82 (CH_{arom.}), 128.34 (¹J_{CP} = 189.2 Hz, HC=CHP), 129.03 (CH_{arom.}), 130.17 (CH_{arom.}), 132.86 (CH_{arom.}), 137.55 (C_{quat.,arom.}), 145.72 (²J_{CP} = 5.8 Hz, HC=CHP), 162.69 (³J_{CP} = 30.0 Hz, HC=N) ppm. ³¹P NMR (121 MHz, CDCl₃): δ = 16.50 ppm. IR: ν_{max.} = 1020 (P–O), 1242 (P=O) cm^{−1}. MS (ESI, pos. mode): *m/z* (%) = 360/362 (100/100) [M + H⁺]. Chromatography: PE/EtOAc (2:8) *R*_f = 0.41.

[Diethyl (1*E*,3*E*)-3-(Prop-2-ynylimino)prop-1-en-1-yl]phosphonate (2e**):** Yellowish oil (2.33 g, 97%). ¹H NMR (300 MHz, CDCl₃): δ = 1.36 (t, *J* = 7.2 Hz, 6 H, 2 × OCH₂CH₃), 2.58 (t, *J* = 2.2 Hz, 1 H, NCH₂CCH), 4.14 (dq, ²J_{HP} = 7.7, *J* = 7.2 Hz, 4 H, 2 × OCH₂CH₃), 4.51 (s, 2 H, NCH₂), 6.31 (dd, ²J_{HP} = 17.6, *J* = 17.4 Hz, 1 H, HC=CHP), 7.14 (ddd, ³J_{HP} = 20.4, *J* = 17.4, *J* = 8.8 Hz, 1 H, HC=CHP), 8.30 (dd, *J* = 8.8, *J* = 1.7 Hz, 1 H, HC=N) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 16.35 (³J_{CP} = 5.8 Hz, 2 × OCH₂CH₃), 47.16 (NCH₂), 62.25 (²J_{CP} = 5.8 Hz, 2 × OCH₂CH₃), 76.46 (NCH₂CCH), 77.79 (NCH₂CCH), 128.37 (¹J_{CP} = 189.2 Hz,

HC=CHP), 145.31 (²J_{CP} = 5.8 Hz, HC=CHP), 161.94 (³J_{CP} = 30.0 Hz, HC=N) ppm. ³¹P NMR (121 MHz, CDCl₃): δ = 16.45 ppm. IR: ν_{max.} = 1018, 1047 (P–O), 1245 (P=O) cm^{−1}. MS (ESI, pos. mode): *m/z* (%) = 230 (100/100) [M + H⁺].

Synthesis of Dialkyl {(*E*)-2-[(*cis*)-4-Oxoazetidin-2-yl]vinyl}-phosphonates **3a–h:** As a representative example, the synthesis of dimethyl {(*E*)-2-[(*cis*)-1-(2-bromobenzyl)-4-oxo-3-phenoxyazetidin-2-yl]vinyl}phosphonate (**3a**) is described here. A solution of dimethyl [(1*E*,3*E*)-3-(2-bromobenzylimino)prop-1-en-1-yl]phosphonate (**2a**, 0.95 g, 2.86 mmol) and Et₃N (0.87 g, 8.58 mmol) was stirred in dry CH₂Cl₂ (15 mL) under nitrogen at 0 °C. To this solution, phenoxyacetyl chloride was added dropwise (0.63 g, 3.72 mmol) and then stirred for 20 h at room temperature. Subsequently, the reaction mixture was poured into water (20 mL) and extracted with CH₂Cl₂ (2 × 15 mL). The combined organic layers were dried (MgSO₄), filtered and the solvent was removed in vacuo to yield dimethyl {(*E*)-2-[(*cis*)-1-(2-bromobenzyl)-4-oxo-3-phenoxyazetidin-2-yl]vinyl}phosphonate (**3a**). The product was purified through column chromatography on silica gel (petroleum ether/EtOAc, 3:7) and was isolated in 88% yield (1.17 g).

Dimethyl {(*E*)-2-[(*cis*)-1-(2-Bromobenzyl)-4-oxo-3-phenoxyazetidin-2-yl]vinyl}phosphonate (3a**):** Yellow oil (1.17 g, 88%). ¹H NMR (CDCl₃, 300 MHz): δ = 3.48 [d, ³J_{HP} = 11.0 Hz, 3 H, P(O)OCH₃], 3.52 [d, ³J_{HP} = 11.0 Hz, 3 H, P(O)OCH₃], 4.35 (d, *J* = 14.9 Hz, 1 H, NCH_AH_BPh), 4.40 (dddd, *J* = 7.7, *J* = 4.7, ⁴J_{HP} = 1.4, *J* = 0.8 Hz, 1 H, NCH), 4.82 (d, *J* = 14.9 Hz, 1 H, NCH_AH_BPh), 5.35 (d, *J* = 4.7 Hz, 1 H, CHOPh), 5.86 (ddd, ²J_{HP} = 19.3, *J* = 17.3, *J* = 0.8 Hz, 1 H, CHP), 6.61 (ddd, ³J_{HP} = 21.2, *J* = 17.3, *J* = 7.7 Hz, 1 H, HC=CHP), 6.88–7.01 (m, 3 H, 3 × CH_{arom.}), 7.18–7.38 (m, 5 H, 5 × CH_{arom.}), 7.57–7.60 (m, 1 H, CH_{arom.}) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 45.27 (NCH₂Ph), 52.27 [²J_{CP} = 5.8 Hz, P(O)OCH₃], 52.38 [²J_{CP} = 5.8 Hz, P(O)OCH₃], 60.11 (³J_{CP} = 25.4 Hz, NCH), 81.82 (CHOPh), 115.23 (2 × CH_{arom.}), 122.50 (CH_{arom.}), 122.82 (¹J_{CP} = 185.8 Hz, CHP), 123.99 (C_{quat.,arom.}), 128.13 (CH_{arom.}), 129.64 (2 × CH_{arom.}), 130.15 (CH_{arom.}), 131.41 (CH_{arom.}), 133.24 (CH_{arom.}), 133.86 (C_{quat.,arom.}), 145.13 (²J_{CP} = 5.8 Hz, HC=CHP), 156.76 (C_{quat.,arom.}), 164.61 (C=O) ppm. ³¹P NMR (121 MHz, CDCl₃): δ = 18.55 ppm. IR: ν_{max.} = 1026 (P–O), 1232 (P=O), 1761 (C=O) cm^{−1}. MS (ESI, pos. mode): *m/z* (%) = 466/468 (100) [M + H⁺]. Chromatography: PE/EtOAc (3:7) *R*_f = 0.20.

Dimethyl {(*E*)-2-[(*cis*)-3-Benzyloxy-1-(2-bromobenzyl)-4-oxoazetidin-2-yl]vinyl}phosphonate (3b**):** Yellowish oil (1.01 g, 70%). ¹H NMR (CDCl₃, 300 MHz): δ = 3.62 [d, ³J_{HP} = 11.0 Hz, 3 H, P(O)OCH₃], 3.65 [d, ³J_{HP} = 11.0 Hz, 3 H, P(O)OCH₃], 4.13–4.18 (m, 1 H, NCH), 4.29 (d, *J* = 14.8 Hz, 1 H, NCH_AH_BPh), 4.59 (d, *J* = 11.6 Hz, 1 H, OCH_AH_BPh), 4.68 (d, *J* = 11.6 Hz, 1 H, OCH_AH_BPh), 4.74 (d, *J* = 14.8 Hz, 1 H, NCH_AH_BPh), 4.80 (d, CHOPh, = 5.0 Hz, 1 H, *J*), 5.85 (dd, ²J_{HP} = 19.5, *J* = 17.1 Hz, 1 H, CHP), 6.62 (ddd, ³J_{HP} = 21.5, *J* = 17.1, *J* = 7.4 Hz, 1 H, HC=CHP), 7.14–7.22 (m, 1 H, CH_{arom.}), 7.28–7.38 (m, 7 H, 7 × CH_{arom.}), 7.55 (ps d, *J* = 8.3 Hz, 1 H, CH_{arom.}) ppm. ¹³C NMR (75 MHz, CDCl₃, ref TMS): δ = 44.92 (NCH₂Ph), 52.45 [²J_{CP} = 4.6 Hz, P(O)OCH₃], 52.52 [²J_{CP} = 4.6 Hz, P(O)OCH₃], 59.95 (³J_{CP} = 24.2 Hz, NCH), 73.03 (OCH₂Ph), 83.59 (CHOPh), 121.76 (¹J_{CP} = 187.0 Hz, CHP), 123.88 (C_{quat.,arom.}), 128.03 (CH_{arom.}), 128.17 (2 × CH_{arom.}), 128.22 (CH_{arom.}), 128.48 (2 × CH_{arom.}), 129.95 (CH_{arom.}), 131.21 (CH_{arom.}), 133.14 (CH_{arom.}), 134.08 (C_{quat.,arom.}), 136.30 (C_{quat.,arom.}), 146.17 (²J_{CP} = 5.8 Hz, HC=CHP), 166.41 (C=O) ppm. ³¹P NMR (121 MHz, CDCl₃): δ = 19.02 ppm. IR: ν_{max.} = 1025 (P–O), 1249 (P=O), 1757 (C=O) cm^{−1}. MS (ESI, pos. mode): *m/z* (%) = 480/482 (100) [M + H⁺]. Chromatography: PE/EtOAc (4:6) *R*_f = 0.11.

Dimethyl {(E)-2-[(cis)-1-Isopropyl-4-oxo-3-phenoxyazetidin-2-yl]-vinyl}phosphonate (3c): Pale yellow crystals (1.63 g, 74%). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.25 [d, J = 6.6 Hz, 3 H, $\text{CH}(\text{CH}_3)$], 1.30 [d, J = 6.6 Hz, 3 H, $\text{CH}(\text{CH}_3)$], 3.49 [d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.53 [d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.92 [sept, J = 6.6 Hz, 1 H, $\text{CH}(\text{CH}_3)_2$], 4.54 (dd, J = 8.3, J = 4.4 Hz, 1 H, NCH), 5.29 (d, J = 4.4 Hz, 1 H, CHOPh), 5.99 (dd, $^2J_{\text{HP}}$ = 17.9, J = 17.3 Hz, 1 H, HC=CHP), 6.75 (ddd, $^3J_{\text{HP}}$ = 21.2, J = 17.3, J = 8.3 Hz, 1 H, HC=CHP), 6.90–7.03 (m, 3 H, $3 \times \text{CH}_{\text{arom.}}$), 7.21–7.33 (m, 2 H, $2 \times \text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 20.20 [$\text{CH}(\text{CH}_3)$], 21.66 [$\text{CH}(\text{CH}_3)$], 45.13 [$\text{NCH}(\text{CH}_3)_2$], 52.32 [$^2J_{\text{CP}}$ = 5.8 Hz, $\text{P}(\text{O})\text{OCH}_3$], 52.39 [$^2J_{\text{CP}}$ = 5.8 Hz, $\text{P}(\text{O})\text{OCH}_3$], 59.11 ($^3J_{\text{CP}}$ = 26.5 Hz, NCH), 80.68 (CHOPh), 115.20 ($2 \times \text{CH}_{\text{arom.}}$), 122.39 ($\text{CH}_{\text{arom.}}$), 122.39 ($^1J_{\text{CP}}$ = 185.8 Hz, HC=CHP), 129.70 ($2 \times \text{CH}_{\text{arom.}}$), 147.28 ($^2J_{\text{CP}}$ = 5.8 Hz, HC=CHP), 156.80 ($\text{C}_{\text{quat.,arom.}}$), 164.09 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 18.50 ppm. IR: $\tilde{\nu}_{\text{max.}}$ = 1015, 1048 (P–O), 1245 (P=O), 1737 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 340 (100) [$\text{M} + \text{H}^+$]. M.p. 105–107 °C.

Dimethyl {(E)-2-[(cis)-3-(2-Bromophenoxy)-1-isopropyl-4-oxoazetidin-2-yl]vinyl}phosphonate (3d): Yellow oil (0.97 g, 60%). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.25 [d, J = 6.6 Hz, 3 H, $\text{CH}(\text{CH}_3)$], 1.30 [d, J = 6.6 Hz, 3 H, $\text{CH}(\text{CH}_3)$], 3.65 [d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.66 [d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.91 [sept, J = 6.6 Hz, 1 H, $\text{CH}(\text{CH}_3)_2$], 4.56 (dd, J = 8.3, J = 4.7 Hz, 1 H, NCH), 5.28 (d, J = 5.0 Hz, 1 H, CHOPh), 6.06 (ddd, $^2J_{\text{HP}}$ = 18.2, J = 17.3, J = 0.8 Hz, 1 H, CHP), 6.85 (ddd, $^3J_{\text{HP}}$ = 21.2, J = 17.3, J = 8.3 Hz, 1 H, HC=CHP), 6.89 (dxt, J = 7.4, J = 1.7 Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.15 (dd, J = 8.3, J = 1.7 Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.25 (ddd, J = 8.3, J = 7.4, J = 1.7 Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.50 (dd, J = 7.4, J = 1.7 Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 20.29 [$\text{CH}(\text{CH}_3)$], 21.74 [$\text{CH}(\text{CH}_3)$], 45.26 [$\text{NCH}(\text{CH}_3)_2$], 52.72 [$^2J_{\text{CP}}$ = 5.8 Hz, $\text{P}(\text{O})\text{OCH}_3$], 52.80 [$^2J_{\text{CP}}$ = 5.8 Hz, $\text{P}(\text{O})\text{OCH}_3$], 58.68 ($^3J_{\text{CP}}$ = 26.5 Hz, NCH), 81.68 (CHOPh), 112.23 ($\text{C}_{\text{quat.,arom.}}$), 115.59 ($\text{CH}_{\text{arom.}}$), 122.63 ($^1J_{\text{CP}}$ = 186.9 Hz, CHP), 123.79 ($\text{CH}_{\text{arom.}}$), 128.70 ($\text{CH}_{\text{arom.}}$), 133.59 ($\text{CH}_{\text{arom.}}$), 147.02 ($^2J_{\text{CP}}$ = 5.8 Hz, HC=CHP), 153.71 ($\text{C}_{\text{quat.,arom.}}$), 164.10 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 18.48 ppm. IR: $\tilde{\nu}_{\text{max.}}$ = 1031, 1049 (P–O), 1245 (P=O), 1759 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 418/420 (75) [$\text{M} + \text{H}^+$]. Chromatography: Hex/EtOAc (1:1) R_f = 0.05.

Dimethyl {(E)-2-[(cis)-1-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-2-yl]vinyl}phosphonate (3e): Pale brown oil (1.37 g, 76%). ^1H NMR (CDCl_3 , 300 MHz): δ = 3.52 [d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.55 [d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.80 (s, 3 H, OCH_3), 4.98 (dddd, J = 6.3, J = 5.0, $^4J_{\text{HP}}$ = 1.9, J = 0.8 Hz, 1 H, NCH), 5.49 (d, J = 5.0 Hz, 1 H, CHOPh), 6.03 (ddd, $^2J_{\text{HP}}$ = 17.9, J = 17.3, J = 0.8 Hz, 1 H, CHP), 6.80 (ddd, $^3J_{\text{HP}}$ = 22.9, J = 17.3, J = 6.3 Hz, 1 H, HC=CHP), 6.88 (d, J = 9.1 Hz, 2 H, $2 \times \text{CH}_{\text{arom.}}$), 6.97–7.06 (m, 3 H, $3 \times \text{CH}_{\text{arom.}}$), 7.28–7.31 (m, 2 H, $2 \times \text{CH}_{\text{arom.}}$), 7.35 (d, J = 9.1 Hz, 2 H, $2 \times \text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 52.36 [$^2J_{\text{CP}}$ = 5.8 Hz, $\text{P}(\text{O})\text{OCH}_3$], 52.45 [$^2J_{\text{CP}}$ = 5.8 Hz, $\text{P}(\text{O})\text{OCH}_3$], 55.53 (OCH_3), 59.76 ($^3J_{\text{CP}}$ = 25.4 Hz, NCH), 81.01 (CHOPh), 114.62 ($2 \times \text{CH}_{\text{arom.}}$), 115.32 ($2 \times \text{CH}_{\text{arom.}}$), 118.57 ($2 \times \text{CH}_{\text{arom.}}$), 122.69 ($\text{CH}_{\text{arom.}}$), 122.75 ($^1J_{\text{CP}}$ = 185.8 Hz, CHP), 129.76 ($2 \times \text{CH}_{\text{arom.}}$), 130.22 ($\text{C}_{\text{quat.,arom.}}$), 144.80 ($^2J_{\text{CP}}$ = 5.8 Hz, HC=CHP), 156.90 ($2 \times \text{C}_{\text{quat.,arom.}}$), 161.35 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 18.61 ppm. IR: $\tilde{\nu}_{\text{max.}}$ = 1031 (P–O), 1247 (P=O), 1759 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 404 (100) [$\text{M} + \text{H}^+$]. Chromatography: Hex/EtOAc (1:9) R_f = 0.22.

Diethyl {(E)-2-[(cis)-1-(2-Bromobenzyl)-4-oxo-3-phenoxyazetidin-2-yl]vinyl}phosphonate (3f): Yellowish oil (0.80 g, 62%). ^1H NMR

(CDCl_3 , 300 MHz): δ = 1.20 [t, J = 7.2 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 1.21 [t, J = 7.2 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 3.67–3.94 [m, 4 H, $2 \times \text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 4.33 (d, J = 14.9 Hz, 1 H, $\text{NCH}_A\text{H}_B\text{Ph}$), 4.40 (dddd, J = 7.7, J = 4.4, J = 1.0, $^4J_{\text{HP}}$ = 1.1 Hz, 1 H, NCH), 4.83 (d, J = 14.9 Hz, 1 H, $\text{NCH}_A\text{H}_B\text{Ph}$), 5.35 (d, J = 4.4 Hz, 1 H, CHOPh), 5.90 (ddd, $^2J_{\text{HP}}$ = 18.2, J = 17.1, J = 1.0 Hz, 1 H, CHP), 6.59 (ddd, $^3J_{\text{HP}}$ = 20.9, J = 17.1, J = 7.7 Hz, 1 H, HC=CHP), 6.88–6.91 (m, 2 H, $2 \times \text{CH}_{\text{arom.}}$), 6.99 (dd, J = 7.5 Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.18–7.37 (m, 5 H, $5 \times \text{CH}_{\text{arom.}}$), 7.59 (ps d, J = 7.2 Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 16.33 ($^3J_{\text{CP}}$ = 6.9 Hz, $2 \times \text{OCH}_2\text{CH}_3$), 45.28 (NCH_2Ph), 60.21 ($^3J_{\text{CP}}$ = 24.2 Hz, NCH), 61.93 ($^2J_{\text{CP}}$ = 5.8 Hz, OCH_2CH_3), 62.02 ($^2J_{\text{CP}}$ = 5.8 Hz, OCH_2CH_3), 81.76 (CHOPh), 115.18 ($2 \times \text{CH}_{\text{arom.}}$), 122.48 ($\text{CH}_{\text{arom.}}$), 123.97 ($\text{C}_{\text{quat.,arom.}}$), 124.28 ($^1J_{\text{CP}}$ = 184.6 Hz, CHP), 128.16 ($\text{CH}_{\text{arom.}}$), 129.67 ($2 \times \text{CH}_{\text{arom.}}$), 130.18 ($\text{CH}_{\text{arom.}}$), 131.41 ($\text{CH}_{\text{arom.}}$), 133.27 ($\text{CH}_{\text{arom.}}$), 133.87 ($\text{C}_{\text{quat.,arom.}}$), 144.20 ($^2J_{\text{CP}}$ = 5.8 Hz, HC=CHP), 156.78 ($\text{C}_{\text{quat.,arom.}}$), 164.69 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 15.73 ppm. IR: $\tilde{\nu}_{\text{max.}}$ = 1022 (P–O), 1233 (P=O), 1764 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 494/496 (100) [$\text{M} + \text{H}^+$]. Chromatography: PE/EtOAc (3:7) R_f = 0.24.

Diethyl {(E)-2-[(cis)-3-Benzyloxy-1-(2-bromobenzyl)-4-oxoazetidin-2-yl]vinyl}phosphonate (3g): Yellow oil (0.19 g, 56%). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.24 [t, J = 7.2 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 1.28 [t, J = 7.2 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 4.13–4.17 (m, 1 H, NCH), 4.28 (d, J = 15.1 Hz, 1 H, $\text{NCH}_A\text{H}_B\text{Ph}$), 4.58 (d, J = 11.6 Hz, 1 H, $\text{OCH}_A\text{H}_B\text{Ph}$), 4.67 (d, J = 11.6 Hz, 1 H, $\text{OCH}_A\text{H}_B\text{Ph}$), 4.75 (d, J = 15.1 Hz, 1 H, $\text{NCH}_A\text{H}_B\text{Ph}$), 4.80 (d, J = 5.0 Hz, 1 H, CHOPh), 5.89 (ddd, $^2J_{\text{HP}}$ = 18.9, J = 17.1, J = 1.1 Hz, 1 H, CHP), 6.62 (ddd, $^3J_{\text{HP}}$ = 21.5, J = 17.1, J = 7.4 Hz, 1 H, HC=CHP), 7.14–7.22 (m, 1 H, $\text{CH}_{\text{arom.}}$), 7.28–7.36 (m, 7 H, $7 \times \text{CH}_{\text{arom.}}$), 7.55 (ps d, J = 7.7 Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 16.37 ($^3J_{\text{CP}}$ = 5.8 Hz, OCH_2CH_3), 16.45 ($^3J_{\text{CP}}$ = 5.8 Hz, OCH_2CH_3), 44.99 (NCH_2Ph), 60.07 ($^3J_{\text{CP}}$ = 24.2 Hz, NCH), 62.10 ($^2J_{\text{CP}}$ = 5.8 Hz, OCH_2CH_3), 62.17 ($^2J_{\text{CP}}$ = 5.8 Hz, OCH_2CH_3), 73.05 (OCH_2Ph), 83.69 (CHOPh), 123.32 ($^1J_{\text{CP}}$ = 187.0 Hz, CHP), 123.93 ($\text{C}_{\text{quat.,arom.}}$), 128.09 ($\text{CH}_{\text{arom.}}$), 128.23 ($2 \times \text{CH}_{\text{arom.}}$), 128.26 ($\text{CH}_{\text{arom.}}$), 128.54 ($2 \times \text{CH}_{\text{arom.}}$), 130.02 ($\text{CH}_{\text{arom.}}$), 131.24 ($\text{CH}_{\text{arom.}}$), 133.22 ($\text{CH}_{\text{arom.}}$), 134.17 ($\text{C}_{\text{quat.,arom.}}$), 136.42 ($\text{C}_{\text{quat.,arom.}}$), 145.26 ($^2J_{\text{CP}}$ = 5.8 Hz, HC=CHP), 166.55 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 16.27 ppm. IR: $\tilde{\nu}_{\text{max.}}$ = 1022, 1048 (P–O), 1248 (P=O), 1759 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 508/510 (100) [$\text{M} + \text{H}^+$]. Chromatography: PE/EtOAc (3:7) R_f = 0.16.

Diethyl {(E)-2-[(cis)-4-Oxo-3-phenoxy-1-(prop-2-ynyl)azetidin-2-yl]vinyl}phosphonate (3h): This preparation was slightly different from the general method. In this case, the phenoxyacetyl chloride (0.48 g, 2.84 mmol) was first stirred together with Et_3N (0.29 g, 2.84 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen atmosphere at 0 °C to form the ketene. To this mixture, a solution of diethyl (1*E*,3*E*)-3-(prop-2-ynylimino)prop-1-en-1-ylphosphonate (**2e**) in dry CH_2Cl_2 (5 mL) was added dropwise and then stirred overnight at room temperature. The work-up was the same as in the general method and yielded after purification 0.52 g (66%) of **3h**.

Diethyl {(E)-2-[(cis)-4-Oxo-3-phenoxy-1-(prop-2-ynyl)azetidin-2-yl]vinyl}phosphonate (3h): Yellow oil (0.52 g, 66%). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.22 [t, J = 7.2 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 1.24 [t, J = 7.2 Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 2.32 (t, J = 2.2 Hz, 1 H, NCH_2CCH), 3.74–3.99 [m, 4 H, $2 \times \text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 3.85 (dd, J = 17.6, J = 2.8 Hz, 1 H, $\text{NCH}_A\text{H}_B\text{CCH}$), 4.36 (dd, J = 17.6, J = 2.8 Hz, 1 H, $\text{NCH}_A\text{H}_B\text{CCH}$), 4.67 (dddd, J = 7.7, J = 4.4, J = 1.1, $^4J_{\text{HP}}$ = 1.1 Hz, 1 H, NCH), 5.39 (d, J = 4.4 Hz, 1 H, CHOPh),

6.06 (ddd, $^2J_{\text{HP}} = 18.2$, $J = 18.2$, $J = 1.1$ Hz, 1 H, *CHP*), 6.69 (ddd, $^3J_{\text{HP}} = 20.9$, $J = 17.1$, $J = 7.7$ Hz, 1 H, *HC=CHP*), 6.89–6.95 (m, 2 H, $2 \times \text{CH}_{\text{arom.}}$), 7.01 (dd, $J = 7.5$ Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.22–7.33 (m, 2 H, $2 \times \text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 16.28$ ($^3J_{\text{CP}} = 6.9$ Hz, $2 \times \text{OCH}_2\text{CH}_3$), 30.29 (NCH_2CCH), 59.74 ($^3J_{\text{CP}} = 24.2$ Hz, *NCH*), 61.98 ($^2J_{\text{CP}} = 5.8$ Hz, OCH_2CH_3), 62.06 ($^2J_{\text{CP}} = 5.8$ Hz, OCH_2CH_3), 73.70 (NCH_2CCH), 75.59 (NCH_2CCH), 81.91 (*CHOPh*), 115.15 ($2 \times \text{CH}_{\text{arom.}}$), 122.54 ($\text{CH}_{\text{arom.}}$), 124.53 ($^1J_{\text{CP}} = 185.8$ Hz, *CHP*), 129.67 ($2 \times \text{CH}_{\text{arom.}}$), 143.70 ($^2J_{\text{CP}} = 5.8$ Hz, *HC=CHP*), 156.71 ($\text{C}_{\text{quat.,arom.}}$), 164.09 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): $\delta = 15.77$ ppm. IR: $\tilde{\nu}_{\text{max.}} = 1021$, 1048 (*P=O*), 1233 (*P=O*), 1767 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 364 (100) [*M* + *H*⁺]. Chromatography: PE/EtOAc (3:7) $R_f = 0.11$.

Synthesis of Dialkyl $\{[(1\text{S}^*,9\text{R}^*,9\text{aR}^*)\text{-2-Oxo-1,4,9,9a-tetrahydro-2H-azeto[1,2-*b*]isoquinolin-9-yl)methyl}]\text{phosphonates 4a-d and Dimethyl $\{[(2\text{aR}^*,8\text{R}^*,8\text{aS}^*)\text{-1-Isopropyl-2-oxo-2,2a,8,8a-tetrahydro-1H-chromeno[3,2-*b*]azet-8-yl)methyl}]\text{phosphonate (4e)}$:$ As a representative example, the synthesis of dimethyl $\{[(1\text{S}^*,9\text{R}^*,9\text{aR}^*)\text{-2-oxo-1-phenoxy-1,4,9,9a-tetrahydro-2H-azeto[1,2-*b*]isoquinolin-9-yl)methyl}]\text{phosphonate (4a)}$ is described here. A solution of dimethyl $\{(E)\text{-2-}[(\text{cis})\text{-1-(2-bromobenzyl)-4-oxo-3-phenoxyazetidin-2-yl]vinyl}\}\text{phosphonate (3a)}$, 0.3 g, 0.607 mmol) in dry toluene (10 mL) was flushed with Ar for 20 min simultaneously with a separate solution of Bu_3SnH (0.21 g, 0.728 mmol) and AIBN (0.01 g, 0.061 mmol) in dry toluene (5 mL). The solution of Bu_3SnH and AIBN was slowly added to the stirring solution of β -lactam **3a** at reflux temperature. The reaction could be followed with ^{31}P NMR and after 6 h, the toluene was evaporated. The product was dissolved in 10 mL of Et_2O and 10 mL of an aqueous KF solution and then stirred for 30 min. The white solid (Bu_3SnF) could then be filtered off and washed with CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried (MgSO_4), filtered and the solvents evaporated in vacuo. The resulting product **4a** was purified through column chromatography on silica gel (petroleum ether/EtOAc, 1:9) and was isolated pure in 62% yield (0.15 g).

Dimethyl $\{[(1\text{S}^*,9\text{R}^*,9\text{aR}^*)\text{-2-Oxo-1-phenoxy-1,4,9,9a-tetrahydro-2H-azeto[1,2-*b*]isoquinolin-9-yl)methyl}]\text{phosphonate (4a)}$: Pale yellow oil (0.15 g, 62%). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 2.25\text{--}2.46$ (m, 2 H, CH_2P), 3.58 [d, $^3J_{\text{HP}} = 11.0$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.65 [d, $^3J_{\text{HP}} = 11.0$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.65–3.78 (m, 1 H, CHCH_2P), 4.16 (dd, $J = 8.5$, $J = 4.4$ Hz, 1 H, *NCH*), 4.27 (d, $J = 16.8$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 4.82 (d, $J = 16.8$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 5.51 (dd, $J = 4.4$, $J = 1.7$ Hz, 1 H, *CHOPh*), 7.01–7.37 (m, 8 H, $8 \times \text{CH}_{\text{arom.}}$), 7.55 (d, $J = 7.7$ Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 27.73$ ($^1J_{\text{CP}} = 141.9$ Hz, CH_2P), 31.48 ($^2J_{\text{CP}} = 3.5$ Hz, CHCH_2P), 40.63 (NCH_2), 52.26 ($^2J_{\text{CP}} = 6.9$ Hz, $\text{P}(\text{O})\text{OCH}_3$), 52.55 ($^2J_{\text{CP}} = 6.9$ Hz, $\text{P}(\text{O})\text{OCH}_3$), 54.80 ($^3J_{\text{CP}} = 9.2$ Hz, *NCH*), 81.65 (*CHOPh*), 115.78 ($2 \times \text{CH}_{\text{arom.}}$), 122.39 ($\text{CH}_{\text{arom.}}$), 126.91 ($\text{CH}_{\text{arom.}}$), 127.00 ($\text{CH}_{\text{arom.}}$), 127.53 ($\text{CH}_{\text{arom.}}$), 128.02 ($\text{CH}_{\text{arom.}}$), 129.64 ($2 \times \text{CH}_{\text{arom.}}$), 131.37 ($\text{C}_{\text{quat.,arom.}}$), 134.86 ($^3J_{\text{CP}} = 6.9$ Hz, $\text{C}_{\text{quat.,arom.}}$), 157.57 ($\text{C}_{\text{quat.,arom.}}$), 166.59 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): $\delta = 32.12$ ppm. IR: $\tilde{\nu}_{\text{max.}} = 1026$, 1054 (*P=O*), 1233 (*P=O*), 1755 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 388 (100) [*M* + *H*⁺], 360 (65) [*M*⁺ – 28]. HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{P}$ [*M* + *H*⁺] 388.1309; found 388.1314. Chromatography: PE/EtOAc (1:9) $R_f = 0.15$.

Dimethyl $\{[(1\text{S}^*,9\text{R}^*,9\text{aR}^*)\text{-1-Benzyloxy-1,4,9,9a-tetrahydro-2H-2-oxoazeto[1,2-*b*]isoquinolin-9-yl)methyl}]\text{phosphonate (4b)}$: Yellow oil (0.31 g, 66%). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 2.21\text{--}2.41$ (m, 2 H, CH_2P), 3.52 [d, $^3J_{\text{HP}} = 11.0$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.60 [d, $^3J_{\text{HP}} = 11.0$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_3$], 3.65–3.77 (m, 1 H, CHCH_2P), 3.90

(dd, $J = 8.8$, $J = 4.4$ Hz, 1 H, *NCH*), 4.20 (d, $J = 16.5$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 4.76 (d, $J = 16.5$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 4.77 (d, $J = 11.5$ Hz, 1 H, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.93 (dd, $J = 4.4$, $J = 1.7$ Hz, 1 H, *CHOPh*), 5.01 (d, $J = 11.5$ Hz, 1 H, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ph}$), 7.09 (psd, $J = 7.7$ Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.19–7.42 (m, 7 H, $7 \times \text{CH}_{\text{arom.}}$), 7.52 (ps d, $J = 7.7$ Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 27.74$ ($^1J_{\text{CP}} = 140.8$ Hz, CH_2P), 31.57 ($^2J_{\text{CP}} = 4.6$ Hz, CHCH_2P), 40.59 (NCH_2Ph), 52.29 ($^2J_{\text{CP}} = 6.9$ Hz, $\text{P}(\text{O})\text{OCH}_3$), 52.52 ($^2J_{\text{CP}} = 6.9$ Hz, $\text{P}(\text{O})\text{OCH}_3$), 54.94 ($^3J_{\text{CP}} = 10.4$ Hz, *NCH*), 73.04 (OCH_2Ph), 82.55 (*CHOPh*), 127.00 ($2 \times \text{CH}_{\text{arom.}}$), 127.55 ($\text{CH}_{\text{arom.}}$), 128.10 ($2 \times \text{CH}_{\text{arom.}}$), 128.14 ($2 \times \text{CH}_{\text{arom.}}$), 128.55 ($2 \times \text{CH}_{\text{arom.}}$), 131.59 ($\text{C}_{\text{quat.,arom.}}$), 135.42 ($^3J_{\text{CP}} = 5.8$ Hz, $\text{C}_{\text{quat.,arom.}}$), 137.29 ($\text{C}_{\text{quat.,arom.}}$), 168.56 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): $\delta = 32.34$ ppm. IR: $\tilde{\nu}_{\text{max.}} = 1027$, 1055 (*P=O*), 1247 (*P=O*), 1754 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 402 (100) [*M* + *H*⁺]. HRMS (ESI) m/z calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{P}$ [*M* + *H*⁺] 402.1465; found 402.1471. Chromatography: PE/EtOAc (2:8) $R_f = 0.30$.

Diethyl $\{[(1\text{S}^*,9\text{R}^*,9\text{aR}^*)\text{-2-Oxo-1-phenoxy-1,4,9,9a-tetrahydro-2H-azeto[1,2-*b*]isoquinolin-9-yl)methyl}]\text{phosphonate (4c)}$: Yellowish oil (0.09 g, 69%). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 1.18$ [t, $J = 7.2$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 1.23 [t, $J = 7.2$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 2.29 (ddd, $^2J_{\text{HP}} = 17.9$, $J = 15.8$, $J = 6.1$ Hz, 1 H, $\text{CH}_\text{A}\text{H}_\text{B}\text{P}$), 2.40 (ddd, $^2J_{\text{HP}} = 19.3$, $J = 15.8$, $J = 5.0$ Hz, 1 H, $\text{CH}_\text{A}\text{H}_\text{B}\text{P}$), 3.62–3.77 (m, 1 H, CHCH_2P), 3.80–4.06 [m, 4 H, $2 \times \text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 4.21 (dd, $J = 8.8$, $J = 4.4$ Hz, 1 H, *NCH*), 4.27 (d, $J = 16.8$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 4.82 (d, $J = 16.8$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 5.51 (dd, $J = 4.4$, $J = 1.7$ Hz, 1 H, *CHOPh*), 7.01–7.37 (m, 8 H, $8 \times \text{CH}_{\text{arom.}}$), 7.57 (d, $J = 7.7$ Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 16.48$ ($^3J_{\text{CP}} = 5.8$ Hz, $2 \times \text{OCH}_2\text{CH}_3$), 28.49 ($^1J_{\text{CP}} = 140.8$ Hz, CH_2P), 31.83 ($^2J_{\text{CP}} = 4.6$ Hz, CHCH_2P), 40.78 (NCH_2Ph), 54.87 ($^3J_{\text{CP}} = 9.2$ Hz, *NCH*), 61.74 ($^2J_{\text{CP}} = 6.9$ Hz, OCH_2CH_3), 61.88 ($^2J_{\text{CP}} = 6.9$ Hz, OCH_2CH_3), 77.16 (CDCl_3), 81.85 (*CHOPh*), 115.97 ($2 \times \text{CH}_{\text{arom.}}$), 122.49 ($\text{CH}_{\text{arom.}}$), 126.95 ($\text{CH}_{\text{arom.}}$), 127.03 ($\text{CH}_{\text{arom.}}$), 127.55 ($\text{CH}_{\text{arom.}}$), 128.31 ($\text{CH}_{\text{arom.}}$), 129.73 ($2 \times \text{CH}_{\text{arom.}}$), 131.48 ($\text{C}_{\text{quat.,arom.}}$), 135.08 ($^3J_{\text{CP}} = 5.8$ Hz, $\text{C}_{\text{quat.,arom.}}$), 157.75 ($\text{C}_{\text{quat.,arom.}}$), 166.80 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): $\delta = 29.50$ ppm. IR: $\tilde{\nu}_{\text{max.}} = 1022$, 1052 (*P=O*), 1233 (*P=O*), 1757 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 416 (100) [*M* + *H*⁺]. HRMS (ESI) m/z calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_5\text{P}$ [*M* + *H*⁺] 416.1622; found 416.1632. Chromatography: PE/EtOAc (1:2) $R_f = 0.14$.

Diethyl $\{[(1\text{S}^*,9\text{R}^*,9\text{aR}^*)\text{-1-Benzyloxy-1,4,9,9a-tetrahydro-2H-2-oxoazeto[1,2-*b*]isoquinolin-9-yl)methyl}]\text{phosphonate (4d)}$: Pale yellow oil (0.10 g, 71%). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 1.16$ [t, $J = 7.2$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 1.21 [t, $J = 7.2$ Hz, 3 H, $\text{P}(\text{O})\text{OCH}_2\text{CH}_3$], 2.27 (ddd, $^2J_{\text{HP}} = 17.9$, $J = 16.0$, $J = 6.1$ Hz, 1 H, $\text{CH}_\text{A}\text{H}_\text{B}\text{P}$), 2.34 (ddd, $^2J_{\text{HP}} = 18.4$, $J = 16.0$, $J = 5.0$ Hz, 1 H, $\text{CH}_\text{A}\text{H}_\text{B}\text{P}$), 3.54–3.69 (m, 1 H, CHCH_2P), 3.80–4.06 [m, 5 H, $2 \times \text{P}(\text{O})\text{OCH}_2\text{CH}_3$, *NCH*], 4.18 (d, $J = 16.8$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 4.75 (d, $J = 16.8$ Hz, 1 H, $\text{NCH}_\text{A}\text{H}_\text{B}\text{C}_{\text{arom.}}$), 4.79 (d, $J = 11.6$ Hz, 1 H, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.91 (dd, $J = 4.4$, $J = 1.7$ Hz, 1 H, *CHOPh*), 4.99 (d, $J = 11.6$ Hz, 1 H, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ph}$), 7.08 (ps d, $J = 7.2$ Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.18–7.42 (m, 7 H, $7 \times \text{CH}_{\text{arom.}}$), 7.53 (ps d, $J = 7.2$ Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 16.47$ ($^3J_{\text{CP}} = 6.9$ Hz, $2 \times \text{OCH}_2\text{CH}_3$), 28.68 ($^1J_{\text{CP}} = 140.8$ Hz, CH_2P), 31.78 ($^2J_{\text{CP}} = 4.6$ Hz, CHCH_2P), 40.65 (NCH_2Ph), 54.97 ($^3J_{\text{CP}} = 9.2$ Hz, *NCH*), 61.72 ($^2J_{\text{CP}} = 6.9$ Hz, OCH_2CH_3), 61.81 ($^2J_{\text{CP}} = 6.9$ Hz, OCH_2CH_3), 73.04 (OCH_2Ph), 82.63 (*CHOPh*), 126.90 ($\text{CH}_{\text{arom.}}$), 126.97 ($\text{CH}_{\text{arom.}}$), 127.47 ($\text{CH}_{\text{arom.}}$), 128.10 ($\text{CH}_{\text{arom.}}$), 128.14 ($2 \times \text{CH}_{\text{arom.}}$), 128.34 ($\text{CH}_{\text{arom.}}$), 128.57 ($2 \times \text{CH}_{\text{arom.}}$), 131.68 ($\text{C}_{\text{quat.,arom.}}$), 135.63 ($^3J_{\text{CP}} = 5.8$ Hz, $\text{C}_{\text{quat.,arom.}}$), 137.38 ($\text{C}_{\text{quat.,arom.}}$), 168.65 (C=O) ppm. ^{31}P NMR (121 MHz,

CDCl_3): δ = 29.61 ppm. IR: $\tilde{\nu}_{\text{max}}$ = 1024, 1053 (P=O), 1243 (P=O), 1753 (C=O) cm^{-1} . MS (ESI, pos. mode): m/z (%) = 430 (100) [$\text{M} + \text{H}^+$]. HRMS (ESI) m/z calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_5\text{P}$ [$\text{M} + \text{H}^+$] 430.1778; found 430.1768. Chromatography: PE/EtOAc (3:7) R_f = 0.14.

Dimethyl $\{[(2aR^*,8R^*,8aS^*)\text{-1-Isopropyl-2,2a,8,8a-tetrahydro-2-oxo-1H-chromeno}[3,2-b]\text{azet-8-yl}\}\text{methyl}\}$ phosphonate (4e): Yellow oil (0.50 g, 63%). ^1H NMR (300 MHz, CDCl_3): δ = 1.13 [d, J = 6.9 Hz, 3 H, $\text{CH}(\text{CH}_3)$], 1.21 [d, J = 6.9 Hz, 3 H, $\text{CH}(\text{CH}_3)$], 1.98 (ddd, $^2J_{\text{HP}}$ = 18.7, J = 15.7, J = 6.9 Hz, 1 H, $\text{NCHCHCH}_A\text{H}_B$), 2.10 (ddd, $^2J_{\text{HP}}$ = 23.9, J = 15.7, J = 8.3 Hz, 1 H, $\text{NCHCHCH}_A\text{H}_B$), 3.49–3.58 (m, 1 H, NCHCHCH_2), 3.59 (d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, OCH_3), 3.70 (d, $^3J_{\text{HP}}$ = 11.0 Hz, 3 H, OCH_3), 3.79 [sept, J = 6.9 Hz, 1 H, $\text{CH}(\text{CH}_3)_2$], 4.45 (dd, J = 5.0, J = 1.7 Hz, 1 H, NCHCHCH_2), 5.22 (d, J = 5.0 Hz, 1 H, OCH), 7.01–7.07 (m, 2 H, $2 \times \text{CH}_{\text{arom.}}$), 7.16 (dd, J = 7.7, J = 1.9 Hz, 1 H, $\text{CH}_{\text{arom.}}$), 7.25 (ddd, J = 8.5, J = 7.4, J = 1.9 Hz, 1 H, $\text{CH}_{\text{arom.}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 19.89 [$\text{CH}(\text{CH}_3)$], 21.63 [$\text{CH}(\text{CH}_3)$], 27.84 ($^1J_{\text{CP}}$ = 139.6 Hz, $\text{NCHCHCH}_2\text{P}$), 35.32 ($^2J_{\text{CP}}$ = 3.5 Hz, $\text{NCHCHCH}_2\text{P}$), 44.05 [$\text{CH}(\text{CH}_3)_2$], 52.34 ($^3J_{\text{CP}}$ = 6.9 Hz, OCH_3), 52.45 ($^3J_{\text{CP}}$ = 6.9 Hz, OCH_3), 59.09 ($^3J_{\text{CP}}$ = 10.4 Hz, NCHCHCH_2), 79.88 (OCH), 119.15 ($\text{CH}_{\text{arom.}}$), 124.02 ($\text{CH}_{\text{arom.}}$), 126.59 ($^3J_{\text{CP}}$ = 10.4 Hz, $\text{C}_{\text{quat.,arom.}}$), 129.56 ($\text{CH}_{\text{arom.}}$), 130.00 ($\text{CH}_{\text{arom.}}$), 152.31 ($\text{C}_{\text{quat.,arom.}}$), 164.03 (C=O) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 32.02 ppm. IR: $\tilde{\nu}_{\text{max}}$ = 1751 (C=O) cm^{-1} . MS: m/z (%) = (ES, pos.): m/z (%) = 340 (100) [$\text{M} + \text{H}^+$]. HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_5\text{P}$ [$\text{M} + \text{H}^+$] 340.1309; found 340.1313. Chromatography: EtOAc/MeOH (95:5) R_f = 0.25.

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- [1] G. Veinberg, M. Vorona, I. Shestakova, I. Kanepe, E. Lukevics, *Curr. Med. Chem.* **2003**, *10*, 1741.
- [2] a) B. Alcaide, P. Almendros, A. Rodríguez-Vicente, M. P. Ruiz, *Tetrahedron* **2005**, *61*, 2767–2778; b) A. Sato, T. Hirata, N.

- Nakamizo, *Agric. Biol. Chem.* **1986**, *47*, 799–806; c) T. Hirata, A. Sato, N. Nakamizo, *Jpn. Kokai Tokkyo Koho* **1979**, JP 54130596 19791009; d) T. Hirata, A. Sato, N. Nakamizo, *Jpn. Kokai Tokkyo Koho* **1979**, JP 54130553 19791009; e) G. H. Hakimelahi, G. Just, *Can. J. Chem.* **1979**, *57*, 1939–1944; f) H. W. Moore, *Tetrahedron Lett.* **1971**, *12*, 1621–1624; g) L. M. Monleon, M. Grande, J. Anaya, *Synlett* **2007**, 1243–1246; h) T. Gilchrist, A. Rahman, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1203–1208; i) C. Palomo, J. M. Aizpurua, J. M. Garcia, I. Ganboa, F. P. Cossio, B. Lecea, C. Lopez, *J. Org. Chem.* **1990**, *55*, 2498–2503; j) R. Joyeau, L. D. S. Yadav, M. Wakselman, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1899–1907; k) R. Joyeau, H. Molines, R. Labia, M. Wakselman, *J. Med. Chem.* **1988**, *31*, 370–374; l) G. Just, G. Sacripante, *Can. J. Chem.* **1987**, *65*, 104–109.
- [3] a) J. Finkelstein, K. G. Holden, C. D. Perchonock, *Tetrahedron Lett.* **1978**, *19*, 1629–1632; b) A. K. Bose, B. Ram, N. A. Hoffman, A. J. Hutchinson, M. S. Manhas, *J. Heterocycl. Chem.* **1979**, *16*, 1313–1316; c) H. Miyake, N. Tokutake, M. Kirisawa, *Synthesis* **1983**, 833–835; d) M. D. Bachi, J. Klein, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1925–1928; e) L. S. Hegedus, M. A. McGuire, L. M. Schultze, C. Yijun, O. P. Anderson, *J. Am. Chem. Soc.* **1984**, *106*, 2680–2687; f) K. H. Ongania, M. Wallnoefer, *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 2–10.
- [4] a) S. S. Ng, I. Banik, A. Okawa, F. F. Becker, B. K. Banik, *J. Chem. Res. Synop.* **2001**, 118–119; b) B. K. Banik, G. V. Subbaraju, M. S. Manhas, A. K. Bose, *Tetrahedron Lett.* **1996**, *37*, 1363–1366; c) S. D. Sharma, S. Kaur, U. Mehra, *Indian J. Chem. Sect. B* **1983**, *22*, 238–242.
- [5] a) C. Stevens, M. Gallant, N. De Kimpe, *Tetrahedron Lett.* **1999**, *40*, 3457–3460; b) B. Vanderhoydonck, C. V. Stevens, *Synthesis* **2004**, *5*, 722–734; c) B. Vanderhoydonck, C. V. Stevens, *J. Org. Chem.* **2005**, *70*, 191–198.
- [6] a) K. G. R. Masschelein, C. V. Stevens, *J. Org. Chem.* **2007**, *72*, 9248–9252; b) K. G. R. Masschelein, C. V. Stevens, *Tetrahedron Lett.* **2008**, *49*, 4336–4338.
- [7] a) C. E. Griffin, S. K. Kundu, *J. Org. Chem.* **1969**, *34*, 1532–1539; b) G. Just, P. Potvin, G. H. Hakimelahi, *Can. J. Chem.* **1980**, *58*, 2780–2783.
- [8] a) P. A. Baguley, J. C. Walton, *Angew. Chem.* **1998**, *110*, 3072–3082; b) A. Parsons, *Chem. Br.* **2002**, *38*, 42–44.
- [9] J. E. Leibner, J. Jacobus, *J. Org. Chem.* **1979**, *44*, 449–450.

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