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

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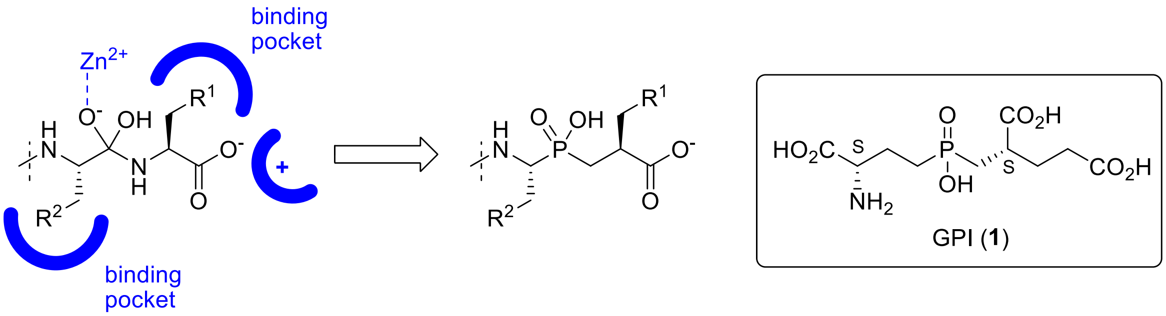
Introduction

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 neoplasy. 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.

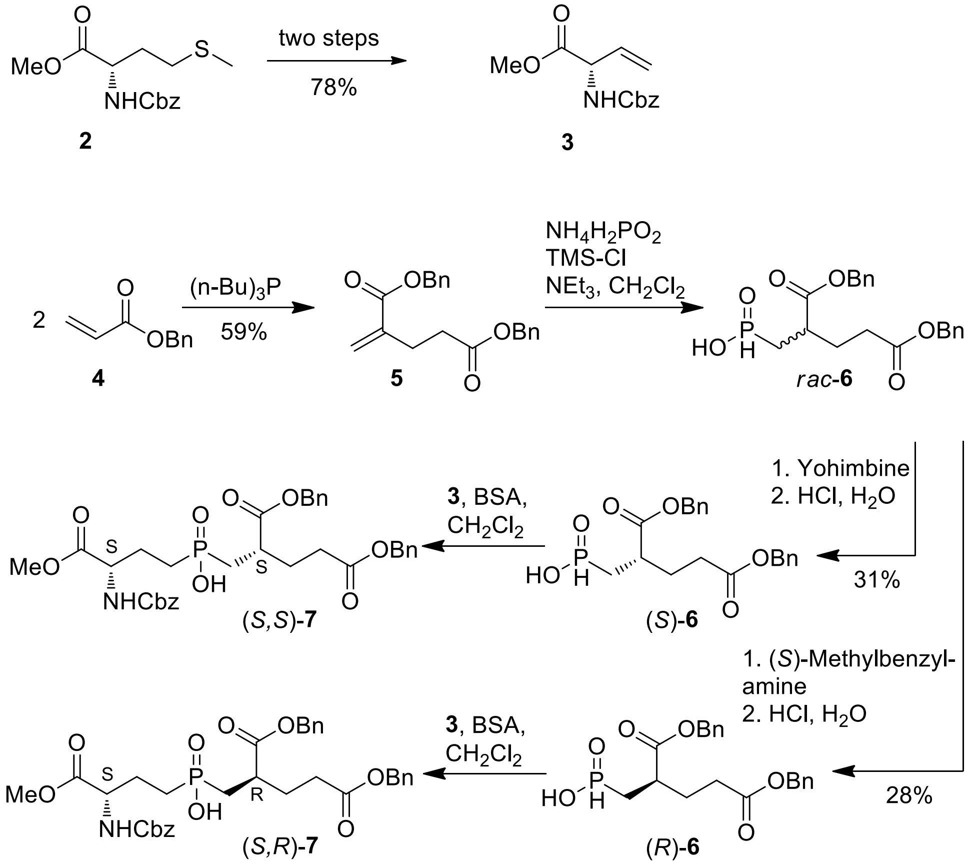
Despite their large pharmaceutical potential, the synthesis of many phosphinates remains challenging.[11-16] An additional drawback for many applications is the high polarity of the phosphinate group.

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

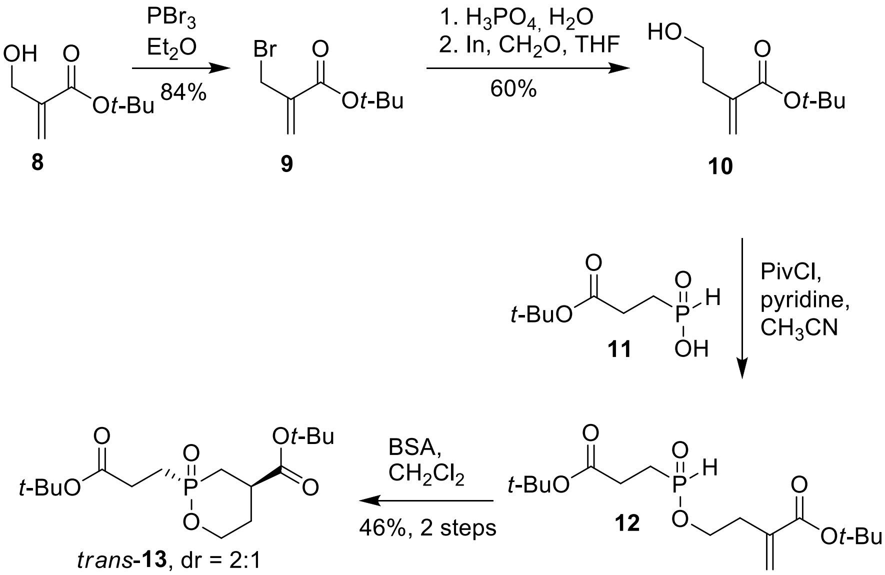
GPI (**1**), a mimic of the native dipeptide NAAG (*N*-acetylaspartylglutamic acid), is a high affinity binder for the tumor marker PSMA and has been used for prostate cancer targeting (Scheme 2).[17-19] It has been shown that the (*S*,*S*) diastereoisomer of GPI is the eutomer with significantly higher 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 $(n\text{-}Bu)_3P$.[24] Addition of ammonium hypophosphite gave phosphinic acid **6** as a racemate. Following a protocol of

Vitharana et al.,[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.



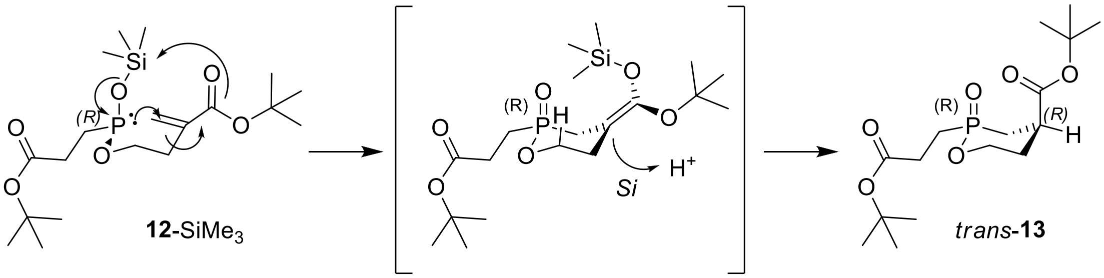
Scheme 2. Synthesis of (*S*)-vinylglycine (**3**) and isomerically pure (*S*,*S*)-**7** and (*S*,*R*)-**7**. BSA = Bis(trimethylsilyl)acetamide.

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]



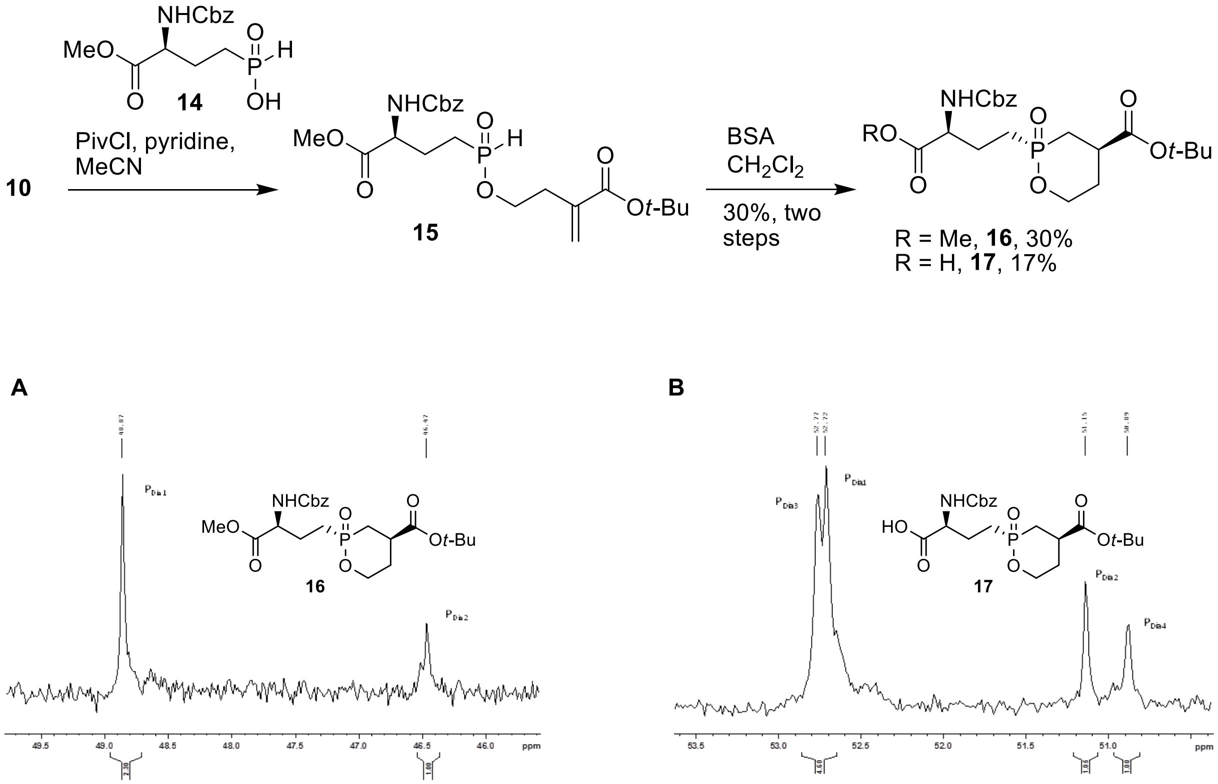
Scheme 3. Synthesis of the cyclic phosphinate **13** *via* intramolecular cyclization of ester **12**. BSA = Bis(trimethylsilyl)acetamide; PivCl = pivaloyl chloride; only one enantiomer of racemic compound *trans*-**13** is shown.

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.

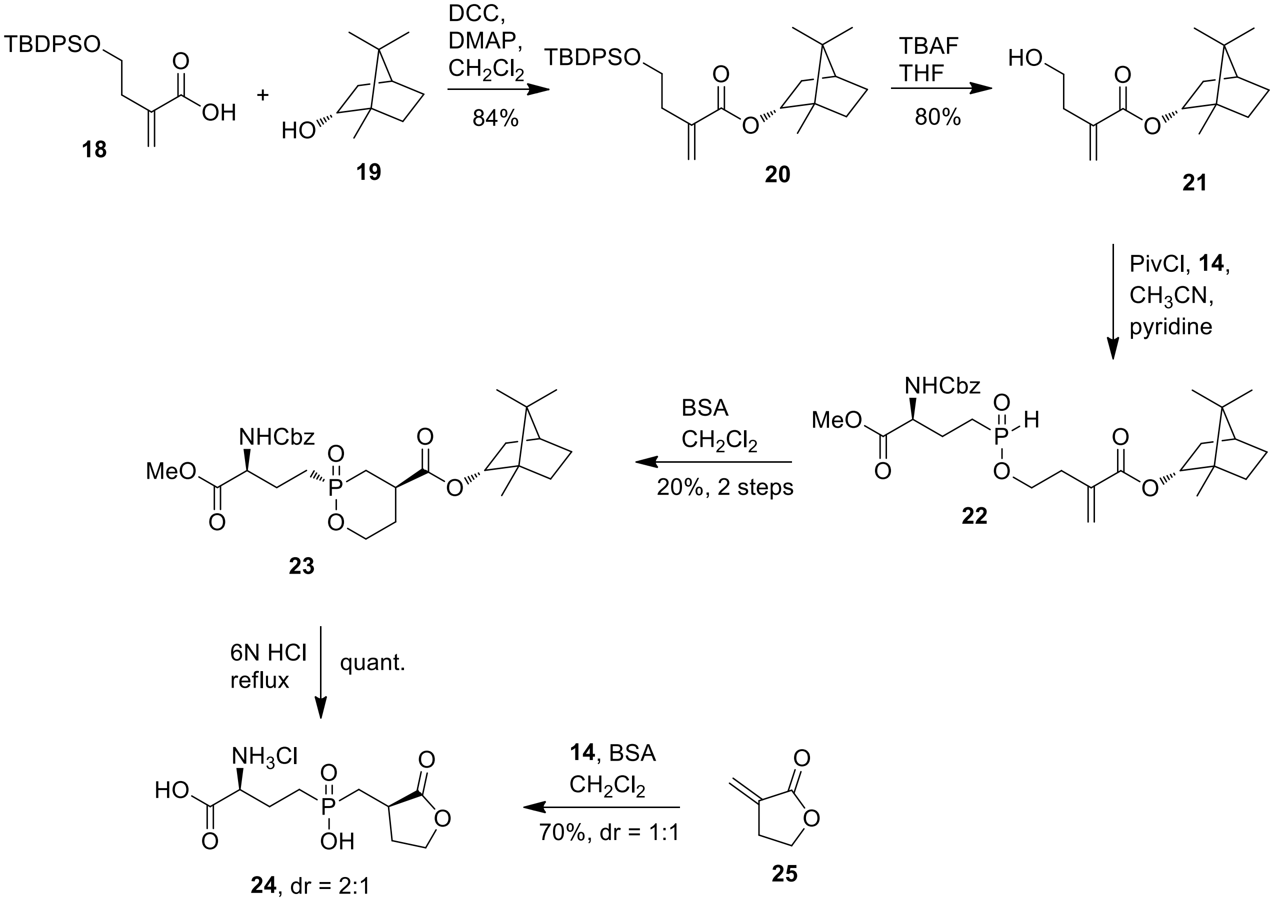
Using the same approach, we have treated homoallyl alcohol **10** with phosphinic acid **14,** which is readily available from (*S*)-vinylglycine (**3**). Ester **15** was again formed *via* the mixed anhydride of **14** with PivCl. Subsequent intramolecular cyclization gave the target cyclic phosphinate **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 then 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 to 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 α-methylene-γ-butyrolactone (**25**) gave also dipeptide mimic **24**, but with no diastereoselectivity at all.



Scheme 6. Auxiliary synthesis of dipeptide mimic **24** *via* intramolecular cyclization of ester **22** and an alternative approach from α-methylene-γ-butyrolactone (**25**). Only one major stereoisomer for **23** and **24** is shown.

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 H_2O) or 10% sulfuric acid in ethanol. Flash column chromatography was performed on silica gel (Macherey and Nagel, 60 – 200 µm). ^{1}H chemical shifts are calibrated to residual non-deuterated solvent ($CDCl_3$, δ_H 7.26 ppm; DMSO-d_6, δ_H 2.50 ppm; CD_3OD, δ_H 3.31 ppm). ^{13}C chemical shifts are calibrated to the solvent signal ($CDCl_3$, δ_C 77.2 ppm; DMSO-d_6, δ_C 39.5 ppm; CD_3OD, δ_H 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/H_2O 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 (νmax) 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-methylenglutarate (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 ° 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. ^{1}H-NMR (600 MHz, $CDCl_3$): 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, CH_2-Ph), 5.11 (s, 2 H, CH_2-Ph), 2.69 (t, ^3J 7.5 Hz, 2 H, 3-H), 2.59 (t, ^3J 7.5 Hz, 2 H, 4-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 172.5 (C5), 166.4 (C1), 138.8 (C2), 135.9 (Ar-C), 135.90 (Ar-C), 128.6 (Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 66.5 (CH_2-Ph), 66.3 (CH_2-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-oxopentyl)phosphinic acid (*rac*-6): TMSCl (5.17 mL, 40.7 mmol, 13.2 eq.) and NEt_3 (5.13 mL, 37.0 mmol, 12.0 eq.) were added to a suspension of $NH_4H_2PO_4$ (1.30 g, 15.4 mmol, 5.00 eq.) in dry CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2, 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. ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.34 (s_b, 1 H, OH), 7.29 – 7.40 (m, 10 H, Ar-H), 6.55 (s, 1 H, P-H), 5.11 (s, 2 H, CH_2-Ph), 5.11 (s, 2 H, CH_2-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). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2-Ph), 66.4 (CH_2-Ph), 38.1 (d, *J* 8.0 Hz, C2), 31.3 (C4), 30.7 (C1), 28.1 (d, *J* 46.8 Hz, C3).^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 34.9. MS (ESI): *m/z* (%) 391.13 (18) $[M + H]^+$, 413.11 (100) $[M + Na]^+$, 803.23 (32) $[2M + Na]^+$.

(*R*)-(5-(Benzyloxy)-2-((benzyloxy)carbonyl)-5-oxopentyl)phosphinic acid ((*R*)-6): NEt_3 (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, 94 %) as a white solid. 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 CH_2Cl_2 (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. ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.32 – 7.37 (m, 10 H, Ar-H), 6.42 (s, 1 H, P-H), 5.11 (s, 2 H, CH_2-Ph), 5.08 (s, 2 H, CH_2-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). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 173.5 (C5), 172.2 (C2'), 135.8 (Ar-C), 135.4 (Ar-C), 128.6 (Ar-C), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 67.1 (CH_2-Ph), 66.4 (CH_2-Ph), 38.1 (d, *J* 8.0 Hz, C2), 31.3 (C4), 30.7 (C1), 28.1 (d, *J* 46.8 Hz, C3). ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 34.7. MS (ESI): *m/z* (%) 391.13 (12) $[M + H]^+$, 413.11 (100) $[M + Na]^+$, 803.23 (34) $[2M + Na]^+$.

(*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 CH_2Cl_2 (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. ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.32 – 7.35 (m, 10 H, Ar-H), 5.11 (s, 2 H, CH_2-Ph), 5.08 (s, 2 H, CH_2-Ph), 2.91 (s_b, 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). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2-Ph), 66.5 (CH_2-Ph), 38.1 (C2), 31.3 (C4), 31.3 (C1). ^{31}P-NMR (162 MHz, $CDCl_3$): 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 CH_2Cl_2 (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. ^{1}H-NMR (400 MHz, MeOD): δ [ppm] 7.20 – 7.23 (m, 15 H, Ar-H), 4.95 – 5.02 (m, 6 H, CH_2-Ph), 4.19 (d, ^3J 18.6 Hz, 1 H, 3'-H), 3.58 (m, 3 H, OCH_3), 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). ^{13}C-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), 129.2 (Ar-CH), 129.1 (Ar-CH), 129.1 (Ar-CH), 129.0 (Ar-CH), 129.0 (Ar-CH), 128,8 (Ar-CH), 67.9 (CH_2-Ph), 67.8 (CH_2-Ph), 67.6 (CH_2-Ph), 58.0 (C3'), 52.8 (OCH_3), 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 CH_2Cl_2 (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. ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.20 – 7.35 (m, 15 H, Ar-H), 4.88 – 5.12 (m, 6 H, CH_2-Ph), 4.48 (s, 1 H, 3'-H), 3.45 - 3.60 (m, 3 H, OCH_3), 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). ^{13}C-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), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 69.8 (CH_2-Ph), 65.6 (CH_2-Ph), 65.4 (CH_2-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%). R_f: 0.66 (SiO_2, EtOAc:Cyclohexan-1:2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 6.22 (dd, $^2J_{1H\text{-}1H}$ =0.8 Hz, 1 H, H-3b), 5.96 (dd, $^2J_{1H\text{-}1H}$ =0.8 Hz, 1 H, H-3a), 4.14 (d, $^4J_{1H\text{-}1H}$ =0.7 Hz, 2 H, 2'-H), 1.52 (s, 9 H, ^{t}Bu-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 164.1 (C1), 139.0 (C2), 128.1 (C3), 81.9 (^{t}Bu-C), 30.0 (C2'), 28.1 (^{t}Bu-CH_3). 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. R_f: 0.29 (SiO_2, EtOAc:hexanes-1:2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 6.13 (m, 1 H, H-2'b), 5.58 (m, 1 H, H-2'a), 3.74 (t, $^3J_{1H\text{-}1H}$ 6.1 Hz, 2 H, H-4), 2.53 (td, $^3J_{1H\text{-}1H}$ 6.0 Hz, $^4J_{1H\text{-}1H}$ =0.8 Hz, 2 H, H-3), 2.27 (s_b, 1 H, OH), 1.49 (s, 9 H, ^{t}Bu-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 167.0 (C1), 139.3 (C2), 126.4 (C2'), 81.2 (^{t}Bu-C), 62.0 (C4), 35.8 (C3), 28.2 (^{t}Bu-CH_3). CHN: found (calcd) [%]: C 61.89 (62.77); H 9.34 (9.36). HRMS (ESI) [*m/z*]: calcd for $C_9H_{16}O_3$ $[M + Na]^+$: 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 CH_2Cl_2 (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**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.86 + 6.49 (dt, $^1J_{31P\text{-}1H}$ 547.3 Hz, $^3J_{1H\text{-}1H}$ 1.9 Hz, 1 H, P-H), 6.16 (d, ^2J 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, $^3J_{1H\text{-}1H}$ 6.5 Hz, 2 H, 3-H), 2.62-2.44 (m, 2 H, 6-H), 2.01 (dtd, J 15.2 Hz, J 7.3 Hz, J 2.0 Hz, 2 H, 5-H), 1.47 (s, 9 H, ^{t}Bu-H), 1.42 (s, 9 H, ^{t}Bu-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 137.4 (C2), 127.1 (C2'), 81.6 (^{t}Bu-C), 81.2 (^{t}Bu-C), 65.0 (C4, $^2J_{31P\text{-}13C}$ 6.8 Hz), 33.4 (C3, $^3J_{31P\text{-}13C}$ 6.2 Hz), 28.1 (^{t}Bu-CH_3), 27.2 (C6, $^2J_{31P\text{-}13C}$ 2.7 Hz), 24.6 + 23.7 (C5, $^1J_{31P\text{-}13C}$ 95.6 Hz), C1 and C7 not observed. ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 38.07. HRMS (ESI) [*m/z*]: calcd for $C_{16}H_{29}O_6P$ $[M + H]^+$: 349.1775, found: 349.1771; $[M + Na]^+$: 371.1594, found: 371.1594. Analytical data for **13**: R_f: 0.43 + 0.47

(SiO_2, EtOAc:MeOH-10:1). ^{1}H-NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 172.4 (C4, $^3J_{31P\text{-}13C}$ 16.2 Hz), 171.6 (C4, $^3J_{31P\text{-}13C}$ 12.7 Hz), 171.5 (C3', $^3J_{31P\text{-}13C}$ 15.6 Hz), 171.1 (C3', $^3J_{31P\text{-}13C}$ 14.8 Hz), 81.8 (^{t}Bu-C), 81.4 (^{t}Bu-C), 81.2 (^{t}Bu-C), 81.2 (^{t}Bu-C), 66.7 (C1, $^2J_{31P\text{-}13C}$ 5.9 Hz), 64.6 (C1, $^2J_{31P\text{-}13C}$ 6.2 Hz), 39.3 (C3, $^2J_{31P\text{-}13C}$ 4.4 Hz), 37.3 (C3, $^2J_{31P\text{-}13C}$ 5.9 Hz), 29.3 (C2, $^3J_{31P\text{-}13C}$ 4.4 Hz), 28.0 (^{t}Bu-CH_3), 27.9 (^{t}Bu-CH_3), 27.3 (C2', $^2J_{31P\text{-}13C}$ 2.9 Hz), 27.7 + 26.9 (C3'', $^1J_{31P\text{-}13C}$ 83.0 Hz), 26.7 (C2', $^2J_{31P\text{-}13C}$ 3.1 Hz), 24.6 + 23.6 (C1', $^1J_{31P\text{-}13C}$ 98.6 Hz), 21.4 + 20.5 (C1', $^1J_{31P\text{-}13C}$ 91.0 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 49.88 (diastereomer A) + 47.51 (diastereomer B) (integration: 2.2 : 1.0). HRMS (ESI) [*m/z*]: calcd for $C_{16}H_{29}O_6P$ $[M + Na]^+$: 371.1594, found: 371.1603. IR (film): ν [cm^{-1}] 3434.1 (w), 2977.0 (m), 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), 957.4 (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 CH_2Cl_2 (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**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.71 + 6.36 (d, $^1J_{31P\text{-}1H}$ 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, ^3J 7.9 Hz, 1 H, N-H), 5.04 (s, 2 H, CH_2-Ph), 4.35 (m, 1 H, 3'-H), 4.21-4.02 (m, 2 H, 1-H), 3.69 (s, 3 H, OCH_3), 2.59 (t, $^3J_{1H\text{-}1H}$ 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, ^{t}Bu H). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (^{t}Bu-C), 67.2 (CH_2-Ph), 65.0 (C1), 54.0 (C3'), 52.7 (OCH_3), 33.3 (C2, $^3J_{31P\text{-}13C}$ 6.1 Hz), 28.0 (^{t}Bu-CH_3), 24.0 (C2'), C1' not observed. ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 37.64. HRMS (ESI) [*m/z*]: calcd for $C_{22}H_{32}NO_8P$ $[M + H]^+$: 470.192, found: 470.202. Analytical data for **15**: R_f: 0.38 + 0.44 (SiO_2, EtOAc:MeOH-10:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.33-7.25 (m, 5 H, Ar-H), 6.07 (m, 1 H, N-H), 5.06 (s, 2 H, CH_2-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, OCH_3), 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, ^{t}Bu-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 172.5 (C4, $^3J_{31P\text{-}13C}$ 16.1 Hz), 172.0 (C4'), 156.1 (Cbz-COO), 136.2 (Ar-C), 128.7 + 128.4 + 128.3 (Ar-CH), 81.7 (^{t}Bu-C), 67.3 (CH_2-Ph), 66.7 (C1, $^2J_{31P\text{-}13C}$ 7.4 Hz), 64.7 (C1, $^2J_{31P\text{-}13C}$ 6.0 Hz), 54.1

(C3’, $^{3}J_{31P\text{-}13C}$ 16.9 Hz), 52.9 (OCH_3), 52.8 (OCH_3), 39.5 (C3, $^{2}J_{31P\text{-}13C}$ 4.0 Hz), 37.6 (C3, $^{2}J_{31P\text{-}13C}$ 5.8 Hz), 29.5 (C2, $^{3}J_{31P\text{-}13C}$ 4.0 Hz), 28.6 (C2, $^{3}J_{31P\text{-}13C}$ 6.5 Hz), 28.1 (^{t}Bu-CH_3), 28.5 + 27.7 (C3’’, $^{1}J_{31P\text{-}13C}$ 81.0 Hz), 27.9 + 27.0 (C3’’, $^{1}J_{31P\text{-}13C}$ 85.8 Hz), 25.7 + 24.8 (C1’, $^{1}J_{31P\text{-}13C}$ 92.4 Hz), 24.8 (C2’), 24.4 (C2’). ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 48.87 (diastereomer A) + 46.47 (diastereomer B) (integration: 2.3 : 1.0). HRMS (ESI) [*m/z*]**:** calcd for $C_{22}H_{32}NO_8P$ [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), 2974.8 (m), 1720.7 (s), 1535.2 (m), 1454.1 (m), 1392.8 (w), 1368.1 (m), 1251.4 (m), 1156.1 (m), 1103.3 (w), 1055.6 (m), 1028.4 (m), 983.3 (w), 958.2 (w), 906.4 (w), 872.5 (w), 831.5 (w), 740.6 (w), 698.7 (w).

4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylenebutanoic acid 18. 4-Hydroxy-2-methylenbutanoic acid (1.0 g, 8.6 mmol; 1 eq.) in CH_2Cl_2 (10 mL) was treated with imidazole (1.18 g, 17.2 mmol; 2 eq.) and cooled to 0 °C under nitrogen atmosphere. TBDPSCl (4.73 g, 17.2 mmol; 2eq.) 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 CH_2Cl_2. The combined organics were dried over Na_2SO_4, 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 CH_2Cl_2 were added. The phases were separated and the aqueous phase was extracted three times with each 20 mL CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica (CH_2Cl_2:MeOH-10:1) to give the title compound **18** as a colorless solid (2.54 g, 83%). mp 63 °C. R_f: 0.19 (SiO_2, CH_2Cl_2:MeOH-30:1). ^{1}H-NMR (400 MHz, DMSO-d_6): 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, $^{2}J_{\text{geminal}}$ 1.7 Hz, 1 H, 2’b-H), 5.65 (m, 1 H, 2’a-H), 3.74 (t $^{3}J_{1H\text{-}1H}$ 6.5 Hz, 2 H, 4-H), 2.50 (m, 2 H, 3-H), 0.97 (s, 9 H, ^{t}Bu-H). ^{13}C-NMR (100 MHz, DMSO-d_6): 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 (^{t}Bu-CH_3), 18.8 (^{t}Bu-C). CHN: found (calcd) [%]: C 70.91 (71.15); H 7.40 (7.39). HRMS (ESI) [*m/z*]: calcd for $C_{21}H_{26}O_3Si$ [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), 2617.3 (w), 1684.0 (s), 1623.6 (s), 1589.1 (w), 1471.9 (m), 1429.7 (s), 1381.9 8w), 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-methylenebutanoate 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 CH_2Cl_2 (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 CH_2Cl_2 was added drop wise. 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 (CH_2Cl_2) to give the title compound **20** as a colorless oil (696 mg, 84%). R_f: 0.72 (SiO_2, CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.66 (m, 4 H, Ar-H), 7.44-7.34 (m, 6 H, Ar-H), 6.25 (d, *J* 1.6 Hz, 1 H, 2’’b-H), 5.62 (d, *J* 1.2 Hz, 1 H, 2’’a-H), 4.89 (m, 1 H, 2’-H), 3.81 (t, *J* 6.4 Hz, 2 H, 4-H), 2.60 (t, *J* 6.3 Hz, 2 H, 3-H), 2.37 (m, 1 H, 3’a-H), 1.92 (m, 1 H, 6’a-H), 1.74 (m, 1 H, 5’a-H), 1.68 (t, *J* 4.5 Hz, 1 H, 4’-H), 1.30 (m, 1 H, 6’b-H), 1.19 (m, 1 H, 5’b-H), 1.04 (s, 9 H, ^{t}Bu-CH_3), 0.95 (dd, *J* 13.8 H, *J* 3.5 Hz, 1 H, 3b-H), 0.92 (s, 3 H, 8-H), 0.88 (s, 3 H, 8-H), 0.81 (s, 3 H, 1’’-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] 167.4 (C1), 138.0 (C2), 135.7 (Ar-CH), 134.0 (Ar-C), 129.7 (C9 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 (^{t}Bu-CH_3), 19.8 +19.0 (C8), 19.3 (^{t}Bu-C), 13.7 (C1’’). CHN: found (calcd) [%]: C 75.45 (75.87); H 8.63 (8.63). HRMS (ESI) [*m/z*]: calcd for $C_{31}H_{42}O_3Si$ [M + H]$^+$: 491.2976, found: 491.2985; [M + Na]$^+$: 513.2795, found: 513.2802. IR (Film): ν [cm^{-1}] 3071.3 (m), 3049.4 (w), 2956.6 (s), 2879.4 (s), 2858.0 (s), 2119.6 (w), 1715.3 (s), 1632.0 (w), 1589.6 (w), 1472.7 (m), 1454.0 (m), 1428.1 (s), 1390.3 (m), 1361.7 (m), 1337.9 (m), 1305.9 (m), 1265.0 (m), 1215.5 (m), 1157.1 (s), 1112.5 (s), 1048.0 (m), 1020.0 (m), 993.4 (m), 981.2 (w), 932.5 (m), 888.7 (w), 823.5 (m), 777.9 (w), 738.1 (s), 702.2 (s), 621.9 (w), 613.9 (m), 505.3 (s), 490.1 (m).

(*1R*,*2R*,*4S*)-1,7,7-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 H_2O (644 mg, 2.04 mmol; 2 eq.) was coevaporated three times with CH_2Cl_2, dissolved in THF (5 mL) and added to the reaction mixture drop wise. The solution was stirred for 5 h at 0 °C und nitrogen atmosphere. Aqueous saturated NH_4Cl solution (10 mL) was added and the mixture was extracted three times with each 20 mL EtOAc. The combined organics were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica (CH_2Cl_2:MeOH-20:1) to give the title compound **21** as a colorless oil (207 mg, 80%). R_f: 0.08 (SiO_2, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 6.26 (d, *J* 1.2 Hz, 1 H, 2’’b-H), 5.65 (d, *J* 0.9 Hz, 1 H, 2’’a-H), 4.92 (m, 1 H, 2’-H), 3.77 (t, *J* 6.1 Hz, 2 H, 4-H), 2.59 (t, *J* 6.1 Hz, 2 H, 3-H), 2.39 (m, 1 H, 3’a-H), 2.01 (s_{sb}, 1 H, OH), 1.95 (m, 1 H, 6’a-H), 1.76 (m, 1 H, 5’a-H), 1.70 (t, *J* 4.5 Hz, 1 H, 4’-H), 1.34 (m, 1 H, 6’b-H), 1.24 (m, 1 H, 4’b-H), 1.00 (dd, *J* 13.8 Hz, *J* 5.7 Hz, 1 H, 3b-H), 0.92 (s, 3 H, 8’-H), 0.88 (s, 3 H, 8’-H), 0.85 (s, 3 H, 1’’-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [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 $C_{15}H_{24}O_3$ [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 (m), 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).

(*2R*,*4S*)-(*1R*,*2R*,*4S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-((*S*)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)-1,2-oxaphosphinane-4-carboxylate 2-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 phosphinate **22**, which was dissolved in CH_2Cl_2 (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 **23** (18 mg, 20%) as a mixture of diastereoisomers. Analytical data for **22**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.78 + 6.43 (d, $^1J_{\text{31P-1H}}$ 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, CH_2-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, OCH_3), 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). ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] 37.65. MS (ESI) [*m/z*]: calcd for $C_{28}H_{40}NO_8P$ $[M + Na]^+$: 572.023, found: 572.238. Analytical data for **23**: R_f: 0.33 + 0.37 (SiO_2, EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.41-7.28 (m, 5 H, Ar-H), 5.66 (m, 1 H, N-H), 5.11 (m, 2 H, CH_2-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). ^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 172.4 (C4, $^3J_{\text{31P-13C}}$ 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 (CH_2-Ph), 66.7 (C1), 64.6 (C1), 54.1 (C3’), 52.9 + 52.9 + 52.8 (OCH_3), 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, $^3J_{\text{31P-13C}}$ 3.7 Hz), 29.5 (C2, $^3J_{\text{31P-13C}}$ 3.9 Hz), 28.6 (C2, $^3J_{\text{31P-13C}}$ 6.4 Hz), 28.5 (C11, $^3J_{\text{31P-13C}}$ 6.4 Hz), 28.3 + 27.7 (C3’’, $^1J_{\text{31P-13C}}$ 81.6 Hz), 28.2 + 27.7 (C3’’, $^1J_{\text{31P-13C}}$ 81.5 Hz), 28.3 (C8), 28.1 (C8), 27.7 + 27.1 (C3’’, $^1J_{\text{31P-13C}}$ 82.6 Hz), 27.3 (C9), 27.3 (C9), 25.5 + 24.9 (C1’, $^1J_{\text{31P-13C}}$ 94.2 Hz), 24.7 + 24.3 (C2’), 19.8 + 18.9 (C12), 13.7 + 13.7 + 13.6 (C10’’). ^{31}P-NMR (243 MHz, $CDCl_3$): δ [ppm] 49.09, 48.96, 46.40 (integration 1.0 : 1.0 : 4.4). MS (EI) [*m/z*]: 549 (12 %, $[M]^+$), 490 (27 %, $[M\text{-}COOMe]^+$), 442 (8 %, $[M\text{-}OBenzyl]^+$), 414 (21 %, $[M\text{-}Cbz]^+$), 396 (22 %, $[M\text{-}OBorneyl]^+$), 370 (15 %, $[C_{17}H_{25}NO_6P]^+$), 306 (54 %, $[M\text{-}Benzyl\text{-}OBorneyl{+}H]^+$), 146 (29 %, $[C_5H_7O_3P]^+$), 91 (100 %, $[Benzyl]^+$). HRMS (EI) [*m/z*]: calcd for $C_{28}H_{40}NO_8P$ $[M]^+$: 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 phosphinate **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 Et_2O three times (each 20 mL). The aqueous solution was evaporated to dryness to give the target compound **24** (50 mg, quant). ^{1}H-NMR (600 MHz, D_2O): 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_2O, Inverse gated coupling): δ [ppm] 181.9 (C7, $^{3}J_{31P\text{-}13C}$ 16.4 Hz), 170.9 (C1), 68.1 (C8), 52.7 (C2, $^{3}J_{31P\text{-}13C}$ 15.4 Hz), 52.7 (C2, $^{3}J_{31P\text{-}13C}$ 15.4 Hz), 34.0 (C6, $^{2}J_{31P\text{-}13C}$ 3.8 Hz), 28.9 (C9, $^{3}J_{31P\text{-}13C}$ 2.8 Hz), 28.9 (C9, $^{3}J_{31P\text{-}13C}$ 2.6 Hz), 28.8 + 28.2 (C5, $^{1}J_{31P\text{-}13C}$ 93.6 Hz), 24.9 + 24.2 (C4, $^{1}J_{31P\text{-}13C}$ 91.6 Hz), 24.8 + 24.2 (C4, $^{1}J_{31P\text{-}13C}$ 91.8 Hz), 22.3 (C3, $^{2}J_{31P\text{-}13C}$ 2.3 Hz), 22.3 (C3, $^{2}J_{31P\text{-}13C}$ 2.7 Hz). ^{31}P-NMR (162 MHz, D_2O): δ [ppm] 51.74. HRMS (ESI) [*m/z*]: calcd for $C_9H_{16}NO_6P$ [M - H]$^-$: 264.0642, found: 264.0631.

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