Synthesis of dipeptide mimics based on amino phosphinate backbones and cyclic derivatives

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Dedicated to Prof. Dr. Jürgen Martens on the occasion of his 65th birthday

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Abstract
Dialkyl phosphinates are valuable peptide mimics for metallopeptidase targets. Despite their large pharmaceutical potential, the synthesis of many phosphinates remains challenging. An additional drawback for many applications is the high polarity of the phosphinate group. Herein we describe the synthesis of stereoisomerically pure GPI (1), a phosphinate with high binding affinity for the cancer specific zinc peptidase PSMA (prostate specific membrane antigen). In addition, analogous cyclic phosphinate esters 13, 16 and 23 are reported that might be useful as less polar ligands for metallo peptidase binding. The key step to these new 1,2-oxaphosphorinan-2-ones is an intramolecular cyclization of an intermediate H-phosphinate. The cyclizations work with modest diastereoselectivities of ~2:1 in favor of the trans arrangement of substituents at 2- and 4-position of the 1,2-oxaphosphorinan-2-one scaffolds.

Keywords: Carboxypeptidase inhibitors, phosphinates, tumor targeting, amino phosphinic acids

Introduction
Zinc containing peptidases constitute an important class of enzymes involved in tumor progression, angiogenesis, embryogenesis, ovulation and differentiation.1–2 An altered level of expression is often associated with malignant neoplasia. A range of metallopeptidases have therefore been used as tumor markers and are valuable targets for the development of targeted cancer therapeutics and imaging reagents. In consequence, the design and synthesis of small molecules binding to zinc peptidases with high affinity and specificity is an attractive field of Medicinal Chemistry.3–5
The general structural requirements for small molecules in this context are a peptidomimetic backbone for recognition of the peptidase and a zinc binding moiety (Scheme 1). Suitable zinc binding groups are thiols, carboxylates, hydroxamates, phosphonates and phosphinates. In this context, thiols, hydroxamates and phosphinates belong to the strongest zinc binders and the introduction of these groups into peptidase ligands is often increasing the affinity of the ligand to the target peptidase by three to four orders of magnitude.\(^6\)\(^-\)\(^10\)

![Scheme 1. Tetrahedral intermediate upon peptide hydrolysis in an active site of a zinc peptidase and a phosphinate analogue. In addition, the PSMA-specific ligand GPI (1) is shown.](image_url)

Despite their large pharmaceutical potential, the synthesis of many phosphinates remains challenging.\(^11\)\(^-\)\(^16\) An additional drawback for many applications is the high polarity of the phosphinate group.

Herein we describe the synthesis of stereoisomerically pure GPI (1), a phosphinate with high binding affinity to the cancer specific zinc peptidase PSMA (prostate specific membrane antigen). In addition, analogous cyclic phosphinates are reported that might be useful as less polar precursors for metallo peptidase binding.

**Results and Discussion**

GPI (1), a mimic of the native dipeptide NAAG (N-acetylaspartylglutamic acid), is a high affinity binder for the tumor marker PSMA and has been used for prostate cancer targeting (Scheme 2).\(^17\)\(^-\)\(^19\) It has been shown that the \((S,S)\) diastereoisomer of GPI is the eutomer with significantly higher affinity to the target protein than the corresponding \((S,R)\) isomer.\(^20\)\(^-\)\(^21\) However, the stereoselective synthesis of GPI proved to be difficult and only low diastereoselectivities have been realized so far.\(^22\) For a comparative study of stereoisomeric imaging reagents based on GPI as a targeting ligand, we needed both the \((S,S)\) and the corresponding \((S,R)\) isomer. Following a known protocol, we started our synthesis with enantiomerically pure Cbz-(S)-vinylglycine (3), which is readily available by a two-step synthesis from Cbz-(S)-methionine (2).\(^23\) In parallel, dibenzyl glutarate (5) was prepared from benzyl acrylate (4) via a Baylis-Hilman type reaction with \((n-Bu)_3P.\(^24\) Addition of ammonium hypophosphite gave phosphinic acid 6 as a racemate. Following a protocol of
Vitharana et al.,\textsuperscript{25} stepwise crystallization with first yohimbine and second (S)-methylbenzylamine gave (S)-6 and (R)-6 in 31 and 28\% yield, respectively over two steps. Both enantiomers of 6 were then treated with vinylglycine (3) and BSA to the target compounds (S,S)-7 and (S,R)-7. Both diastereomers were obtained with a de > 95 according to \(^1\)H-NMR, proving indirectly the high enantiomeric purity of intermediate phosphinic acids (S)-6 and (R)-6 after crystallization.

![Scheme 2. Synthesis of (S)-vinylglycine (3) and isomerically pure (S,S)-7 and (S,R)-7. BSA = Bis(trimethylsilyl)acetamide.](image)

The high polarity of the phosphinic acid group in peptidase inhibitors like GPI (1) is an inherent problem not only for the bioavailability of the compounds but also for workup of protected derivatives like 7. The affinity of phosphinates for silica often leads to significant loss of yield upon column chromatography. To decrease the polarity of the target compounds, we planned to introduce the dialkyl phosphinate part of the peptidase binders as a cyclic phosphinate ester (1,2-oxaphosphorinan-2-one), which upon hydrolysis would then release the phosphinic acid and an alcohol group. Our first attempt started with the conversion of allyl alcohol 8 to homoallyl alcohol 10 in a two-step procedure involving bromination and a subsequent In-mediated Barbier reaction of bromide 9 with formaldehyde (Scheme 3). The resulting homoallyl alcohol 10 was converted to the corresponding phosphinic acid ester 12. In our hands, the mixed-anhydride of
phosphinic acid 11 which was prepared with pivaloyl chloride gave the best yields for this esterification. Ester 12 was then treated with BSA to give the cyclic phosphinate 13 upon intramolecular cyclization in reasonable 46% yield for the two-step sequence. Similar cyclic phosphinates have only rarely been described in the literature so far.\(^{26-29}\)

**Scheme 3.** Synthesis of the cyclic phosphinate 13 via intramolecular cyclization of ester 12. BSA = Bis(trimethylsilyl)acetamide; PivCl = pivaloyl chloride; only one enantiomer of racemic compound trans-13 is shown.

The intramolecular cyclization of ester 12 to cyclic phosphinate 13 proceeds with a moderate diastereoselectivity of 2:1 in favor of trans-13. The preferred formation of trans-13 may be rationalized with the mechanistic proposal depicted in Scheme 4.

**Scheme 4.** Mechanistic proposal for the intramolecular cyclization of ester 12 to the cyclic phosphinate trans-13. Only one enantiomer of racemic compound trans-13 is shown.

Using the same approach, we have treated homoallyl alcohol 10 with phosphinic acid 14, which is readily available from \((S)\)-vinylglycine (3). Ester 15 was again formed via the mixed
anhydride of 14 with PivCl. Subsequent intramolecular cyclization gave the target cyclic phosphinate 16, which is a dipeptide mimic. Along with the methyl ester 16, we isolated a significant amount of the corresponding acid 17. Because we have used enantiomerically pure phosphonic acid 14 as a starting material, we expected the formation of all four possible stereoisomers in 16. To our surprise, we observed only two diastereoisomers in the $^{31}$P-NMR spectra of 16 (Scheme 5, A). However, this seems to be the consequence of a coincidental signal overlap of each two stereoisomers. In the corresponding acid derivative 17, which was formed as a deprotected side product, all four isomers are observable in the $^{31}$P-NMR spectra (Scheme 5, B).

Scheme 5. Synthesis of dipeptide mimic 16 via intramolecular cyclization of ester 15. Only one out of four stereoisomers for 16 and 17 is shown. A: stretch of the $^{31}$P-NMR spectra of 16; B: stretch of the $^{31}$P-NMR spectra of 17.

One of the reasons for synthesizing cyclic phosphinates like 13 and 16 was their decreased polarity compared to phosphinic acid analogues. In addition, we hoped that the intramolecular alkylation of the H-phosphinate intermediate might give better diastereoselectivities than acyclic variants. To introduce a chiral auxiliary in the vicinity of the newly formed stereogenic centers, we have prepared the chiral ester 20 by reaction of (-)-borneol (19) with acid 18 (Scheme 6).

Deprotection with TBAF gave alcohol 21, which was coupled to the mixed anhydride of phosphinic acid 14 to give ester 22. Intramolecular cyclization gave cyclic phosphinate 23 as a mixture of four stereoisomers. Finally, hydrolysis with aqueous HCl to 24 was performed.
decrease the number of possible stereoisomers and a 2:1-mixture of two diastereoisomers was observed in the $^{13}$C-NMR-spectra. Alternatively, the alkylation of $H$-phosphinate 14 with $\alpha$-methylene-$\gamma$-butyrolactone (25) gave also dipeptide mimic 24, but with no diastereoselectivity at all.

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\text{Scheme 6. Auxiliary synthesis of dipeptide mimic 24 via intramolecular cyclization of ester 22 and an alternative approach from $\alpha$-methylene-$\gamma$-butyrolactone (25). Only one major stereoisomer for 23 and 24 is shown.}
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Conclusions

We have described the synthesis of isomerically pure (S,S)- and (S,R)-7 via fractional crystallization of the intermediate $H$-phosphinate rac-6. The target compounds 7 are protected GPI (1) derivatives and thus ligands for the prostate cancer specific peptidase PSMA. To reduce the polarity of the targeted phosphinic acids, we synthesized cyclic phosphinate esters. The key step to these new 1,2-oxaphosphorinan-2-ones is an intramolecular cyclization of an intermediate $H$-phosphinate. The cyclizations work with modest diastereoselectivities of ~2:1 in favor of the trans
arrangement of substituents at 2- and 4-position of the 1,2-oxaphosphorinan-2-one. The resulting cyclic phosphinates are peptide mimetics of relatively low polarity compared to the corresponding acyclic phosphinic acids.

**Experimental Section**

**General.** TLC was performed on silica gel aluminium sheets (Macherey and Nagel). The reagent used for developing TLC plates was cerium stain (5g ammonium molybdate, 0.1 g cerium sulfate tetrahydrate, 10 mL sulfuric acid and 90 mL H2O) or 10% sulfuric acid in ethanol. Flash column chromatography was performed on silica gel (Macherey and Nagel, 60 – 200 µm). 1H chemical shifts are calibrated to residual non-deuterated solvent (CDCl3, δH 7.26 ppm; DMSO-d6, δH 2.50 ppm; CD3OD, δH 3.31 ppm). 13C chemical shifts are calibrated to the solvent signal (CDCl3, δC 77.2 ppm; DMSO-d6, δC 39.5 ppm; CD3OD, δH 49.0 ppm). NMR spectra were recorded at 400 (100), or 600 (150) MHz on Bruker Avance instruments. NMR-signals have been assigned on the basis of 2D-NMR (HH-COSY, HMBC and HSQC) experiments. ESI mass spectra were recorded on a Bruker MicroTOF-Q instrument operating in positive or negative mode. Samples were dissolved in MeCN/H2O mixtures or pure MeOH and were injected directly via syringe. If indicated with abs, solvents were dried according to standard procedures prior to use. IR spectra were recorded on a Shimadzu FT-IR IR Affinity-1 instrument. The wavelengths of selected characteristic bands (vmax) are quoted in cm⁻¹.

The following compounds have been prepared according to literature procedures: 3,23 8,30 11,31 14.22

**Dibenzyl 2-methylglutarate (5):** Tributylphosphine (1.50 mL, 5.99 mmol, 0.12 eq.) was added to benzyl acrylate (4) (7.50 mL, 49.9 mmol, 1.00 eq.) at 0 °C under inert atmosphere and the resulting mixture was stirred for 15 min at 0 °C and further 16 h at rt. Compressed air was bubbled through the solution for 2 h. The crude mixture was purified by flash chromatography on silica (PE/EtOAc, 1:1) to give the target compound 5 (4.80 g, 14.8 mmol, 59%) as a colorless oil. 1H-NMR (600 MHz, CDCl3): δ [ppm] 7.29 – 7.38 (m, 10 H, Ar-H), 6.23 (s, 1 H, 2'-H), 5.60 (s, 1 H, 2'-H), 5.20 (s, 2 H, CH2-Ph), 5.11 (s, 2 H, CH2-Ph), 2.69 (t, J 7.5 Hz, 2 H, 3-H), 2.59 (t, J 7.5 Hz, 2 H, 4-H). 13C-NMR (100 MHz, CDCl3): δ [ppm] 172.5 (C5), 166.4 (C1), 138.8 (C2), 135.9 (Ar-C), 135.90 (Ar-C), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 66.5 (CH2-Ph), 66.3 (CH2-Ph), 33.1 (C4), 27.4 (C3). MS (ESI): m/z (%) 325.14 (50) [M + H]+, 347.13 (100) [M + Na]+, 671.26 (29) [2M + Na]+.

**5-(Benzyloxy)-2-((benzyloxy)carbonyl)-5-oxopentylphosphinic acid (rac-6):** TMSCl (5.17 mL, 40.7 mmol, 13.2 eq.) and NEt3 (5.13 mL, 37.0 mmol, 12.0 eq.) were added to a suspension of NH4H2PO4 (1.30 g, 15.4 mmol, 5.00 eq.) in dry CH2Cl2 (25 mL) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and a solution of 5 (1.00 g, 3.10 mmol, 1.00 eq.) in dry CH2Cl2 (1.1 mL) was added. The reaction was allowed to warm to rt and stirring was continued for
20 h before quenching with 3 M aqueous hydrochloric acid (11 mL). The residue was extracted with CH₂Cl₂, washed with 3 M aqueous hydrochloric acid (4 × 10 mL) and water (2 × 10 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave the target compound 6 (0.90 g, 2.31 mmol, 75%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ [ppm] 8.34 (s, 1 H, OH), 7.29 – 7.40 (m, 10 H, Ar-H), 6.55 (s, 1 H, P-H), 5.11 (s, 2 H, CH₂-Ph), 2.86 – 2.94 (m, 1 H, 2-H), 2.30 – 2.38 (m, 2 H, 4-H), 2.13 – 2.21 (m, 1 H, 3-H), 1.97 – 2.04 (m, 2 H, 1-H, 3-H), 1.81 – 1.88 (m, 1 H, 1-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 173.4 (C5), 172.2 (C2’), 135.8 (Ar-C), 135.4 (Ar-C), 128.6 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 127.0 (Ar-CH), 67.0 (CH₂-Ph), 66.2 (CH₂-Ph), 38.1 (d, J 8.0 Hz, C2), 31.3 (C4), 30.7 (C1), 28.1 (d, J 46.8 Hz, C3). ³¹P-NMR (162 MHz, CDCl₃): δ [ppm] 34.9. MS (ESI): m/z (%) 391.13 (18) [M + H]⁺, 413.11 (100) [M + Na]⁺, 803.23 (32) [2M + Na]⁺.

(R)-(S)-5-(Benzyloxy)-2-(benzyloxy)carbonyl-5-oxopentyl) phosphinic acid ((R)-6): NEt₃ (0.83 mL, 6.00 mmol, 1.00 eq.) was added to a solution of yohimbine·HCl (2.30 g, 6.00 mmol, 1.00 eq.) in water (10 mL) and stirred for 3 h at rt. The mixture was filtered, and the filter cake was washed with water (2 × 10 mL) and with MeOH (10 mL). Removal of the solvent in vacuo gave yohimbine (2.00 g, 5.64 mmol, 1.00 eq.) was added to a solution of rac-6 (2.20 g, 5.64 mmol, 1.00 eq.) in acetone (11 mL) and heated to reflux for 3 h. Water (1.23 mL) was added and the mixture was cooled to −20°C, filtered and the collected solid was washed with cold acetone. The filtrate is kept for the synthesis of (S)-6. The solid was dissolved in CH₂Cl₂ (13 mL) and 10% sulfuric acid (2.35 mL) was added. The mixture was stirred for 30 min at rt and the phases were separated. The organic phase was washed with 10% sulfuric acid (2 × 10 mL) and water (2 × 10 mL). Removal of the solvent in vacuo gave the target molecule (R)-6 (0.62 g, 1.59 mmol, 28%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ [ppm] 7.32 – 7.37 (m, 10 H, Ar-H), 6.42 (s, 1 H, P-H), 5.11 (s, 2 H, CH₂-Ph), 5.08 (s, 2 H, CH₂-Ph), 2.87 – 2.96 (m, 1 H, 2-H), 2.34 – 2.39 (m, 2 H, 4-H), 2.13 - 2.25 (m, 1 H, 3-H), 1.99 – 2.05 (m, 2 H, 1-H, 3-H), 1.81 – 1.90 (m, 1 H, 1-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 173.5 (C5), 172.2 (C2’), 135.8 (Ar-C), 135.4 (Ar-C), 128.6 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 127.0 (Ar-CH), 67.1 (CH₂-Ph), 66.2 (CH₂-Ph), 38.1 (d, J 8.0 Hz, C2), 31.3 (C4), 30.7 (C1), 28.1 (d, J 46.8 Hz, C3). ³¹P-NMR (162 MHz, CDCl₃): δ [ppm] 34.7. MS (ESI): m/z (%) 391.13 (12) [M + H]⁺, 413.11 (100) [M + Na]⁺, 803.23 (34) [2M + Na]⁺.

(S)-(S)-5-(Benzyloxy)-2-(benzyloxy)carbonyl-5-oxopentyl) phosphinic acid ((S)-6): (S)-α-Methylbenzylamine (2.20 mL, 17.1 mmol, 1.00 eq.) was added to the filtrate of the procedure above and the resulting mixture was heated to reflux for 3 h. The reaction was cooled to −20°C, filtered and the collected solid was washed with cold acetone. The solid was dissolved in CH₂Cl₂ (20 mL) and 2 M aqueous hydrochloric acid (10 mL) was added. The solution was stirred for 30 min at rt and the phases were separated. The organic phase was washed with 2 M aqueous hydrochloric acid (2 × 20 mL) and water (2 × 20 mL). Removal of the solvent in vacuo gave the target molecule (S)-6 (0.74 g, 1.90 mmol, 31%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ [ppm] 7.32 – 7.35 (m, 10 H, Ar-H), 5.11 (s, 2 H, CH₂-Ph), 5.08 (s, 2 H, CH₂-Ph), 2.91 (s, 1 H,
2-H), 2.34 – 2.39 (m, 2 H, 4-H), 2.17 – 2.29 (m, 1 H, 3-H), 2.02 – 2.05 (m, 2 H, 1-H, 3-H), 1.83 – 1.90 (m, 1 H, 1-H). 13C-NMR (100 MHz, CDCl3): δ [ppm] 173.4 (C5), 172.2 (C2’), 135.8 (Ar-C), 135.4 (Ar-C), 128.6 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 67.1 (CH2-Ph), 66.5 (CH2-Ph), 38.1 (C2), 31.3 (C4), 31.3 (C1). 13P-NMR (162 MHz, CDCl3): δ [ppm] 35.4. MS (ESI): m/z (% 391.13 (100) [M + H]+, 413.11 (54) [M + Na]+, 781.25 (80) [2M + H]+, 803.23 (88) [2M + Na]+, 1171.37 (12) [3M + Na]+, 1193.38 (31) [2M + Na]+.

((R)-5-(Benzyloxy)-2-((benzyloxy)carbonyl)-5-oxopentyl)((S)-3-((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)phosphinic acid ((S,R)-7): To a solution of (R)-6 (0.31 g, 0.79 mmol, 1.00 eq.) in CH2Cl2 (5 mL) was added N,O-Bis(trimethylsilyl)acetamide (0.59 mL, 1.59 mmol, 2.00 eq.) and the mixture was heated to reflux for 4 h. (S)-Vinylglycine (3) (0.20 g, 0.79 mmol, 1.00 eq.) was added and the reaction was heated to reflux for 72 h. The reaction was quenched with 2 M aqueous hydrochloric acid (3 mL) and the mixture was washed with 2 M aqueous hydrochloric acid (2 × 5 mL). The solvent was removed in vacuo and the residue was purified by flash chromatography (EtOAc → EtOH) to give the target compound (S,R)-7 (0.29 g, 0.45 mmol, 56%) as a colorless solid. 1H-NMR (400 MHz, MeOD): δ [ppm] 7.20 – 7.23 (m, 15 H, Ar-H), 4.95 – 5.02 (m, 6 H, CH2-Ph), 4.19 (d, 3J 18.6 Hz, 1 H, 3’-H), 3.58 (m, 3 H, OCH3), 2.72 – 2.79 (m, 1 H, 2-H), 2.17 – 2.25 (m, 2 H, 4-H), 1.99 – 2.05 (m, 2 H, 1-H, 2’-H), 1.76 – 1.97 (m, 3 H, 2’-H, 3-H), 1.43 – 1.53 (m, 1 H, 1-H), 1.20 (t, 3J 12.0 Hz, 1 H, 1’-H), 0.76 – 0.80 (m, 1 H, 1-H). 13C-NMR (100 MHz, MeOD): δ [ppm] 174.4 (C2’’), 174.3 (C5), 174.3 (C4’), 158.5 (Cbz-COOBn), 138.0 (Ar-C), 137.5 (Ar-C), 137.5 (Ar-C), 129.5 (Ar-CH), 129.5 (Ar-CH), 129.4 (Ar-CH), 129.4 (Ar-CH), 129.3 (Ar-CH), 129.3 (Ar-CH), 129.2 (Ar-CH), 129.2 (Ar-CH), 129.1 (Ar-CH), 129.1 (Ar-CH), 129.0 (Ar-CH), 129.0 (Ar-CH), 128.8 (Ar-CH), 67.9 (CH2-Ph), 67.8 (CH2-Ph), 67.6 (CH2-Ph), 58.0 (C3’), 52.8 (OCH3), 40.5 (C2), 32.5 (C4), 32.4 (C1), 32.4 (C1), 30.0 (C3), 29.9 (C1’). MS (ESI): m/z (%) 640.23 (100) [M + H]+, 662.21 (43) [M + Na]+, 678.18 (27) [M + K]+.

((S)-5-(Benzyloxy)-2-((benzyloxy)carbonyl)-5-oxopentyl)((S)-3-((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)phosphinic acid ((S,S)-7): To a solution of (S)-6 (0.44 g, 1.13 mmol, 1.00 eq.) in CH2Cl2 (10 mL) was added N,O-Bis(trimethylsilyl)acetamide (1.11 mL, 4.52 mmol, 4.00 eq.) and the mixture was heated to reflux for 4 h. (S)-Vinylglycine (3) (0.28 g, 1.13 mmol, 1.00 eq.) was added and the reaction was heated to reflux for 120 h. The reaction was quenched with 2 M aqueous hydrochloric acid (3 mL) and the organic phase was washed with 2 M aqueous hydrochloric acid (2 × 10 mL). The solvent was removed in vacuo and the residue was purified by flash chromatography (EtOAc/PE, 1:1 → EtOH) to give the target compound (S,S)-7 (0.38 g, 0.59 mmol, 53%) as a colorless solid. 1H-NMR (400 MHz, CDCl3): δ [ppm] 7.20 – 7.35 (m, 15 H, Ar-H), 4.88 – 5.12 (m, 6 H, CH2-Ph), 4.48 (s, 1 H, 3’-H), 3.45 – 3.60 (m, 3 H, OCH3), 3.11 (m, 1 H, 2-H), 2.21 – 2.33 (m, 2 H, 4-H), 2.06 – 2.15 (m, 1 H, 2’-H), 1.86 – 1.94 (m, 1 H, 1-H), 1.74 – 1.85 (m, 1 H, 2’-H) 1.67 – 1.73 (m, 1 H, 3-H), 1.55 – 1.64 (m, 1 H, 3-H), 1.42 – 1.52 (m, 1 H, 1-H), 1.19 – 1.25 (m, 1 H, 1’-H), 0.94 – 1.02 (m, 1 H, 1’-H). 13C-NMR (100 MHz, MeOD): δ [ppm] 174.2 (C2’’), 174.2 (C5), 172.2 (C4’), 136.2
(Ar-C), 136.11 (Ar-C), 128.4 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 69.8 (CH₂-Ph), 65.6 (CH₂-Ph), 65.4 (CH₂-Ph), 40.1 (C2), 31.1 (C4), 31.0 (C1), 31.0 (C1), 29.2 (C3), 29.1 (C1'). MS (ESI): m/z (%) 640.22 (100) [M + H]^+, 662.20 (70) [M + Na]^+.

**tert-Butyl 2-(bromomethyl)acrylate (9).** The title compound 9 was synthesized as a colorless liquid according to a literature procedure for the methyl ester analogue from alcohol 8 (3.92 mL, 25.2 mmol).32 Yield: 4.70 g (21.28 mmol, 84%). Rf: 0.66 (SiO₂, EtOAc:Cyclohexan-1:2). ¹H-NMR (400 MHz, CDCl₃): δ [ppm] 6.22 (dd, 2J_H-H =0.8 Hz, 1 H, H-3b), 5.96 (dd, 2J_H-H=0.8 Hz, 1 H, H-3a), 4.14 (d, 4J_H-H=0.7 Hz, 2 H, H'-2), 1.52 (s, 9 H, 3°Bu-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 164.1 (C1), 139.0 (C2), 128.1 (C3), 81.9 (3°Bu-C), 30.0 (C2'), 28.1 (3°Bu-CH₃). CHN: found (calculated) [%]: C 42.36 (43.46); H 5.80 (5.93).

**tert-Butyl 4-hydroxy-2-methylenebutanoate 10.** The title compound was prepared following a procedure of O’Leary et al from bromide 9 (1.63 g 5.4 mmol). Title compound 10 was obtained as a colorless liquid in 60% yield. Rf: 0.29 (SiO₂, EtOAc:hexanes-1:2). ¹H-NMR (400 MHz, CDCl₃): δ [ppm] 6.13 (m, 1 H, H-2'b), 5.58 (m, 1 H, H-2'a), 3.74 (t, 3J_H-H=6.1 Hz, 2 H, H-4), 2.53 (td, 3J_H-H=6.0 Hz, 4J_H-H=0.8 Hz, 2 H, H-3), 2.27 (s, 1 H, OH), 1.49 (s, 9 H, 3°Bu-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 167.0 (C1), 139.3 (C2), 126.4 (C2'), 81.2 (3°Bu-C), 62.0 (C4), 35.8 (C3), 28.2 (3°Bu-CH₃). CHN: found (calcd) [%]: C 61.89 (62.77); H 9.34 (9.36). HRMS (ESI) [m/z]: calcd for C₄H₇O₃ [M + Na]^+: 195.0992, found: 195.0991. IR (film): ν [cm⁻¹] 3413.8 (m), 2978.4 (m), 2934.4 (m), 2884.1 (w), 1711.3 (s), 1631.6 (m), 1478.5 (w), 1458.2 (w), 1393.3 (m), 1369.1 (s), 1341.2 (m), 1314.4 (m), 1254.8 (m), 1214.6 (m), 1150.3 (s), 1049.7 (m), 946.4 (w), 852.1 (w), 818.8 (w), 759.5 (w), 683.6 (w).

**(2R,4S)-tert-Butyl 2-(3-((tert-butoxy)-3-oxopropyl)-1,2-oxaphosphinane-4-carboxylate 2-oxide 13.** H-Phosphinate 11 (47 mg, 0.24 mmol; 1 eq.) was dissolved in 3 mL dry MeCN and 1 mL dry pyridine. Pivaloyl chloride (60 µL, 0.48 mmol; 2 eq.) and ester 10 (41 mg, 0.24 mmol; 1 eq.) were added and the solution was stirred at rt under nitrogen atmosphere for 1h. The solvent was removed *in vacuo* to give the crude phosphinate 12, which was dissolved in CH₂Cl₂ (4 mL). N,O-Bis(trimethylsilyl)acetamid (BSA) (0.24 mL, 0.95 mmol; 6 eq.) was added and the solution was stirred for 96 h at rt under nitrogen atmosphere. The solution was treated with aqueous 1N HCl (2 mL), phases were separated and the organic phase was evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica (EtOAc:MeOH, 50:3) to give the title compound 13 (38 mg, 46%) as a 2:2:1-mixture of two diastereoisomers. Analytical data for 12: ¹H-NMR (400 MHz, CDCl₃): δ [ppm] 7.86 + 6.49 (dt, ²J₃J₃₃P = 547.3 Hz, ³J₉H₉H = 1.9 Hz, 1 H, P-H), 6.16 (d, ²J_H = 1.2 Hz, 1 H, 2'b-H), 5.58 (d, ²J = 1.2 Hz, 1 H, 2'a-H), 4.25-4.07 (m, 2 H, 4'-H), 2.64 (t, ³J_H-H = 6.5 Hz, 2 H, 3-H). 2.62-2.44 (m, 2 H, 6-H), 2.01 (dt, J = 15.2 Hz, J = 7.3 Hz, J = 2.0 Hz, 2 H, 5-H), 1.47 (s, 9 H, 3°Bu-H), 1.42 (s, 9 H, 3°Bu-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 137.4 (C2), 127.1 (C2'), 81.6 (Bu-C), 81.2 (Bu-C), 65.0 (C4, ²J₃J₃₃P = 6.8 Hz), 33.4 (C3, ²J₃J₃₃P = 6.2 Hz), 28.1 (Bu-CH₃), 27.2 (C6, ²J₃J₃₃P = 2.7 Hz), 24.6 + 23.7 (C5, ¹J₃J₃₃P = 95.6 Hz), C1 and C7 not observed. ³¹P-NMR (162 MHz, CDCl₃): δ [ppm] 38.07. HRMS (ESI) [m/z]: calcd for C₁₀H₁₉O₇P [M + H]^+: 349.1775, found: 349.1771; [M + Na]^+: 371.1594, found: 371.1594. Analytical data for 13: Rf: 0.43 + 0.47
(SiO₂, EtOAc:MeOH-10:1). ¹H-NMR (400 MHz, CDCl₃): δ [ppm] 4.41 (m, 1 H, 1a-H), 4.14 (m, 1 H, 1b-H), 4.05 (m, 1 H, 1b-H), 3.06 (m, 1 H, 3-H), 2.73 (m, 1 H, 3-H), 2.56 (m, 2 H, 2’a-H, 3’-a-H), 2.20 (m, 1 H, 2’b-H), 2.04 (m, 3 H, 1’-H, 2a-H), 1.82 (m, 1 H, 2b-H), 1.71 (m, 1 H, 3’-b-H), 1.44 + 1.43 + 1.42 + 1.42 (s, 18 H, 'Bu-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 172.4 (C₄), 31P₃1P-13C 16.2 Hz), 171.6 (C₄, 31P₃1P-13C 12.7 Hz), 171.5 (C₃, 31P₃1P-13C 15.6 Hz), 171.1 (C₃’, 31P₃1P-13C 14.8 Hz), 81.8 (‘Bu-C), 81.4 (‘Bu-C), 81.2 (‘Bu-C), 81.2 (‘Bu-C), 66.7 (C₁, 21J₃1P-13C 5.9 Hz), 64.6 (C₁, 21J₃1P-13C 6.2 Hz), 39.3 (C₃, 21J₃1P-13C 4.4 Hz), 37.3 (C₃, 21J₃1P-13C 5.9 Hz), 29.3 (C₂, 21J₃1P-13C 4.4 Hz), 28.0 (‘Bu-CH₃), 27.9 (‘Bu-CH₃), 27.3 (C₂’, 21J₃1P-13C 2.9 Hz), 27.7 + 26.9 (C₃’, 13C₃1P-13C 83.0 Hz), 26.7 (C₂’, 21J₃1P-13C 3.1 Hz), 24.6 + 23.6 (C₁’, 13J₃1P-13C 98.6 Hz), 21.4 + 20.5 (C₁’, 13J₃1P-13C 91.0 Hz). ³¹P-NMR (162 MHz, CDCl₃): δ [ppm] 49.88 (diastereomer A) + 47.51 (diastereomer B) (integration: 2.2 : 1.0). HRMS (ESI) [m/z]: calcd for C₁₆H₂₉O₅P [M + Na]⁺: 371.1594, found: 371.1603. IR (film): ν [cm⁻¹] 3434.1 (w), 2977.0 (w), 2931.6 (m), 1726.6 (s), 1477.4 (w), 1457.4 (w), 1393.4 (m), 1367.8 (s), 1250.6 (s), 1158.2 (s), 1056.1 (m), 1025.5 (m), 983.3 (m), 906.7 (m), 873.8 (w), 841.0 (m), 752.7 (m), 664.6 (w), 544.7 (w).

tert-Butyl 2-((S)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)-1,2-oxaphosphinane-4-carboxylate 2-oxide 16. H-Phosphinate 14 (50 mg, 0.16 mmol; 1 eq.) was dissolved in 3 mL dry MeCN and 1 mL dry pyridine. Pivaloyl chloride (60 μL, 0.48 mmol; 3 eq.) and ester 10 (28 mg, 0.16 mmol; 1 eq.) were added and the solution was stirred at rt under nitrogen atmosphere for 48h. The solvent was removed in vacuo to give the crude phosphinate 15, which was dissolved in CH₂Cl₂ (4 mL). N,O-Bis(trimethylsilyl)acetamid (BSA) (0.24 mL, 0.95 mmol; 6 eq.) was added and the solution was stirred for 96 h at rt under nitrogen atmosphere. The solution was treated with aqueous 1N HCl (2 mL), phases were separated and the organic phase was evaporated to dryness in vacuo. The residue was purified by column chromatography on silica (EtOAc:MeOH, 25:1) to give the title compound 16 (22 mg, 31%) as a mixture of diastereoisomers. Analytical data for 15: ¹H-NMR (400 MHz, CDCl₃): δ [ppm] 7.71 + 6.36 (d, 13J₃1P-1H 540.9 Hz, 1 H, P-H), 7.31-7.22 (m, 5 H, Ar-H), 6.11 (s, H, 3′-b-H), 5.53 (s, 1 H, 3′-a-H), 5.63 (d, 3J₃1P-1H 7.9 Hz, 1 H, N-H), 5.04 (s, 2 H, CH₂-Ph), 3.25 (t, 3J₃1P-1H 6.4 Hz, 2 H, 2-H), 2.20-2.06 (m, 1 H, 2’a-H), 1.99-1.85 (m, 1 H, 2’b-H), 1.85-1.70 (m, 2 H, 1’-H), 1.42 (s, 9 H, ‘Bu-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 171.9 (C₄’), 165.6 (C₄), 155.8 (Cbz-COO), 137.2 (C₃), 128.6 + 128.3 + 128.1 (Ar-C), 127.0 (C₃’), 81.1 (‘Bu-C), 67.2 (CH₂-Ph), 65.0 (C₁), 54.0 (C₃’), 52.7 (OCH₃), 33.3 (C₂, 3J₃1P-13C 6.1 Hz), 28.0 (‘Bu-CH₃), 24.0 (C₂’). C₁’ not observed. ³¹P-NMR (162 MHz, CDCl₃): δ [ppm] 37.64. HRMS (ESI) [m/z]: calcd for C₂₂H₃₂NO₅P [M + H]⁺: 470.202, found: 470.202. Analytical data for 15: Rᵣ: 0.38 + 0.44 (SiO₂, EtOAc:MeOH-10:1). ¹H-NMR (400 MHz, CDCl₃): δ [ppm] 7.33-7.25 (m, 5 H, Ar-H), 6.07 (m, 1 H, N-H), 5.06 (s, 2 H, CH₂-Ph), 4.33 (m, 2 H, 3’-H, H-1a), 4.08 (m, 1 H, 1b-H), 3.87 (m, 1 H, 1b-H), 3.69 (s, 3 H, OCH₃), 2.98 (m, 1 H, 3-H), 2.59 (m, 1 H, 3-H), 2.24-2.02 (m, 2 H, 2’a-H, 3’-a-H), 2.02-1.86 (m, 2 H, 2’b-H, 2a-H), 1.86-1.70 (m, 3 H, H-2b, 1’-H), 1.70-1.53 (m, 1 H, 3’-b-H), 1.48-1.35 (m, 9 H, ‘Bu-H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 172.5 (C₄), 31P₃1P-13C 16.1 Hz), 172.0 (C₄’), 156.1 (Cbz-COO), 136.2 (Ar-C), 128.7 + 128.4 + 128.3 (Ar-CH), 81.7 (‘Bu-C), 67.3 (CH₂-Ph), 66.7 (C₁, 21J₃1P-13C 7.4 Hz), 64.7 (C₁, 21J₃1P-13C 6.0 Hz), 54.1
(C3', t3J18C 16.9 Hz), 52.9 (OCH3), 52.8 (OCH3), 39.5 (C3, t2J31P-13C 4.0 Hz), 37.6 (C3, t2J31P-13C 5.8 Hz), 29.5 (C2, t3J31P-13C 4.0 Hz), 28.6 (C2, t3J31P-13C 6.5 Hz), 28.1 ('Bu-CH3), 28.5 + 27.7 (C3''), t1J31P-13C 81.0 Hz), 27.9 + 27.0 (C3''), t1J31P-13C 85.8 Hz), 25.7 + 24.8 (C1'), t1J31P-13C 92.4 Hz), 24.8 (C2'), 24.4 (C2'). 

31P-NMR (162 MHz, CDCl3): δ [ppm] 48.87 (diastereomer A) + 46.47 (diastereomer B) (integration: 2.3:1.0). HRMS (ESI) [m/z]: calcld for C22H23NO5P [M + H]+: 470.1938, found: 470.1944; [M + Na]+: 492.1758, found: 492.1745. IR (Film): ν [cm⁻¹] 3228.8 (w), 3033.1 (w), 2974 (m), 2959 (m), 2942 (m), 2857 (m), 1720.7 (s), 1535.2 (m), 1545.1 (m), 1392.8 (w), 1368.1 (m), 1251.4 (m), 1156.1 (m), 1055.6 (m), 1028.4 (m), 983.4 (w), 958.2 (w), 906.4 (w), 872.5 (w), 831.5 (w), 740.6 (w), 698.7 (w).

4-((tert-Butyldiphenylsilyl)oxy)-2-methylenbutanoic acid 18. 4-Hydroxy-2-methylenbutanoic acid (1.0 g, 8.6 mmol; 1 eq.) in CH2Cl2 (10 mL) was treated with imidazole (1.18 g, 17.2 mmol; 2 eq.) and cooled to 0 °C under nitrogen atmosphere. TBDPSCI (4.73 g, 17.2 mmol; 2 eq.) were added and the mixture was stirred at rt for 12 h. Water (10 mL) was added and the phases were separated. The aqueous phase was extracted three times with each 10 mL CH2Cl2. The combined organics were dried over Na2SO4, filtered and the solvent was removed in vacuo. The crude product was dissolved in THF (25 mL) and cooled to 0 °C. An aqueous 2.9 N KOH solution (8.9 mL, 25.8 mmol) was added dropwise and the solution was stirred for 2 h at rt. The pH was adjusted with 1 N HCl to ~2 and 40 mL CH2Cl2 were added. The phases were separated and the aqueous phase was extracted three times with each 20 mL CH2Cl2. The combined organics were dried over Na2SO4, filtered and the solvent was removed in vacuo. The residue was purified by column chromatography on silica (CH2Cl2:MeOH-10:1) to give the title compound 18 as a colorless solid (2.54 g, 83%). mp 63 °C. Rf: 0.19 (SiO2, CH2Cl2:MeOH-30:1).

1H-NMR (400 MHz, DMSO-d6): δ [ppm] 12.46 (breites s, 1 H, COOH), 7.60 (m, 4 H, Ar-H), 7.49-7.38 (m, 6 H, Ar-H), 6.11 (d, Jg 1.7 Hz, 1 H, 2'b-H), 5.65 (m, 1 H, 2'a-H), 3.74 (t, JIH1H 6.5 Hz, 2 H, 4-H), 2.50 (m, 2 H, 3-H), 0.97 (s, 9 H, 'Bu-H). 13C-NMR (100 MHz, DMSO-d6): δ [ppm] 167.9 (C1), 137.8 (C2), 135.0 (Ar-CH), 133.2 (Ar-C), 129.8 (Ar-CH), 127.5 (Ar-CH), 126.4 (C2'), 62.4 (C4), 34.8 (C3), 26.6 (‘Bu-CH3), 18.8 (‘Bu-C). CHN: found (calcd) [%]: C 70.91 (71.15); H 7.40 (7.39).

HRMS (ESI) [m/z]: calcld for C21H20O3Si [M + H]+: 355.1724, found: 355.1734; [M + Na]+: 377.1543, gef.: 377.1554. IR (KBr): ν [cm⁻¹] 3074.0 (m), 3054.9 (m), 3017.4 (m), 2958.3 (m), 2928.8 (s), 2883.0 (m), 2854.9 (s), 2671.3 (w), 1684.0 (s), 1623.6 (s), 1589.1 (w), 1471.9 (m), 1429.7 (s), 1381.9 (w), 1336.8 (w), 1314.4 (m), 1262.0 (m), 1231.5 (m), 1167.9 (m), 1106.7 (s), 1094.4 (s), 1045.0 (w), 1007.7 (w), 997.9 (w), 960.7 (m), 935.4 (m), 822.5 (m), 793.4 (w), 752.1 (m), 737.4 (m), 701.8 (s), 684.0 (m), 614.0 (s), 595.9 (w), 551.7 (w), 506.3 (s), 489.0 (m).

(1R,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 4-((tert-butyldiphenylsilyl)oxy)-2-methylenbutanoate 20. Carboxylic acid 18 (600 mg, 1.69 mmol; 1 eq.), (-)-borneol (19) (782 mg, 5.07 mmol; 3 eq.) and DMAP (248 mg, 2.03 mmol, 1.2 eq.) were dissolved in dry CH2Cl2 (10 mL). The mixture was cooled to 0 °C and a solution of 419 mg DCC (2.0 mmol; 1.2 eq.) in 8 mL in dry CH2Cl2 was added dropwise. The solution was stirred for 12 h at rt, filtered over celite and the solvent was removed in vacuo. The residue was purified by column chromatography on silica (CH2Cl2) to give the title compound 20 as a colorless oil (696 mg, 84%). Rf: 0.72 (SiO2, CH2Cl2).
\[ ^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta [\text{ppm}] \ 7.66 \ (m, \ 4 \text{ H, Ar-H}), 7.44-7.34 \ (m, \ 6 \text{ H, Ar-H}), 6.25 \ (d, J 1.6 \text{ Hz, 1 H, 2'''-b-H}), 5.62 \ (d, J 1.2 \text{ Hz, 1 H, 2''-a-H}), 4.89 \ (m, \ 1 \text{ H, 2'-H}), 3.81 \ (t, J 6.4 \text{ Hz, 2 H, 4-H}), 2.60 \ (t, J 6.3 \text{ Hz, 2 H, 3-H}), 2.37 \ (m, \ 1 \text{ H, 3'a-H}), 1.92 \ (m, \ 1 \text{ H, 6'a-H}), 1.74 \ (m, \ 1 \text{ H, 5'a-H}), 1.68 \ (t, J 4.5 \text{ Hz, 1 H, 4'-H}), 1.30 \ (m, \ 1 \text{ H, 6'b-H}), 1.19 \ (m, \ 1 \text{ H, 5'b-H}), 1.04 \ (s, \ 9 \text{ H, } ^1\text{Bu-CH}_3), 0.95 \ (dd, J 13.8 \text{ Hz, J 3.5 Hz, 1 H, 3b-H}), 0.92 \ (s, \ 3 \text{ H, 8-H}), 0.88 \ (s, \ 3 \text{ H, 8-H}), 0.81 \ (s, \ 3 \text{ H, 1''-H}). \]

\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta [\text{ppm}] \ 167.4 \ (C1), 138.0 \ (C2), 135.7 \ (Ar-CH), 134.0 \ (Ar-C), 129.7 \ (C9 \text{ Ar-CH}) 127.8 \ (Ar-CH), 126.8 \ (C2), 80.3 \ (C2'), 62.6 \ (C4), 49.0 \ (C1'), 47.9 \ (C7'), 45.0 \ (C4'), 37.0 \ (C3'), 35.4 \ (C3), 28.1 \ (C5'), 27.4 \ (C6'), 27.0 \ (^

\( ^{4}\text{S-}^{6}\text{A,B,C,D}-1,7,7-\text{Trimethylbicyclo[2.2.1]heptan-2-yl} \) 4-hydroxy-2-methylenebutanoate 21: The TBDPS-protected ester 20 (500 mg, 1.02 mmol; 1 eq.) was dissolved in abs THF (10 mL) and cooled to 0 °C. TBAF : 3 H2O (644 mg, 2.04 mmol; 2 eq.) was coevaporated three times with CH2Cl2, dissolved in THF (5 mL) and added to the reaction mixture drop wise. The solution was stirred for 5 h at 0 °C and nitrogen atmosphere. Aqueous saturated NH4Cl solution (10 mL) was added and the mixture was extracted three times with each 20 mL EtOAc. The combined organics were dried over Na2SO4, filtered and the solvent was removed in vacuo. The residue was purified by column chromatography on silica (CH2Cl2:MeOH-20:1) to give the title compound 21 as a colorless oil (207 mg, 80%). Rf: 0.08 (SiO2, CH2Cl2).

\[ ^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta [\text{ppm}] \ 6.26 \ (d, J 1.2 \text{ Hz, 1 H, 2'''-b-H}), 5.65 \ (d, J 0.9 \text{ Hz, 1 H, 2''-a-H}), 4.92 \ (m, \ 1 \text{ H, 2'-H}), 3.77 \ (t, J 6.1 \text{ Hz, 2 H, 4-H}), 2.59 \ (t, J 6.1 \text{ Hz, 2 H, 3-H}), 2.39 \ (m, \ 1 \text{ H, 3'a-H}), 2.01 \ (s_{8b}, \ 1 \text{ H, OH}), 1.95 \ (m, \ 1 \text{ H, 6'a-H}), 1.76 \ (m, \ 1 \text{ H, 5'a-H}), 1.70 \ (t, J 4.5 \text{ Hz, 1 H, 4'-H}), 1.34 \ (m, \ 1 \text{ H, 6'b-H}), 1.24 \ (m, \ 1 \text{ H, 4'b-H}), 1.00 \ (dd, J 13.8 \text{ Hz, J 5.7 Hz, 1 H, 3b-H}), 0.92 \ (s, \ 3 \text{ H, 8'-H}), 0.88 \ (s, \ 3 \text{ H, 8'-H}), 0.85 \ (s, \ 3 \text{ H, 1''-H}). \]

\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta [\text{ppm}] \ 167.8 \ (C1), 138.1 \ (C2), 127.0 \ (C2''), 80.8 \ (C2'), 61.8 \ (C4), 49.1 \ (C1'), 47.9 \ (C7'), 45.0 \ (C4'), 36.9 \ (C3'), 35.8 \ (C3), 28.2 \ (C5'), 27.4 \ (C6'), 19.8 + 19.0 \ (C8'), 13.7 \ (C1'). \]

CHN: found (calcd) [%]: C 71.12 (71.39); H 9.66 (9.59). HRMS (ESI) [m/z]: calcd for C15H24O3 [M + H]+: 253.1798, found: 253.1798. IR (film): ν [cm⁻¹] 3330.0 (br s), 2954.1 (s), 2880.5 (m), 2361.5 (w), 2336.5 (w), 1714.9 (s), 1652.8 (w), 1629.2 (w), 1472.6 (w), 1455.8 (m), 1390.6 (w), 1307.4 (m), 1199.1 (m), 1152.0 (m), 1113.9 (w), 1046.0 (m), 992.2 (w), 943.3 (w), 867.4 (w), 816.9 (w).

\[ ^{2}(S)-3-\text{((benzylxy)carbonyl)amino}-4\text{-methoxy-4-oxobutyl}-1,2\text{-oxaphosphinane-4-carboxylate} \] 22-(S)-3-((benzylxy)carbonyl)amino)-4-methoxy-4-oxobutyl)-1,2-oxaphosphinane-4-carboxylate 22-oxide 23. H-Phosphinate 14 (50 mg, 0.16 mmol; 1 eq.) was dissolved in 3 mL dry MeCN and 1 mL dry pyridine. Pivaloyl chloride (60 μL, 0.48 mmol; 3 eq.) and ester 21 (40 mg, 0.16 mmol; 1 eq.) were added and the solution was stirred at rt under nitrogen atmosphere for 1h. The solvent
was removed in vacuo to give the crude phosphate 22, which was dissolved in CH₂Cl₂ (4 mL).
N,O-Bis(trimethylsilyl)acetamid (BSA) (0.24 mL, 0.95 mmol; 6 eq.) was added and the solution
was stirred for 96 h at rt under nitrogen atmosphere. The solution was treated with aqueous 1 N
HCl (2 mL), phases were separated and the organic phase was evaporated to dryness in vacuo. The
residue was purified by column chromatography on silica (EtOAc:MeOH, 25:1) to give the title
compound 23 (18 mg, 20%) as a mixture of diastereoisomers. Analytical data for 22: ¹H-NMR
(400 MHz, CDCl₃): δ [ppm] 7.78 + 6.43 (d, ¹J₁₁₃₁P₁₈ 540.4 Hz, 1 H, P-H), 7.42-7.22 (m, 5 H, Ar-
H), 6.29 (m, 1 H, 2''-b-H), 5.67 (m, 1 H, 2''-a-H), 5.61 (m, 1 H, N-H), 5.11 (m, 2 H, CH₂-Ph), 4.93
(m, 1 H, 2'-H), 4.42-4.28 (m, 1 H, 7'-H), 4.20 (m, 2 H, 4-H), 3.76 (s, 3 H, OCH₃), 2.72 (m, 2 H, 3-
H), 2.39 (m, 1 H, 3’a-H), 2.20 (m, 1 H, 6a-H), 2.00-1.70 (m, 3 H, 6b-H, 5-H), 1.92 (m, 1 H, 6’a-
H), 1.77 (m, 1 H, 5’a-H), 1.70 (m, 1 H, 4’-H), 1.34 (m, 1 H, 6’-b-H), 1.25 (m, 1 H, 5’-b-H), 1.00
(m, 1 H, 3’-b-H), 0.92 (s, 3 H, 8’-H), 0.88 (s, 3 H, 8’-H), 0.85 (s, 3 H, 1’’-H). ³¹P-NMR (162 MHz, CDCl₃):
δ [ppm] 37.65. MS (ESI) [m/z]: calcd for C₃₈H₄₀NO₈P [M + Na⁺]: 572.023, found: 572.238.
Analytical data for 23: Rf: 0.33 + 0.37 (SiO₂, EtOAc). ¹H-NMR (400 MHz, CDCl₃): δ [ppm]
7.41-7.28 (m, 5 H, Ar-H), 5.66 (m, 1 H, N-H), 5.11 (m, 2 H, CH₂-Ph), 4.91 (m, 1 H, 5-H),
4.42 (m, 2 H, 3’-H, 1a-H), 4.17 (m, 1 H, 1b-H), 3.95 (m, 1 H, 1b-H), 3.75 (s, 3 H, 8-H), 3.18 (m, 1 H, 3-H),
2.76 (m, 1 H, 3-H), 2.41-2.11 (m, 3 H, 6a-H, 2’a-H, 3’’a-H), 2.11-1.66 (m, 9 H, 2’-b-H, 3’-b-H, 2a-H, 2b-H, 1’a-H, 1’-b-H, 9’a-H, 8’a-H, 7’-H), 1.37-1.17 (m, 2 H, 9’-b-H, 8’-b-H), 0.99 (dd,
J 13.8 Hz, J 3.4 Hz, 1 H, 6’-b-H), 0.95 (dd, J 13.9 Hz, J 3.5 Hz, 1 H, 6’-b-H), 0.90 (s, 3 H, 12’-H),
0.87 (s, 3 H, 12’-H), 0.82 (s, 3 H, 1’’-H). ¹³C-NMR (151 MHz, CDCl₃): δ [ppm] 172.4 (C₄, ³J₃₃₃P₃₈ 14.9 Hz),
172.0 (C₄'), 156.2 (Cbz-COO), 136.3 (Ar-C), 128.7 + 128.4 + 128.3 (Ar-CH), 81.4 +
81.3 + 81.0 (5), 67.3 (CH₂-Ph), 66.7 (C₁), 64.6 (C₁), 54.1 (C₃’), 52.9 + 52.9 + 52.8 (OCH₃), 49.1
(C₁₀), 49.0 (C₁₀), 48.1 (C₁₁), 45.0 (C₇), 38.9 + 38.8 (C₃), 36.9 (C₃), 36.9 (C₆), 36.8 (C₆), 29.7
(C₂, ³J₃₃₃₃₈ 3.7 Hz), 29.5 (C₂, ³J₃₃₃₃₈ 3.9 Hz), 28.6 (C₂, ³J₃₃₃₃₈ 6.4 Hz), 28.5 (C₁₁, ³J₃₃₃₃₈ 6.4 Hz),
28.3 + 27.7 (C₃’'), ³J₃₃₃₃₈ 81.6 Hz), 28.2 + 27.7 (C₃’'), ³J₃₃₃₃₈ 81.5 Hz), 28.3 (C₈), 28.1
(C₈), 27.7 + 27.1 (C₃’'), ³J₃₃₃₃₈ 82.6 Hz), 27.3 (C₈), 27.3 (C₈), 25.5 + 24.9 (C₁', ³J₃₃₃₃₈ 94.2
Hz), 24.7 + 24.3 (C₂'), 19.8 + 18.9 (C₁₂), 13.7 + 13.7 + 13.6 (C₁₀’’). ³¹P-NMR (243 MHz, CDCl₃): δ [ppm]
49.09, 48.96, 46.40 (integration 1.0 : 1.0 : 4.4). MS (EI) [m/z]: 549 (12 %, [M⁺],
490 (27 %, [M-COOMe⁺]), 442 (8 %, [M-O-Benzyl⁺]), 414 (21 %, [M-Cbz⁺]), 396 (22 %, [M-
OBornyeyl⁺]), 370 (15 %, [C₁₇H₂₅NO₆P⁺]), 306 (54 %, [M-Benzyl-OBornyeyl+H⁺]), 146 (29 %,
[C₅H₈O₃P⁺]), 91 (100 %, [Benzyl⁺]). HRMS (EI) [m/z]: calcd for C₃₈H₄₀NO₈P [M⁺]: 549.2492,
found: 549.2470. IR (film): ν [cm⁻¹] 3240.1 (w), 3033.9 (w), 2954.3 (s), 1725.8 (s), 1537.3 (m),
1454.0 (m), 1366.4 (w), 1249.7 (s), 1145.4 (m), 1113.6 (m), 1057.6 (s), 964.4 (m), 904.7 (w),
868.1 (w), 812.3 (w), 741.5 (w), 698.7 (w), 530.5 (w).
(2S)-2-amino-4-(hydroxy(((R)-2-oxotetrahydrofuran-3-yl)methyl)phosphoryl)butanoic acid
hydrochloride 24. Cyclic phosphate 23 (87 mg, 0.16 mmol) was treated with aqueous 6 N HCl
(5 mL) and heated to reflux for 12 h. The resulting mixture was washed with Et₂O three times
(each 20 mL). The aqueous solution was evaporated to dryness to give the target compound 24 (50
mg, quant). ¹H-NMR (600 MHz, D₂O): δ [ppm] 4.60 (m, 1 H, 8a-H), 4.44 (m, 1 H, 8b-H), 4.30 (m,
1 H, 2-H), 3.15 (m, 1 H, 6-H), 2.72 (m, 1 H, 9a-H), 2.47 (m, 1 H, 5a-H), 2.35 (m, 2 H, 3-H), 2.29
(m, 1 H, 9b-H), 2.16 (m, 1 H, 4a-H), 2.10 (m, 1 H, 5b-H), 2.05 (m, 1 H, 4b-H). $^{13}$C-NMR (151 MHz, D$_2$O, Inverse gated coupling): $\delta$ [ppm] 181.9 (C7, $^3$J$_{31P-13C}$ 16.4 Hz), 170.9 (C1), 68.1 (C8), 52.7 (C2, $^3$J$_{31P-13C}$ 15.4 Hz), 52.7 (C2, $^3$J$_{31P-13C}$ 15.4 Hz), 34.0 (C6, $^2$J$_{31P-13C}$ 3.8 Hz), 28.9 (C9, $^3$J$_{31P-13C}$ 2.8 Hz), 28.9 (C9, $^3$J$_{31P-13C}$ 2.6 Hz), 28.8 + 28.2 (C5, $^1$J$_{31P-13C}$ 93.6 Hz), 24.9 + 24.2 (C4, $^1$J$_{31P-13C}$ 91.6 Hz), 24.8 + 24.2 (C4, $^1$J$_{31P-13C}$ 91.8 Hz), 22.3 (C3, $^2$J$_{31P-13C}$ 2.3 Hz), 22.3 (C3, $^2$J$_{31P-13C}$ 2.7 Hz). $^{31}$P-NMR (162 MHz, D$_2$O): $\delta$ [ppm] 51.74. HRMS (ESI) [m/z]: calcd for C$_9$H$_{16}$NO$_6$P [M - H]: 264.0642, found: 264.0631.

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