A Facile Synthesis of Chiral 4-(*tert*-Butylsulfinylamino)-2-oxophosphonates and Their Conversion into 5,5-Disubstituted 2-Benzylidene-3-oxopyrrolidines

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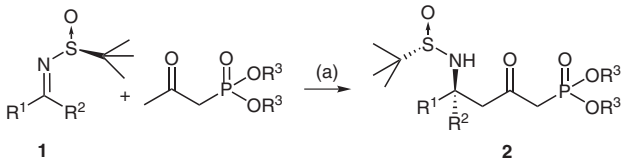
Abstract: The addition of the dianion derived from 2-oxophosphonates to chiral *N*-(*tert*-butylsulfinyl)ketimines or -aldimine under mild reaction conditions afforded 4-(*tert*-butylsulfinylamino)-2-oxoalkylphosphonates with good to excellent diastereoselectivity. The latter was then converted into an enantiopure 5,5-disubstituted 2-(dimethoxyphosphoryl)pyrrolidin-3-one via an intramolecular N–H insertion. Subsequent Horner–Wadsworth–Emmons reaction gave the corresponding 2-benzylidene derivatives.

Key words: chiral N-substituted 4-amino-2-oxophosphonates, *N*-sulfinylimines, asymmetric-induced addition, pyrrolidinone, intramolecular N–H insertion, Horner–Wadsworth–Emmons reaction

The synthesis of oxophosphonates bearing a chiral moiety has aroused significant interest in organic chemistry because of their wide use as building blocks for the construction of compounds with potential biological activity. One of their most important synthetic uses is their conversion to chiral enones via the Horner–Wadsworth–Emmons reaction. These optically active 2-oxophosphonates can also be transformed into enantiopure polyfunctionalized pyrrolidinones that are useful as chiral auxiliaries or ligands in asymmetric synthesis.[1] The classic synthetic routes leading to racemic 2-oxophosphonates are mainly based on the Michaelis–Arbuzov reaction and the acylation of alkylphosphonates.[2] A more convenient chemoenzymatic synthesis of chiral 4-hydroxy-2-oxoalkanephosphonates was reported by our group.[3] To the best of our knowledge, synthetic methods for chiral 4-amino-2-oxoalkanephosphonates are limited. Recently, Davis' group reported a highly stereoselective synthetic protocol based on intramolecular metal carbenoid N–H insertion from an *N*-(4-tolylsulfinyl)aldimine-derived 4-amino-1-diazo-2-oxoalkylphosphonate and subsequent conversion into ring-functionalized *cis*-2,5-disubstituted 3-oxopyrrolidines.[4] Davis' *N*-(4-tolylsulfinyl)imine (sulfinimine) has been shown to be an effective chiral auxiliary. However, the behavior of *N*-(*tert*-butylsulfinyl)aldimine or -ketimine (known as Ellman's sulfinimines) show more specific stereochemical reactivities due to the presence of a bulky *tert*-butyl group on the chiral center of the reagent. As we have previously shown,[5] Ellman's *N*-(sulfinyl)aldimines and/or -ketimines undergo smoothly nucleophilic addition with dialkyl phosphites at room temperature in the presence of potassium carbonate. Herein, we wish to report our synthetic approach to chiral 4-amino-2-oxophosphonates from enantiopure Ellman's *N*-(sulfinyl)imines via the nucleophilic addition of a dianion derived from oxophosphonate to the sp^2 carbon atom of the C=N linkage. The chemical transformations of these molecules are also examined. This study will provide information concerning the difference in chemical reactivity and diastereoselectivity between these two *N*-sulfinylimines. Very recently, as reported by Davis,[4d] the steric effects of substituents on the chiral center have been shown to have a significant effect on the stereochemical-directing behavior of such molecules. In addition, the use of functionalized nucleophiles with Ellman's reagent will broaden the scope of Ellman's *N*-(*tert*-butylsulfinyl)imine methodology.



R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 1-naphthyl, biphenyl-4-yl, Et, *n*-Bu, *t*-Bu, *n*-Hex
R^2 = H, Me; R^3 = Et, Me

Scheme 1 *Reaction conditions*: LiHMDS, THF, –78 °C.

As a new family of ligands for the asymmetric synthesis of amino compounds by nucleophilic 1,2-addition, Ellman's *N*-(sulfinyl)imines[6] are specific due to steric effects. By reacting commercially available (–)-(*S*)-*tert*-butanesulfinamide with various aldehyde and ketone, (–)-(*S*)-*N*-(*tert*-butylsulfinyl)aldimine **1a** and the corresponding ketimines **1b–k** were prepared in the presence of two equivalents of titanium(IV) ethoxide in good yield. Enantiopure 4-(*tert*-butylsulfinylamino)-2-oxophosphonates **2** resulted from treatment of the *N*-(*tert*-butylsulfinyl)aldimine or -ketimines with dimethyl 2-oxopropylphosphonates as the lithium salt, prepared by treatment with lithium hexamethyldisilazanide, in tetrahydrofuran at –78 °C (Scheme 1); the results are summarized in Table 1.

As shown in Table 1, both *N*-(*tert*-butylsulfinyl)aldimine **1a** and -ketimines **1b–k** gave fair chemical yields in their nucleophilic addition with lithium 2-oxoalkylphosphonates; however, ketimines provided excellent diastereo-

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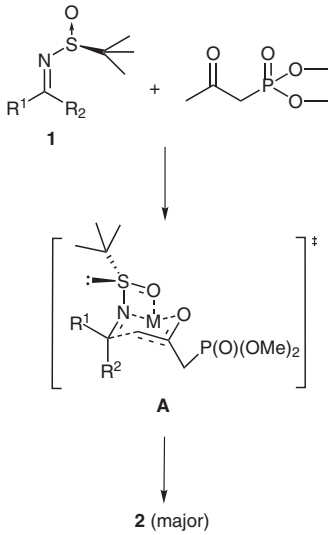
Table 1 Synthesis of 4-(*tert*-Butylsulfinylamino)-2-oxoalkylphosphonates

Entry	Substrate **1**			Product **2**				
		R^1	R^2		R^3	Yield[a] (%)	de[b] (%)
1	**1a**	Ph	H	**2a**	Me	85	52.7 (95[c])
2	**1b**	Ph	Me	**2b**	Me	82	>95
3	**1c**	4-MeC_6H_4	Me	**2c**	Me	81	>95
4	**1d**	4-FC_6H_4	Me	**2d**	Me	80	>95
5	**1e**	4-ClC_6H_4	Me	**2e**	Me	84	>95
6	**1f**	1-naphthyl	Me	**2f**	Me	81	>95
7	**1g**	biphenyl-4-yl	Me	**2g**	Me	79	>95
8	**1h**	Et	Me	**2h**	Me	80	69.8[d]
9	**1i**	Bu	Me	**2i**	Me	83	83.5[d]
10	**1j**	*t*-Bu	Me	**2j**	Me	82	>95
11	**1k**	$(CH_2)_5$Me	Me	**2k**	Me	84	>95

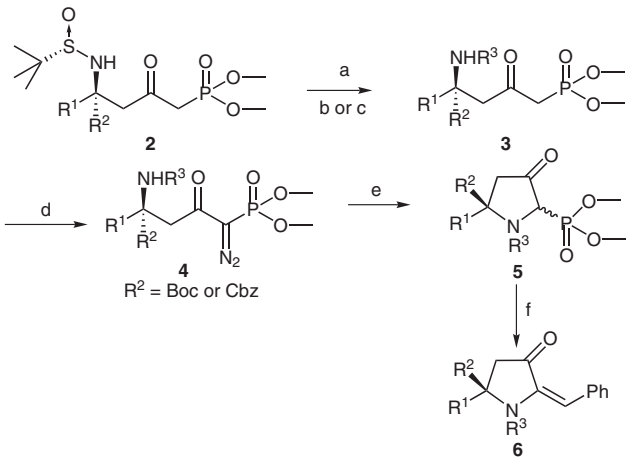
[a] Isolated yield of the diastereomeric mixture.
[b] Determined by ^{31}P NMR of the crude reaction mixture.
[c] The value after column chromatography.
[d] Two diasteromers were inseparable by column chromatography.

selectivity as represented by higher de values (Table 1, entries 2–7, 10, 11). Only one isomer could be detected in the ^{31}P NMR spectra of the crude reaction mixtures. Low de values for entries 8 and 9 in Table 1 might be associated with the presence of both *Z*- and *E*-isomers of **1h** and **1i**.[4d] It is also necessary to point out that during the course of our reaction, the sulfinylimine attacked at position 4 of the 2-oxoalkylphosphonate rather than position 2, which would be expected due to steric effects. The reaction probably underwent a suggested Zimmerman–Traxler-type six-membered transition state **A** (Scheme 2), the metal cation chelated to three heteroatoms at the same time, making the approach of the 2-oxophosphonate from the *re*-face of **1**.

Our unsuccessful attempts to convert *N*-(*tert*-butylsulfinylamino)-1-diazo-2-oxophosphonates into pyrrolidine derivatives could be rationalized by the presence of a strong electron-withdrawing oxygen atom on the sulfoxide and the bulky *tert*-butylsulfinyl group on the amino nitrogen. Based on this postulation, it is not surprised that upon reaction of 4-(benzyloxycarbonylamino- or 4-(*tert*-butoxycarbonylamino)-1-diazo-2-oxophosphonates **4** underwent intramolecular cyclization based on an N–H insertion reaction affording the corresponding 5-substituted 2-(dimethoxyphosphoryl)pyrrolidin-3-ones **5** in fair yield (Scheme 3). Subsequent Horner–Wadsworth–Emmons reaction of **5** with benzaldehyde gave the (*E*)-benzylidene derivatives **6** in the usual manner (Table 2).



Scheme 2



Scheme 3 *Reaction conditions*: (a) 4 M HCl in MeOH; (b) $(Boc)_2O$, Et_3N, DMAP, 0 °C, 5 h; (c) CbzCl, 5% aq $NaHCO_3$, 0 °C, 3 h; (d) K_2CO_3, TsN_3, Et_2O, r.t.; (e) 5 mol% $Rh_2(OAc)_4$, CH_2Cl_2, r.t.; (f) PhCHO, K_2CO_3, THF, H_2O, r.t.

Compounds **4c–g** were treated with dirhodium tetraacetate as catalyst in dichloromethane for 24 hours at room temperature to afford the corresponding 5-substituted 2-(dimethoxyphosphoryl)pyrrolidin-3-ones **5c–g**. However, **4h** gave **5h** in only very low yields under similar conditions; this might be associated with the steric hindrance of the bulky *tert*-butyl group. Enhancement of the reaction conditions including raising the reaction temperature and extending the reaction time only led to decomposition of the reaction mixture.

Compounds **5c–g** reacted smoothly with benzaldehyde in tetrahydrofuran–water solution in the presence of excess potassium carbonate at room temperature for about five hours to afford 2-benzylidenepyrrolidin-3-ones **6c–g** as expected in over 90% yield.

In summary, we have developed a new method for the asymmetric synthesis of chiral 4-amino-2-oxophosphonates by a highly diastereoselective addition of 2-oxo-

Table 2 Preparation of Substituted 2-Benzylidenepyrrolidinones **6**

Entry	R^1	R^2	R^3	**3–6**[a]	Yield[b] (%)			
					3	**4**	**5**	**6**
1	Ph	H	Boc	**a**	87	–	–	–
2	4-MeC_6H_4	Me	Cbz	**b**	83	86	64	–
3	4-MeC_6H_4	Me	Boc	**c**	81	85	61	91
4	Ph	Me	Boc	**d**	80	87	65	93
5	1-naphthyl	Me	Boc	**e**	78	84	74	89
6	biphenyl-4-yl	Me	Boc	**f**	75	84	71	91
7	$(CH_2)_5Me$	Me	Boc	**g**	85	86	77	92
8	*t*-Bu	Me	Boc	**h**	73	83	–[c]	–

[a] The absolute configuration of **3** was based on the comparison of the sign of its optical rotation with that reported in the literature.[4a]
[b] Isolated yield.
[c] Most of compound decomposed during the reaction.

phosphonate to enantiopure *N*-(*tert*-butylsulfinyl)ketimines. The products thus obtained serve as building blocks for the construction of 5-substituted 2-(dimethoxyphosphoryl)pyrrolidin-3-one by intramolecular cyclization based on an N–H insertion reaction. The resulting phosphorylpyrrolidinone was then transformed to the corresponding 2-benzylidenepyrrolidinones using Horner–Wadsworth–Emmons chemistry.

All solvents used were dried by standard procedures. IR spectra were taken on an Shimadzu IR 440 spectrophotometer, ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ (unless otherwise indicated), on an Avance 300 or a Mercury 300 spectrometer and ^{31}P NMR spectra were recorded at 120 MHz in $CDCl_3$ on a Varian EM 390 or a Bruker AM 300 spectrometer (external 85% H_3PO_4). EI-MS measurements were performed on a HP 5989A apparatus. HRMS data were recorded on a Finnigan MAT 8430 spectrometer. Elemental analyses were conducted on a Heraeus Rapid – CHNO apparatus. The optical rotatory value was taken on a Perkin Elmer 241MC polarimeter.

N-(*tert*-Butylsulfinyl)ketimines 1b–k; General Procedure

In a 20-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, was placed (–)-(*S*)-*tert*-butanesulfinamide (1.212 g, 10.0 mmol) in THF (5 mL), then the corresponding ketone (12 mmol) and $Ti(OEt)_4$ (4.565 g, 20 mmol) were added to the soln. The mixture was stirred at 60 °C for 6 h and then quenched with H_2O (5 mL). EtOAc (10 mL) was added to the mixture and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent and the residue was subjected to flash column chromatography (silica gel, petroleum ether–CH_2Cl_2, 2:1).

(*S*)-2-Methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide (1b)[6]

Colorless oil; yield: 85%.

^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 9 H), 2.77 (s, 3 H), 7.45 (m, 3 H), 7.89 (d, *J* = 7.5 Hz, 2 H).

(*S*)-2-Methyl-*N*-[1-(4-methylphenyl)ethylidene]propane-2-sulfinamide (1c)

Yellow solid; yield: 87%; mp 51–54 °C.

$[\alpha]_D^{20}$ –11.1 (*c* 1.0, $CHCl_3$).

IR (KBr): 2962, 1596, 1567, 1277, 1186, 1068, 823 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 9 H), 2.38 (s, 3 H), 2.73 (s, 3 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.1 Hz, 2 H).

MS (ESI): *m*/*z* = 238.1 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90. Found: C, 65.40; H, 8.24; N, 5.70.

(*S*)-*N*-[1-(4-Fluorophenyl)ethylidene]-2-methylpropane-2-sulfinamide (1d)

Colorless oil; yield: 83%.

$[\alpha]_D^{20}$ +4.5 (*c* 3.0, $CHCl_3$).

IR (KBr): 2963, 1687, 1581, 1267, 1068, 840 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 9 H), 2.73 (s, 3 H), 7.08 (t, *J* = 9.0 Hz, 2 H), 7.87 (t, *J* = 6.0 Hz, 2 H).

MS (ESI): *m*/*z* = 242.2 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{16}FNOS$: C, 59.72; H, 6.68; N, 5.80. Found: C, 59.37; H, 6.72; N, 5.49.

(*S*)-*N*-[1-(4-Chlorophenyl)ethylidene]-2-methylpropane-2-sulfinamide (1e)

Yellow solid; yield: 86%; mp 84–86 °C.

$[\alpha]_D^{20}$ –67.5 (*c* 0.5, $CHCl_3$).

IR (KBr): 2964, 1687, 1589, 1262, 1095, 1013, 832 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.26 (s, 9 H), 2.75 (s, 3 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 8.19 (d, *J* = 8.7 Hz, 2 H).

MS (ESI): *m*/*z* = 258.2 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{16}ClNOS$: C, 55.91; H, 6.26; N, 5.43. Found: C, 55.92; H, 6.22; N, 5.23,

(*S*)-2-Methyl-*N*-[1-(1-naphthyl)ethylidene]propane-2-sulfinamide (1f)

Yellow solid; yield: 88%; mp 120–122 °C.

$[\alpha]_D^{20}$ –16.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 2956, 1689, 1592, 1258, 1091,1019, 827 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 9 H), 2.89 (s, 3 H), 7.56 (m, 2 H), 7.84–8.06 (m, 5 H).

MS (ESI): *m*/*z* = 274.2 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12. Found: C, 70.18; H, 6.99; N, 4.79.

(*S*)-*N*-[1-(Biphenyl-4-yl)ethylidene]-2-methylpropane-2-sulfinamide (1g)

Yellow solid; yield: 83%; mp 138–140 °C.

$[\alpha]_D^{20}$ –89.01 (*c* 1.0, $CHCl_3$).

IR (KBr): 2978, 1591, 1364, 1087, 767 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 2.80 (s, 3 H), 7.26 (m, 3 H), 7.61 (m, 4 H), 7.96 (m, 2 H).

MS (ESI): *m*/*z* = 300.2 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 4.68; N, 7.07. Found: C, 72.21; H, 4.42; N, 6.99.

(*S*)-2-Methyl-*N*-(1-methylpropylidene)propane-2-sulfinamide (1h)[4e]

Colorless oil; yield: 74%.

^{1}H NMR ($CDCl_3$): δ = 0.63 (t, *J* = 7.8 Hz, 3 H), 0.76 (s, 9 H), 1.84 (s, 3 H), 1.96 (m, 2 H).

(*S*)-2-Methyl-*N*-(1-methylpentylidene)propane-2-sulfinamide (1i)[6]
Colorless oil, yield: 75%.

^{1}H NMR ($CDCl_3$): δ = 0.47 (m, 3 H), 0.78 (s, 9 H), 0.90 (m, 2 H), 1.13 (m, 2 H), 1.86 (s, 3 H), 1.95 (m, 2 H).

(*S*)-2-Methyl-*N*-(1,2,2-trimethylpropylidene)propane-2-sulfinamide (1j)[6]
Colorless oil, yield: 71%.

^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 9 H), 2.77 (s, 9 H), 2.81 (m, 3 H).

(*S*)-2-Methyl-*N*-(1-methylheptylidene)propane-2-sulfinamide (1k)
Colorless oil, yield: 71%.

$[\alpha]_D^{20}$ +138.7.

IR (KBr): 3240, 2930, 1713, 1592, 1365, 1035, 884, 586 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.21 (t, *J* = 6.9 Hz, 3 H), 0.56 (s, 9 H), 0.62 (m, 6 H), 0.90 (m, 2 H), 1.64 (s, 3 H), 1.72 (m, 2 H).

MS (ESI): *m*/*z* = 232.2 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{25}NOS$: C, 62.29; H, 10.89; N, 6.05. Found: C, 62.01; H, 10.90; N, 5.71.

4-(*tert*-Butylsulfinylamino)-2-oxoalkylphosphonates 2; General Procedure
In a 100-mL, 2-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed dimethyl 2-oxopropylphosphonate (10.0 mmol) in THF (20 mL). The mixture was then cooled to –40 to –20 °C, and followed by addition of 1 M LiHMDS in hexane (22 mL, 22 mmol) with a syringe. After 1 h, the mixture was cooled to –78 °C and the sulfinylamine **1** (3.0 mmol) in THF (2 mL) was added carefully over 10 min. The soln was stirred at –78 °C for an additional 2–5 h, the reaction was quenched by the addition of sat. aq NH_4Cl (10 mL) and warmed to r.t. The soln was diluted with H_2O (10 mL) and extracted with Et_2O (10 mL) and EtOAc (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated. For removal of unreacted dimethyl 2-oxopropylphosphonate, the residue was vacuum distilled (80 °C/2.7 mbar) and then subject to column chromatography (silica gel, acetone–EtOAc, 1:1).

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-phenyl-2-oxobutylphosphonate (2a)
Colorless oil; yield: 85%; 52.7% de.

$[\alpha]_D^{20}$ –58.9 (*c* 1.2, $CHCl_3$).

IR (KBr): 3450, 2979, 1720, 1504, 1254, 1057, 733 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 9 H), 2.85–3.25 (m, 4 H), 3.73 (m, 6 H), 4.45 (m, 1 H), 4.85 (s, 1 H), 7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 200.8, 155.8, 143.0, 132.8, 128.0, 127.5, 126.3, 123.7, 59.2, 53.3, 52.8, 41.4, 29.1 23.0.

^{31}P NMR ($CDCl_3$): δ = 22.44.

MS (ESI): *m*/*z* = 398.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{27}NO_5PS$: 376.1352; found: 376.1342.

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-phenyl-2-oxopentylphosphonate (2b)
Colorless oil; yield: 82%; >95% de.

$[\alpha]_D^{20}$ –29.7 (*c* 0.7, $CHCl_3$).

IR (KBr): 3473, 2960, 1710, 1255, 1036, 813, 702, 539 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 9 H), 1.57 (s, 3 H), 2.82–3.48 (m, 4 H), 3.60 (d, J_{HP} = 11.1 Hz, 3 H), 3.65 (d, J_{HP} = 11.1 Hz, 3 H), 5.15 (s, 1 H), 7.10–7.39 (m, 5 H).

^{31}P NMR ($CDCl_3$): δ = 22.04.

MS (ESI): *m*/*z* = 412.0 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{28}NO_5PS$: C, 52.43; H, 7.25; N, 3.60. Found: C, 52.19; H, 7.06; N, 3.30.

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-(4-methylphenyl)-2-oxopentylphosphonate (2c)
Colorless oil; yield: 81%; >95% de.

$[\alpha]_D^{20}$ –48.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 3473, 2960, 1710, 1255, 1036, 813, 702, 539 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 9 H), 1.62 (s, 3 H), 2.31 (s, 3 H), 2.90–3.41 (m, 4 H), 3.70 (d, J_{HP} = 11.4 Hz, 3 H), 3.76 (d, J_{HP} = 12.3 Hz, 3 H), 5.15 (s, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H).

^{31}P NMR ($CDCl_3$): δ = 22.71.

MS (ESI): *m*/*z* = 426.2 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{30}NO_5PS$: C, 53.58; H, 7.49; N, 3.47. Found: C, 53.11; H, 7.73; N, 3.22.

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-(4-fluorophenyl)-2-oxopentylphosphonate (2d)
Colorless oil; yield: 80%; >95% de.

$[\alpha]_D^{20}$ –26.7 (*c* 1.5, $CHCl_3$).

IR (KBr): 3473, 2960, 1710, 1255, 1036, 813, 702, 539 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 9 H), 1.62 (s, 3 H), 2.90–3.45 (m, 4 H), 3.69 (d, J_{HP} = 11.4 Hz, 3 H), 3.75 (d, J_{HP} = 11.1 Hz, 3 H), 5.17 (s, 1 H), 7.02 (m, 2 H), 7.41 (m, 2 H).

^{31}P NMR ($CDCl_3$): δ = 22.01.

MS (ESI): *m*/*z* = 430.2 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{27}FNO_5PS$: C, 50.11; H, 6.68; N, 3.44. Found: C, 49.95; H, 6.79; N, 3.30.

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-(4-chlorophenyl)-2-oxopentylphosphonate (2e)
Colorless oil; yield: 84%; >95% de.

$[\alpha]_D^{20}$ –41.1 (*c* 1.2, $CHCl_3$).

IR (KBr): 3466, 2960, 1710, 1255, 1031, 813, 539 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 9 H), 1.61 (s, 3 H), 2.92–3.43 (m, 4 H), 3.67 (d, J_{HP} = 11.1 Hz, 3 H), 3.74 (d, J_{HP} = 11.1 Hz, 3 H), 5.16 (s, 1 H), 7.01 (m, 2 H), 7.40 (m, 2 H).

^{31}P NMR ($CDCl_3$): δ = 21.98.

MS (ESI): *m*/*z* = 446.2 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{27}ClNO_5PS$: C, 48.17; H, 6.42; N, 3.30. Found: C, 48.39; H, 6.37; N, 3.07

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-(1-naphthyl)-2-oxopentylphosphonate (2f)
Colorless oil; yield: 81%; >95% de.

$[\alpha]_D^{20}$ –57.2 (*c* 0.4, $CHCl_3$).

IR (KBr): 3461, 2960, 1710, 1458, 1382, 1252, 1031, 821, 568 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.31 (s, 9 H), 1.79 (d, *J* = 28.8 Hz, 3 H), 2.93–3.50 (m, 4 H), 3.66 (d, J_{HP} = 11.1 Hz, 3 H), 3.74 (d, J_{HP} = 11.7 Hz, 3 H), 5.32 (s, 1 H), 7.46 (m, 2 H), 7.58 (m, 1 H), 7.83 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 201.2, 143.2, 133.2, 132.4, 128.3 (d, *J* = 38.4 Hz), 127.4, 126.1 (d, *J* = 44.1 Hz), 123.9 (d, *J* = 43.4 Hz), 59.3, 56.1, 53.2, 52.9, 43.2, 41.5, 29.1 22.9.

^{31}P NMR ($CDCl_3$): δ = 22.05.

MS (ESI): *m*/*z* = 462.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{21}H_{30}NO_5PS$: 462.1492; found: 462.1475.

Dimethyl (*S*)-4-(Biphenyl-4-yl)-4-[(*S*)-*tert*-butylsulfinylamino]-2-oxopentylphosphonate (2g)

Colorless oil; yield: 79%; >95% de.

$[\alpha]_D^{20}$ –61.4 (*c* 0.25, $CHCl_3$).

IR (KBr): 3442, 2961, 1710, 1488, 1348, 1250, 1039, 841, 768 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 9 H), 1.72 (d, *J* = 25.8 Hz, 3 H), 2.92–3.47 (m, 4 H), 3.69 (d, J_{HP} = 11.4 Hz, 3 H), 3.75 (d, J_{HP} = 11.4 Hz, 3 H), 5.23 (s, 1 H), 7.35 (m, 2 H), 7.42 (m, 2 H), 7.56 (m, 5 H).

^{31}P NMR ($CDCl_3$): δ = 22.08.

MS (ESI): *m*/*z* = 488.3 $[M + Na]^+$.

Anal. Calcd for $C_{23}H_{32}NO_5PS$: C, 59.34; H, 6.93; N, 3.01. Found: C, 59.63; H, 6.88; N, 2.58.

Dimethyl (*R*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-methyl-2-oxohexylphosphonate (2h)

Colorless oil; yield: 80%; 69.8% de.

$[\alpha]_D^{20}$ +25.9 (*c* 3.8, $CHCl_3$).

IR (KBr): 3436, 2966, 1710, 1459, 1248, 1036, 817 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.71 (t, 3 H), 1.04 (s, 9 H), 1.14 (s, 3 H), 1.52 (m, 2 H), 2.68–3.05 (m, 4 H), 3.60 (s, 3 H), 3.64 (s, 3 H), 4.52 (s, 1 H).

^{31}P NMR ($CDCl_3$): δ = 23.09.

MS (ESI): *m*/*z* = 364.2 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{28}NO_5PS$: C, 45.74; H, 8.27; N, 4.10. Found: C, 45.38; H, 8.29; N, 3.79.

Dimethyl (*R*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-methyl-2-oxooctylphosphonate (2i)

Colorless oil; yield: 83%; 83.5% de.

$[\alpha]_D^{20}$ +19.30 (*c* 1.5, $CHCl_3$).

IR (KBr): 3436, 2962, 1706, 1364, 1255, 1037 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.40 (m, 3 H), 0.70 (s, 9 H), 0.80 (s, 7 H), 1.25 (m, 2 H), 2.35–2.71 (m, 4 H), 3.62 (d, J_{HP} = 11.4 Hz, 6 H), 4.52 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 201.9, 132.5, 56.5, 55.6, 54.1, 53.0, 43.3, 41.6, 29.3, 25.7, 25.3, 22.7.

^{31}P NMR ($CDCl_3$): δ = 22.46.

MS (ESI): *m*/*z* = 392.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{32}NNaO_5PS$: 392.1650; found: 392.1631.

Dimethyl (*S*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4,5,5-trimethyl-2-oxohexylphosphonate (2j)

Colorless oil; yield: 82%; >95% de.

$[\alpha]_D^{20}$ +25.9 (*c* 3.8, $CHCl_3$).

IR (KBr): 3432, 2958, 1704, 1362, 1252, 1034, 815 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.94 (t, 9 H), 1.28 (s, 9 H), 1.43 (s, 3 H), 3.04–3.60 (m, 4 H), 3.76 (d, J_{HP} = 6.3 Hz, 3 H), 3.81 (d, J_{HP} = 6.3 Hz, 3 H), 5.36 (s, 1 H).

^{31}P NMR ($CDCl_3$): δ = 24.09.

MS (ESI): *m*/*z* = 392.2 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{32}NO_5PS$: C, 48.76; H, 8.74; N, 3.79. Found: C, 48.80; H, 8.79; N, 3.69.

Dimethyl (*R*)-4-[(*S*)-*tert*-Butylsulfinylamino]-4-methyl-2-oxodecylphosphonate (2k)

Colorless oil; yield: 84%; >95% de.

$[\alpha]_D^{20}$ +19.2 (*c* 1.1, $CHCl_3$).

IR (KBr): 3443, 2958, 1713, 1459, 1366, 1250, 1033, 819, 732 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.80 (m, 3 H), 1.12 (s, 9 H), 1.18–1.24 (m, 11 H), 1.55 (m, 2 H), 2.75–3.10 (m, 4 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 4.58 (s, 1 H).

^{31}P NMR ($CDCl_3$): δ = 23.20.

MS (ESI): *m*/*z* = 420.3 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{36}NO_5PS$: C, 51.37; H, 9.13; N, 3.52. Found: C, 51.37; H, 9.30; N, 3.40.

Synthesis of Boc- or Cbz-Protected 4-Amino-2-oxoalkylphosphonates 3; General Procedure

In a 20-mL, single-necked, round-bottom flask equipped with a magnetic stirrer bar was placed **2** (1.0 mmol) in MeOH (5 mL), then 4 M HCl (5 mL) was added to the soln. The mixture was stirred at r.t. and after 6 h concentrated under vacuum for an additional 0.5 h. CH_2Cl_2 (10 mL) was added to the flask, the soln was cooled to 0 °C in an ice bath, and Et_3N was added until the soln was pH 7. Then Et_3N (0.4 mL, 3 mmol), DMAP (0.0030 g), and $(Boc)_2O$ (0.3 g, 1.5 mmol) were added in sequence. The mixture was stirred at 0 °C for 3–6 h, and quenched by the addition of H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed and the residue was subjected to column chromatography (silica gel; petroleum ether–EtOAc, 1:1) For the synthesis of Cbz-protected 4-amino--2-oxoalkylphosphonates, Cbz-Cl (0.26 g, 1.5 mmol) was used and reaction was performed in aqueous soln using $NaHCO_3$ as a base.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-4-phenyl-2-oxobutylphosphonate (3a)

Colorless oil; yield: 87%.

$[\alpha]_D^{20}$ +11.4 (*c* 1.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9 H), 2.95–3.30 (m, 4 H), 3.69 (d, J_{HP} = 2.4 Hz, 3 H), 3.73 (d, J_{HP} = 3.0 Hz, 3 H), 5.10 (m, 1 H), 5.50 (m, 1 H), 7.31 (m, 5 H).

Dimethyl (*S*)-4-(Benzyloxycarbonylamino)-4-(4-methylphenyl)-2-oxopentylphosphonate (3b)

Colorless oil; yield: 83%.

$[\alpha]_D^{20}$ +17.2 (*c* 0.25, $CHCl_3$).

IR (KBr): 3286, 2956, 1721, 1255, 1031, 817, 733 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.75 (s, 3 H), 2.29 (s, 3 H), 2.82–3.19 (m, 4 H), 3.67 (d, J_{HP} = 4.2 Hz, 3 H), 3.71 (d, J_{HP} = 4.5 Hz, 3 H), 5.01 (s, 2 H), 6.00 (s, 1 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.30 (s, 5 H).

^{31}P NMR ($CDCl_3$): δ = 22.83.

MS (ESI): *m*/*z* = 456.2 $[M + Na]^+$.

Anal. Calcd for $C_{22}H_{28}NO_6P$: C, 60.96; H, 6.51; N, 3.23. Found: C, 60.70; H, 6.45; N, 3.01.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-4-(4-methylphenyl)-2-oxopentylphosphonate (3c)
Colorless oil; yield: 81%.

$[\alpha]_D^{20}$ +28.7 (*c* 1.1, $CHCl_3$).

IR (KBr): 2982, 1717, 1255, 1170, 1033, 817 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 (s, 9 H), 1.65 (s, 3 H), 2.24 (s, 3 H), 2.78–3.06 (m, 4 H), 3.64 (d, J_{HP} = 3.9 Hz, 3 H), 3.68 (d, J_{HP} = 3.9 Hz, 3 H), 5.48 (s, 1 H), 7.05 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 200.8, 154.6, 136.5, 129.2, 124.6, 56.5, 53.0 (dd, *J* = 10.2 Hz), 52.9, 43.6, 41.9, 29.3, 27.8, 20.9.

^{31}P NMR ($CDCl_3$): δ = 22.41.

MS (ESI): *m*/*z* = 422.3 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{30}NO_6P$: C, 57.13; H, 7.57; N, 3.51. Found: C, 56.67; H, 7.33; N, 3.04.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-4-phenyl-2-oxopentylphosphonate (3d)
Colorless oil; yield: 80%.

$[\alpha]_D^{20}$ +21.4 (*c* 1.0, $CHCl_3$).

IR (KBr): 2979, 1716, 1253, 1170, 1031, 759 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 (s, 9 H), 1.68 (s, 3 H), 2.78–3.08 (m, 4 H), 3.64 (d, J_{HP} = 5.7 Hz, 3 H), 3.68 (d, J_{HP} = 5.4 Hz, 3 H), 5.51 (s, 1 H), 7.28 (m, 5 H).

^{31}P NMR ($CDCl_3$): δ = 23.74.

MS (ESI): *m*/*z* = 408.1 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.63. Found: C, 55.94; H, 7.69; N, 3.31.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-4-(1-naphthyl)-2-oxopentylphosphonate (3e)
Colorless oil; yield: 78%.

$[\alpha]_D^{20}$ +22.5 (*c* 2.8, $CHCl_3$).

IR (KBr): 3293, 2978, 1716, 1253, 1171, 1033, 818 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.38 (s, 9 H), 1.83 (s, 3 H), 2.88–3.29 (m, 4 H), 3.68 (d, J_{HP} = 7.5 Hz, 3 H), 3.72 (d, J_{HP} = 7.8 Hz, 3 H), 5.73 (s, 1 H), 7.50 (m, 3 H), 7.79 (m, 4 H).

^{31}P NMR ($CDCl_3$): δ = 22.26.

MS (ESI): *m*/*z* = 458.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{30}NNaO_6P$: 458.1717; found: 458.1703.

Dimethyl (*S*)-4-(Biphenyl-4-yl)-4-(*tert*-butoxycarbonylamino)-2-oxopentylphosphonate (3f)
Colorless oil; yield: 75%.

$[\alpha]_D^{20}$ +18.5 (*c* 0.2, $CHCl_3$).

IR (KBr): 3416, 2979, 1718, 1254, 1170, 1033, 766 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.39 (s, 9 H), 1.78 (s, 3 H), 2.91–3.20 (m, 4 H), 3.72 (d, J_{HP} = 5.4 Hz, 3 H), 3.76 (d, J_{HP} = 5.7 Hz, 3 H), 5.63 (s, 1 H), 7.43 (m, 5 H), 7.58 (m, 4 H).

^{31}P NMR ($CDCl_3$): δ = 22.28.

MS (ESI): *m*/*z* = 484.3 $[M + Na]^+$.

Anal. Calcd for $C_{24}H_{32}NO_6P$: C, 62.46; H, 6.99; N, 3.04. Found: C, 62.14; H, 7.31; N, 3.27.

Dimethyl (*R*)-4-(*tert*-Butoxycarbonylamino)-4-methyl-2-oxodecylphosphonate (3g)
Colorless oil; yield: 85%.

$[\alpha]_D^{20}$ +7.6 (*c* 1.5, $CHCl_3$).

IR (KBr): 3318, 2931, 1716, 1253, 1172, 1034, 755 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.28 (m, 11 H), 1.42 (s, 9 H), 1.57 (m, 2 H), 2.89–3.16 (m, 4 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.75 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 200.9, 154.8, 53.9, 52.9 (d, *J* = 19.8 Hz), 50.9, 43.4, 41.6, 39.3, 29.4, 28.4, 24.7, 23.3, 22.5, 14.0.

^{31}P NMR ($CDCl_3$): δ = 22.88.

MS (ESI): *m*/*z* = 416.3 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{36}NO_6P$: C, 54.95; H, 9.22; N, 3.56. Found: C, 54.38; H, 8.86; N, 3.40.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-4,5,5-trimethyl-2-oxohexylphosphonate (3h)
Colorless oil; yield: 73%.

$[\alpha]_D^{20}$ +34.4 (*c* 0.65, $CHCl_3$).

IR (KBr): 3419, 2978, 1716, 1252, 1171, 1031, 701 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (s, 9 H), 1.21 (s, 9 H), 1.36 (s, 3 H), 2.66 (d, *J* = 16.2 Hz, 1 H), 3.05 (m, 1 H), 3.17 (d, *J* = 16.5 Hz, 1 H), 3.47 (m, 1 H), 3.69 (d, J_{HP} = 6.0 Hz, 3 H), 3.73 (d, J_{HP} = 6.6 Hz, 3 H), 5.29 (s, 1 H).

^{31}P NMR ($CDCl_3$): δ = 22.78.

MS (ESI): *m*/*z* = 388.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{32}NNaO_6P$: 388.1578; found: 388.1577.

Boc-Protected 4-Amino-1-diazo-2-oxoalkylphosphonates 4; General Procedure
In a 20-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar was placed **3** (1 mmol) and TsN_3 (0.23 g, 1.2 mmol) in Et_2O (10 mL), K_2CO_3 (0.63 g, 4 mmol) was added. After stirring at r.t. for 3 h, the mixture was quenched by addition of sat. aq NH_4Cl (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (5 mL) and dried (Na_2SO_4). The solvent was then remove under diminished pressure, the residue thus obtained was subject to column chromatography (silica gel, petroleum ether–EtOAc, 3:1).

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-1-diazo-4-(4-methylphenyl)-2-oxopentylphosphonate (4c)
Colorless oil; yield: 85%.

$[\alpha]_D^{20}$ +40.0 (*c* 0.5, $CHCl_3$).

IR (KBr): 3379, 2979, 2123, 1716, 1272, 1165, 1025, 837 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.28 (s, 9 H), 1.79 (s, 3 H), 2.30 (s, 3 H), 2.96 (d, *J* = 15.6 Hz, 1 H), 3.25 (d, *J* = 15.3 Hz, 1 H), 3.73 (d, J_{HP} = 4.8 Hz, 3 H), 3.77 (d, J_{HP} = 4.8 Hz, 3 H), 6.13 (s, 1 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H).

^{31}P NMR ($CDCl_3$): δ = 13.77.

MS (ESI): *m*/*z* = 448.3 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{28}N_3O_6P$: C, 53.64; H, 6.63; N, 9.88. Found: C, 53.33; H, 6.60; N, 9.52.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-1-diazo-4-phenyl-2-oxopentylphosphonate (4d)
Colorless oil; yield: 87%.

$[\alpha]_D^{20}$ +15.1 (*c* 0.75, $CHCl_3$).

IR (KBr): 3381, 2979, 2123, 1717, 1270, 1167, 1029, 733 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 9 H), 1.74 (s, 3 H), 2.90 (d, *J* = 15.3 Hz, 1 H), 3.18 (d, *J* = 15.3 Hz, 1 H), 3.63 (d, J_{HP} = 4.5 Hz, 3 H), 3.67 (d, J_{HP} = 5.1 Hz, 3 H), 6.18 (s, 1 H), 7.25 (m, 5 H).

^{31}P NMR ($CDCl_3$): δ = 15.10.

MS (ESI): *m*/*z* = 434.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + K]^+$ calcd for $C_{18}H_{26}KN_3O_6P$: 450.1200; found: 450.1191.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-1-diazo-4-(1-naphthyl)-2-oxopentylphosphonate (4e)
Colorless oil; yield: 84%.

$[\alpha]_D^{20}$ +39.1 (*c* 2.8, $CHCl_3$).

IR (KBr): 3389, 2872, 2123, 1716, 1272, 1171, 1030, 839 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 9 H), 1.93 (s, 3 H), 3.02 (d, *J* = 15.3 Hz, 1 H), 3.40 (d, *J* = 13.8 Hz, 1 H), 3.64 (d, J_{HP} = 5.4 Hz, 3 H), 3.68 (d, J_{HP} = 5.1 Hz, 3 H), 6.35 (s, 1 H), 7.48 (m, 3 H), 7.79 (m, 4 H).

^{31}P NMR ($CDCl_3$): δ = 13.57.

MS (ESI): *m*/*z* = 484.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{28}N_3NaO_6P$: 484.1619; found: 484.1608.

Dimethyl (*S*)-(4-Biphenyl-4-yl)-4-(*tert*-butoxycarbonylamino)-1-diazo-2-oxopentylphosphonate (4f)
Colorless oil; yield: 84%.

$[\alpha]_D^{20}$ +15.3 (*c* 0.2, $CHCl_3$).

IR (KBr): 3384, 2978, 2123, 1716, 1271, 1170, 1029, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 9 H), 1.85 (s, 3 H), 3.00 (d, *J* = 15.3 Hz, 1 H), 3.31 (d, *J* = 15.6 Hz, 1 H), 3.73 (d, J_{HP} = 1.2 Hz, 3 H), 3.77 (d, J_{HP} = 1.8 Hz, 3 H), 6.24 (s, 1 H), 7.42 (m, 5 H), 7.56 (m, 4 H).

^{31}P NMR ($CDCl_3$): δ = 13.65.

MS (ESI): *m*/*z* = 510.3 $[M + Na]^+$.

Anal. Calcd for $C_{24}H_{30}N_3O_6P$: C, 59.13; H, 6.20; N, 8.62. Found: C, 59.28; H, 6.48; N, 8.26.

Dimethyl (*R*)-4-(*tert*-Butoxycarbonylamino)-1-diazo-4-methyl-2-oxodecylphosphonate (4g)
Colorless oil; yield: 86%.

$[\alpha]_D^{20}$ +1.42 (*c* 1.0, $CHCl_3$).

IR (KBr): 3322, 2932, 2123, 1713, 1270, 1171, 1029, 838 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.80 (t, *J* = 6.6 Hz, 3 H), 1.20 (s, 8 H), 1.27 (s, 3 H), 1.35 (s, 9 H), 1.73 (m, 2 H), 2.75 (d, *J* = 15.3 Hz, 1 H), 2.96 (d, *J* = 15.3 Hz, 1 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.87 (s, 1 H).

^{31}P NMR ($CDCl_3$): δ = 14.34.

MS (ESI): *m*/*z* = 442.3 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{34}N_3O_6P$: C, 51.54; H, 8.17; N, 10.02. Found: C, 51.66; H, 8.38; N, 9.82.

Dimethyl (*S*)-4-(*tert*-Butoxycarbonylamino)-1-diazo-4,5,5-trimethyl-2-oxohexylphosphonate (4h)
Colorless oil; yield: 83%.

$[\alpha]_D^{20}$ +0.08 (*c* 0.5, $CHCl_3$).

IR (KBr): 3326, 2966, 2123, 1715, 1267, 1165, 1027, 840, 587 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.95 (s, 9 H), 1.39 (s, 9 H), 1.43 (s, 3 H), 2.41 (d, *J* = 16.2 Hz, 1 H), 3.55 (d, *J* = 16.5 Hz, 1 H), 3.81 (d, J_{HP} = 3.9 Hz, 3 H), 3.85 (d, J_{HP} = 4.5 Hz, 3 H), 6.28 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 189.0, 167.6, 129.8, 126.5, 116.6 (d, *J* = 40.2 Hz), 53.5, 40.1, 28.8 (d, *J* = 42.0 Hz), 25.7, 21.5, 16.1.

^{31}P NMR ($CDCl_3$): δ = 15.41.

MS (ESI): *m*/*z* = 414.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{30}N_3NaO_6PS$: 414.1779; found: 414.1765.

5-Substituted 2-(Dimethoxyphosphoryl)pyrrolidin-3-ones 5; General Procedure
In a 50-mL round-bottom flask equipped with a magnetic stirring bar and an argon balloon was placed diazophosphonate **4** (1.0 mmol) and $Rh_2(OAc)_4$ (0.020 g, 5 mol%) in CH_2Cl_2 (40 mL). The mixture was stirred at r.t. for 24 h. Then the soln mixture was washed with H_2O (2 × 10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed and residue was subjected to column chromatography (silica gel, petroleum ether–EtOAc, 3:1).

(5*S*)-1-(Benzyloxycarbonyl)-2-(dimethoxyphosphoryl)-5-methyl-5-(4-tolyl)pyrrolidin-3-one (5b)
Colorless oil; yield: 64%.

IR (KBr): 2959, 1702, 1345, 1255, 1048, 820, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 1.5 H), 2.08 (s, 1.5 H), 2.30 (d, *J* = 9.0 Hz, 3 H), 2.70–3.20 (m, 2 H), 3.78 (m, 6 H), 4.66 (d, *J* = 16.5 Hz, 1 H), 4.87 (s, 2 H), 6.81–7.52 (m, 9 H).

^{31}P NMR ($CDCl_3$): δ = 17.59.

MS (ESI): *m*/*z* = 454.2 $[M + Na]^+$.

Anal. Calcd for $C_{22}H_{26}NO_6P$: C, 61.25; H, 6.07; N, 3.25. Found: C, 61.46; H, 6.44; N 2.92.

(5*S*)-1-(*tert*-Butoxycarbonyl)-2-(dimethoxyphosphoryl)-5-methyl-5-(4-tolyl)pyrrolidin-3-one (5c)
Colorless oil; yield: 61%.

$[\alpha]_D^{20}$ +28.1 (*c* 0.5, $CHCl_3$).

IR (KBr): 2977, 1763, 1694, 1367, 1255, 1162, 1037, 819 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 9 H), 1.67 (s, 1.5 H), 2.01 (s, 1.5 H), 2.25 (d, *J* = 7.8 Hz, 3 H), 3.05–3.40 (m, 2 H), 3.76 (d, J_{HP} = 3.0 Hz, 3 H), 3.79 (d, J_{HP} = 3.3 Hz, 3 H), 4.55 (d, *J* = 16.5 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 7.2 Hz, 2 H).

^{31}P NMR ($CDCl_3$): δ = 17.50.

MS (ESI): *m*/*z* = 420.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{28}NNaO_6P$: 420.1560; found: 420.1546.

(5*S*)-1-(*tert*-Butoxycarbonyl)-2-(dimethoxyphosphoryl)-5-methyl-5-phenylpyrrolidin-3-one (5d)
Colorless oil; yield: 65%.

$[\alpha]_D^{20}$ +14.1 (*c* 0.75 $CHCl_3$).

IR (KBr): 2977, 1697, 1367, 1254, 1162, 1037, 820 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 9 H), 1.75 (s, 3 H), 2.86–3.18 (m, 2 H), 3.64 (d, J_{HP} = 4.5 Hz, 3 H), 3.69 (d, J_{HP} = 4.8 Hz, 3 H), 4.05 (m, 1 H), 7.28 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 200.7, 154.9, 128.5, 126.9, 124.8, 57.4, 56.7, 53.0 (d, *J* = 26.1 Hz), 43.6, 42.0, 28.3, 27.8.

^{31}P NMR ($CDCl_3$): δ = 18.09.

MS (ESI): *m*/*z* = 406.1 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{26}NNaO_6P$: 406.1406; found: 406.1390.

(5*S*)-1-(*tert*-Butoxycarbonyl)-2-(dimethoxyphosphoryl)-5-methyl-5-(1-naphthyl)pyrrolidin-3-one (5e)
Colorless oil; yield: 74%.

$[\alpha]_D^{20}$ +20.4 (*c* 0.5, $CHCl_3$).

IR (KBr): 2977, 1763, 1697, 1367, 1161, 1040, 826 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.82 (s, 9 H), 2.15 (s, 3 H), 2.65 (m, 2 H), 3.79 (d, J_{HP} = 2.4 Hz, 3 H), 3.82 (d, J_{HP} = 2.1 Hz, 3 H), 5.21 (s, 1 H), 7.40 (m, 3 H), 7.73 (m, 4 H).

^{31}P NMR ($CDCl_3$): δ = 17.35.

MS (ESI): *m*/*z* = 456.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{28}NNaO_6P$: 456.1562; found: 456.1546.

Anal. Calcd for $C_{22}H_{28}NO_6P$: C, 60.96; H, 6.51; N, 3.23. Found: C, 60.65; H, 6.77; N, 2.88.

(5*S*)-5-(Biphenyl-4-yl)-1-(*tert*-butoxycarbonyl)-2-(dimethoxyphosphoryl)-5-methylpyrrolidin-3-one (5f)
Colorless oil; yield: 71%.

$[\alpha]_D^{20}$ +42.5 (*c* 0.5, $CHCl_3$).

IR (KBr): 2977, 1764, 1699, 1367, 1160, 1033, 769 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.10 (s, 9 H), 1.80 (s, 3 H), 2.65 (m, 1 H), 3.25 (m, 1 H), 3.85 (d, J_{HP} = 3.3 Hz, 3 H), 3.89 (d, J_{HP} = 3.3 Hz, 3 H), 4.63 (s, 1 H), 7.43 (m, 4 H), 7.59 (m, 5 H).

^{31}P NMR ($CDCl_3$): δ = 17.49.

MS (ESI): *m*/*z* = 482.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{30}NNaO_6P$: 482.1716; found: 482.1703

(5*R*)-1-(*tert*-Butoxycarbonyl)-2-(dimethoxyphosphoryl)-5-hexyl-5-methylpyrrolidin-3-one (5g)
Colorless oil; yield: 77%.

$[\alpha]_D^{20}$ +3.7 (*c* 0.5, $CHCl_3$).

IR (KBr): 2931, 1764, 1705, 1252, 1165, 1034, 817 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80 (m, 3 H), 1.23 (m, 9 H), 1.42 (s, 9 H), 1.57 (m, 2 H), 2.30 (m, 2 H), 2.89 (m, 2 H), 3.72 (m, 6 H), 4.45 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 200.5, 154.3, 128.8, 127.0, 125.0, 53.7, 31.4, 27.9, 23.1.

^{31}P NMR ($CDCl_3$): δ = 17.66.

MS (ESI): *m*/*z* = 414.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{34}NNaO_6P$: 414.2034; found: 414.2016.

5-Substituted 2-Benzylidenepyrrolidin-3-ones 6; General Procedure
A soln of **5** (0.5 mmol), K_2CO_3 (0.2 g, 1.5 mmol), THF (2 mL), H_2O (2 mL), and benzaldehyde (1 mmol) was stirred for 2.5 h. Then brine (5 mL) was added to the mixture followed by extraction with EtOAc (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4). After removal of the solvent, the residue was subjected to column chromatography (silica gel, petroleum ether–CH_2Cl_2, 3:2).

(5*S*)-2-Benzylidene-1-(*tert*-butoxycarbonyl)-5-methyl-5-(4-tolyl)pyrrolidin-3-one (6c)
Colorless oil; yield: 91%.

$[\alpha]_D^{20}$ –2.1 (*c* 0.7, $CHCl_3$).

IR (KBr): 2933, 1762, 1702, 1251, 1170, 1029, 815 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.17 (s, 9 H), 1.93 (s, 3 H), 2.34 (s, 3 H), 2.76 (m, 2 H), 7.16 (d, *J* = 6.9 Hz, 2 H), 7.24 (m, 5 H), 7.54 (d, *J* = 6.9 Hz, 2 H), 7.80 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 196.8, 152.6, 144.2, 136.5, 134.7, 130.0, 129.2, 127.7, 127.6, 124.4, 121.3, 81.7, 62.9, 54.9, 27.9, 25.9, 21.0.

MS (ESI): *m*/*z* = 400.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{27}NNaO_3$: 400.1893; found: 400.1883.

(5*S*)-2-Benzylidene-1-(*tert*-butoxycarbonyl)-5-methyl-5-phenylpyrrolidin-3-one (6d)
Yellow solid; yield: 93%; mp 103–105 °C.

$[\alpha]_D^{20}$ –1.5 (*c* 0.7, $CHCl_3$).

IR (KBr): 2982, 1738, 1697, 1333, 1155, 816, 692 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.15 (s, 9 H), 1.96 (s, 3 H), 2.78 (m, 2 H), 7.36 (m, 10 H), 7.82 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 196.8, 152.4, 144.0, 136.3, 134.5, 130.0, 129.1, 127.2, 127.3, 124.2, 121.1, 81.5, 62.9, 54.7, 27.9, 21.1.

MS (ESI): *m*/*z* = 386.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{25}NNaO_3$: 386.1739; found: 386.1727.

(5*S*)-2-Benzylidene-1-(*tert*-butoxycarbonyl)-5-methyl-5-(1-naphthyl)pyrrolidin-3-one (6e)
Yellow solid; yield: 89%; mp 136–139 °C.

$[\alpha]_D^{20}$ –32.2 (*c* 0.2, $CHCl_3$).

IR (KBr): 3058, 1734, 1689, 1338, 1153, 821, 757 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.05 (s, 9 H), 2.07 (s, 3 H), 2.85 (m, 2 H), 7.30 (m, 3 H), 7.51 (m, 5 H), 7.84 (m, 4 H), 7.88 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 196.5, 144.2, 134.6, 133.4, 133.1, 132.2, 130.0, 128.8, 127.9, 127.8, 127.7, 127.6, 126.5, 126.0, 123.0, 122.8, 121.8, 81.8, 63.2, 54.6, 27.8, 25.7.

MS (ESI): *m*/*z* = 436.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{27}NNaO_3$: 436.1886; found: 436.1883.

(5*S*)-2-Benzylidene-5-(biphenyl-4-yl)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-3-one (6f)
Yellow solid; yield: 91%; mp 164–166 °C.

$[\alpha]_D^{20}$ –17.7 (*c* 0.2, $CHCl_3$).

IR (KBr): 2976, 1733, 1691, 1375, 1173, 773, 690 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.11 (s, 9 H), 1.92 (s, 3 H), 2.74 (m, 2 H), 7.19–7.54 (m, 14 H), 7.76 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 196.5, 146.2, 140.5, 139.8, 134.6, 130.0, 128.9, 127.8, 127.6, 127.4, 127.2, 127.0, 124.9, 121.6, 81.9, 63.0, 54.8, 28.0, 25.8 .

MS (ESI): *m*/*z* = 462.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{29}NNaO_3$: 462.2037; found: 462.2039.

(5*R*)-2-Benzylidene-1-(*tert*-butoxycarbonyl)-5-hexyl-5-methylpyrrolidin-3-one (6g)
Colorless oil: yield: 92%.

$[\alpha]_D^{20}$ –11.4 (*c* 1.5, $CHCl_3$).

IR (KBr): 2931, 1738, 1699, 1379, 1159, 857, 765, 693 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (m, 3 H), 1.28 (m, 8 H), 1.56 (s, 3 H), 1.58 (s, 9 H), 1.61 (m, 1 H), 2.15 (m, 1 H), 2.51 (m, 2 H), 7.29–7.44 (m, 5 H), 7.59 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 197.3, 129.8, 127.6, 127.5, 121.2, 81.8, 61.7, 49.5, 39.9, 31.7, 29.5, 28.5, 27.8, 23.9, 22.6, 14.1.

MS (ESI): *m*/*z* = 394.3 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{33}NNaO_3$: 394.2362; found: 394.2352.

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