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Synthesis of both R_P and S_P enantiomers of unsymmetrical methylphosphonates based on a new approach utilizing a P-ester bond with α-hydroxyacids

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Abstract—Condensation of methyl methylphosphonochloridate with the dilithium salt of 2-methyllactic acid gave P-racemic methylphosphonates which unexpectedly contained two units of α-hydroxyacid linked via carboxylic ester bond. The racemic mixture was chromatographically separated via diastereomeric salts with quinine or cinchonine to give, based on the X-ray analysis, pure (R_P)-(+) and (S_P)-(−) enantiomers. Both enantiomers were immobilized on the ArgoGel®–OH solid support. Condensation of methyl methylphosphonochloridate with α-hydroxyacid methyl esters [2-methyllactate, (S_C)-(−)-lactate, methyl (S_C)-(+) and (R_C)-(−)-mandelates] gave chromatographically inseparable 1:1 mixtures of diastereomers in 63–69% yields. A basic hydrolysis of the latter resulted in a selective and unexpected cleavage of the P–OMe group in a quantitative yield [(S_C)-(+) and (R_C)-(−)-mandelates, (S_C)-(−)-lactate] or simultaneous cleavages of P–OMe and C(O)OMe groups (2-methyllactate).

1. Introduction

The aim of this work was the synthesis of P-chiral enantiomerically pure methylphosphonates of type **I** as potential reagents for asymmetric synthesis and combinatorial chemistry, fulfilling the following requirements: (1) cheap and commercially available substrates, (2) an easy access to both R_P and S_P enantiomers and (3) a possibility of immobilization on a solid support (Fig. 1).

Methylphosphonates as key starting reagents for synthesis of higher functionalized analogues have found various applications, of which those in synthesis of natural and biologically active compounds are the most interesting.[1,2] The phosphonates used in such syntheses were P-racemic. Hitherto, the phosphonoester bond has never been used for the resolution of racemic phosphonates. Instead, this bond was utilized to bind phosphonates with a polymer support for synthetic and combinatorial chemistry. Thus, Mjalli et al. condensed the Wang® resin bound H-phosphonates with aldehydes[3] and imines[4] to form α-hydroxyphospho-

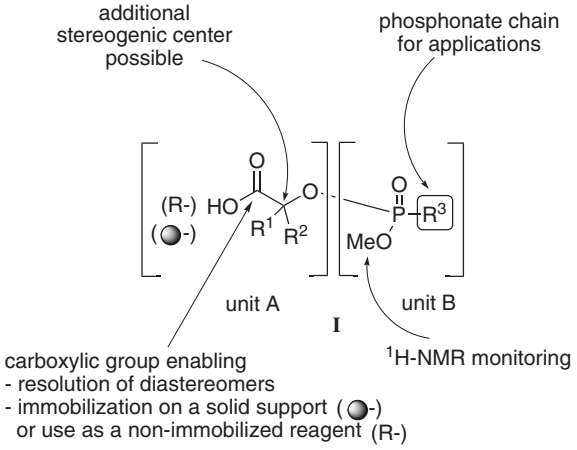

Figure 1. A design of optically active methylphosphonates **I** as new and versatile reagents for organic synthesis.

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nates and α-aminophosphonates, respectively. Johnson and Zhang synthesized phosphonoacetamide linked to the Tentagel® CBz threonine via the P-ester bond.[5] Nicolaou et al.[6] utilized the Merrifield® resin for a synthesis of the polymer supported P-racemic methylphosphonate which was converted to β-ketophosphonate and macrocyclic systems.

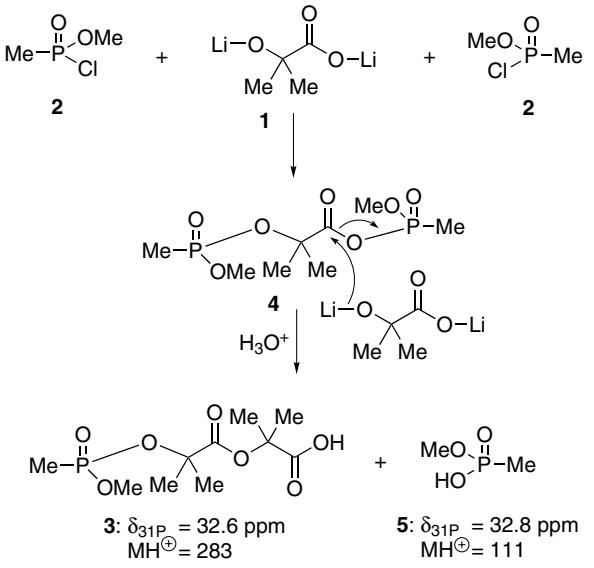
2. Results and discussion

Synthesis of the phosphonates **I** required commercially available α-hydroxyacids or their esters and methyl methylphosphonochloridate **2**. The latter was obtained according to literature procedures by the chlorination of dimethyl methylphosphonate with either PCl_5[7] in benzene, $(COCl)_2$[8] in Et_2O or $(COCl)_2$[9] without solvent.

The condensation reaction of methyl methylphosphonochloridate **2** with dilithium or disodium salt **1** (Z = Y = Na or Li) of 2-methyllactic acid was carried out in THF at 0 °C (then room temperature overnight) and gave, after acidification, methyl methylphosphonate **3**, possessing free terminal carboxylic acid group in the second P-ester function. A similar result was obtained when the monosodium carboxylate **1** (Y = H) and pyridine (1 equiv) in toluene were used (Scheme 1, paths i or ii). The reaction of 2-methyllactic acid with **2** in pyridine as a solvent afforded a complex reaction mixture (vide infra).

The product **3**, unexpectedly, contained two structural units of 2-methyllactic acid linked together via the carboxylic ester bond. In the proposed explanation one assumes a condensation of one molecule of dilithium (disodium) salt **1** (Y = Li or Na) with two molecules of the chloridate **2** to form unstable mixed carboxylic–phosphonic anhydride **4**, which is immediately opened by the nucleophilic attack of **1** at the ester carbonyl group (Scheme 2).

The presence of the lithium salt of *O*-methyl methylphosphonic acid as a leaving group was confirmed after acidification of the reaction mixture and detection of the acid **5** ($MH^+ = 111$, $\delta_{31P} = 32.8$ ppm). Moreover, it was found that the 2-methyllactic acid used in this synthesis contained only 10% of the dimeric form (2-methyllactyl-2-methyllactic acid) and that the dimerization did not occur before addition of **2** to **1**. It is also worthy to note that condensation of **2** with 2-methyllactic acid in the presence of pyridine (1, 2 or 4 equiv) in toluene or in pyridine as a solvent, afforded a mixture of dimeric ($MH^+ = 191$) and even trimeric ($MH^+ = 277$) forms of 2-methyllactic acid as well as phosphonates containing two (**3**, $MH^+ = 283$) and three fragments of α-hydroxyacid ($MH^+ = 369$) in

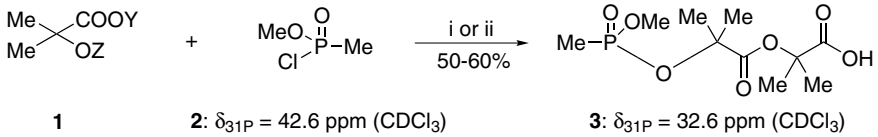


Scheme 2. Proposed reaction mechanism for synthesis of **3**.

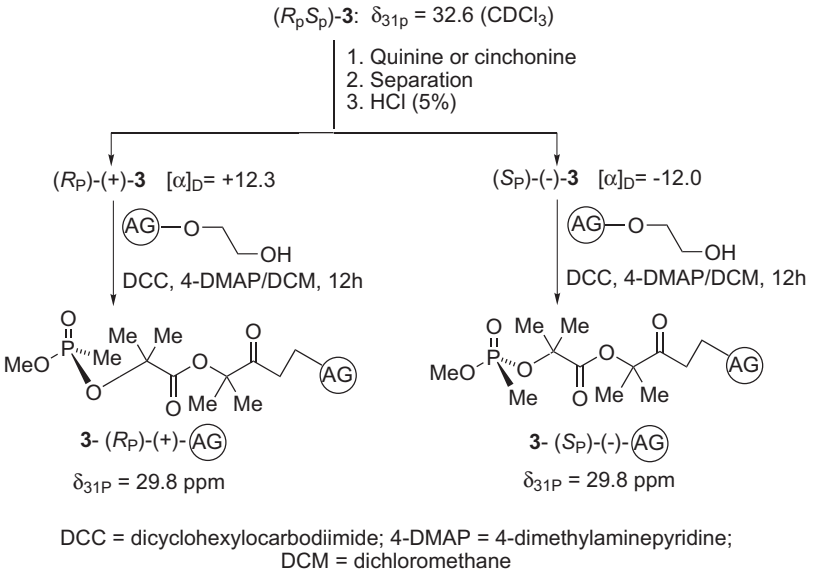
addition to phosphonic acid **5** ($MH^+ = 111$), as revealed by MS-CI spectra of crude reaction mixtures. Next, utilizing the terminal carboxylic group in **3**, the racemic mixture of (R_P,S_P)-**3** was resolved into single (R_P)-**3** and (S_P)-**3** enantiomers via chromatographic separation of their diastereomeric salts with quinine or cinchonine (quinine, 1:1, $\delta_{31P} = 31.37/30.66$ ppm, $R_f = 0.37$ and 0.55; cinchonine, 1:1, $\delta_{31P} = 32.1/28.5$ ppm) over silica gel and then acidification with 5% HCl. Diastereomeric salts were in both cases glassy substances which did not tend to crystallize. Based on the X-ray analysis, the (R_P) and (S_P) configurations were assigned to (+)- and (−)-enantiomers of **3**, respectively (Section 2.1). Suitable crystals were prepared by crystallization from methanol.

Immobilization of pure **3**-(R_P)-(+)- and **3**-(S_P)-(−)-enantiomers on a solid support was done with ArgoGel®–OH using DCC and 4-DMAP in methylene chloride at room temperature. The urea by-products were removed using successive washings with three solvents according to the literature method[10] (Scheme 3).

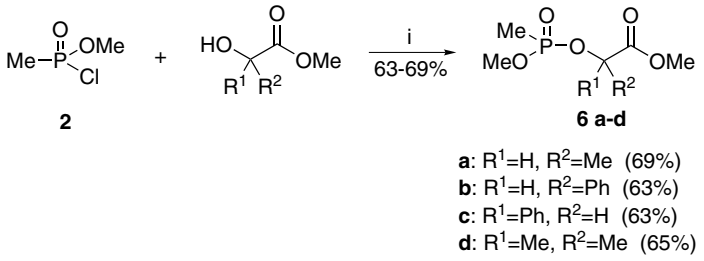
Carboxylic ester analogs of **3** containing a single unit of α-hydroxyacid in the P-ester moiety were obtained by the condensation reactions of the chloridate **2** with methyl esters of various α-hydroxyacids [(S_C)-(−)-lactic, 2-methyllactic, (R_C)-(−)- and (S_C)-(+)-mandelic] in the presence of pyridine to give the corresponding phosphonates **6a**–**d** in 63–69% yields (Scheme 4).



Scheme 1. Reagents and conditions: (i) (1) 0 °C/2 h/THF; (2) 20 °C/24 h; (3) 5% HCl (60%) for Z = Y = Na(Li); (ii) (1) 0 °C/2 h/toluene, Py (1 equiv); (2) 20 °C/24 h; (3) 5% HCl (50%) for Z = H, Y = Na.



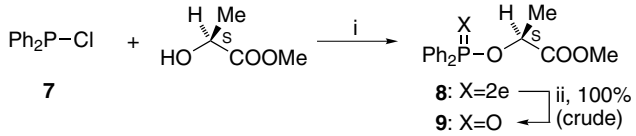
Scheme 3. Resolution of racemic mixture (R_P,S_P)-**3** and immobilization of (+)-(R_P)-**3** and (−)-(S_P)-**3** on the ArgoGel–OH® solid support.



Scheme 4. Preparation of phosphonate esters **6a**–**d**. Reagents and conditions: (i) Py/0 °C, 1 h, then 25 °C overnight, toluene.

Since the obtained compounds were chromatographically inseparable ca. 1:1 mixtures of diastereomers (identical R_f values in various solvent systems), we decided to selectively hydrolyze the C(O)OMe group for the resolution of **6** via diastereomeric salts of the resulting carboxylic acids with alkaloid bases. However, the hydrolysis reaction proceeded in a different way to the literature reports for the phosphonates containing both P–OMe and C(O)OMe groups.[11] Thus, treatment of (S_C)-(−)-**6a** with 1% $NaHCO_3$ in methanol (0 ↗ 25 °C, 3 h) recovered the substrate which was, as we preliminarily assumed, epimerized on the P atom (from 1:1.13 to 1.6:1, based on ^{31}P NMR) while 1% NaOH in methanol (0 ↗ 25 °C, 3 h) caused the hydrolysis of only the P–OMe group in 85% yield (15% of the substrate). Most probably, the epimerization at phosphorus occurred via methoxy groups exchange. In order to check it and to proof the lack of epimerization on the carbon stereogenic centre, a model compound (*S*)-methyl 2-(diphenylphosphoryloxy)propanoate **9** was synthesized from methyl (*S*)-lactate and chlorodiphenylphosphine via oxidation of the intermediate (*S*)-methyl 2-(diphenylphosphinooxy)propanoate **8** (Scheme 5).

Replacement of the (MeO)MeP(O) group with $Ph_2P(O)$ removed the phosphorus stereogenic centre and allowed us to avoid the MeO group exchange and to monitor only the carbon stereogenic centre via changes of optical rotation during hydrolysis attempts. It turned out, that after treatment of **9** both with 1% and 10% aqueous solutions of $NaHCO_3$ in methanol, the configuration at the carbon stereogenic centre was retained.



Scheme 5. Preparation of the phosphinite **8** and phosphinate **9**. Reagents and conditions: (i) Et_3N, MeOH, 0 °C; (ii) H_2O_2, MeOH, −20 °C.

Hydrolysis of (R_C)-(−)-**6b** and (S_C)-(+)-**6c** required 4% NaOH in methanol (−20 ↗ −10 °C, 3 h) and gave exclusive cleavage of the P–OMe group, quantitatively for both diastereomers. On the other hand, an attempt to hydrolyze **6d** with 1% $NaHCO_3$ in methanol (0 ↗ 25 °C, 3 h) led to a quantitative recovery of the substrate; 1% NaOH in methanol (0 ↗ 25 °C, 3 h) gave a mixture of the product with both C(O)OMe and P–OMe groups hydrolyzed and the substrate. Finally, 4% NaOH in methanol (25 °C, 3 h) afforded the product with C(O)OMe and P–OMe groups hydrolyzed quantitatively. All hydrolysis processes were easily monitored by ^1H NMR.

2.1. Crystallographic discussion

The X-ray analysis was carried out in order to establish the absolute configuration of P-stereogenic centres in **3**. Suitable crystals were obtained from crystallization of the sample of **3** (obtained from the diastereomeric salt with $R_f = 0.55$) in methanol. The crystal structure contains two crystallographically independent molecules (designated as **Ia** and **Ib**) in the asymmetry unit. Figure 2 shows the molecular structure and absolute configuration for the title compound. The configuration at the P1 and P2 atoms is *S*. In both molecules **Ia** and **Ib** the phosphorus tetrahedrons are disordered over two sites with occupancy factors of 0.800(2), 0.200(2) and 0.871(2), 0.129(2) for P1, P1*, O1, O1*, C1, C1*, C2, C2* and P2, P2*, O21, O21*, C21, C21*, C22, C22* atoms, respectively. A comparison of conformations of crystallographically independent molecules indicates some resemblance, for example, the backbone chains C5–C3–C6–O5–C7–C9 and C25–C23–C26–O25–C27–C29 adopt an extended conformation in both cases.

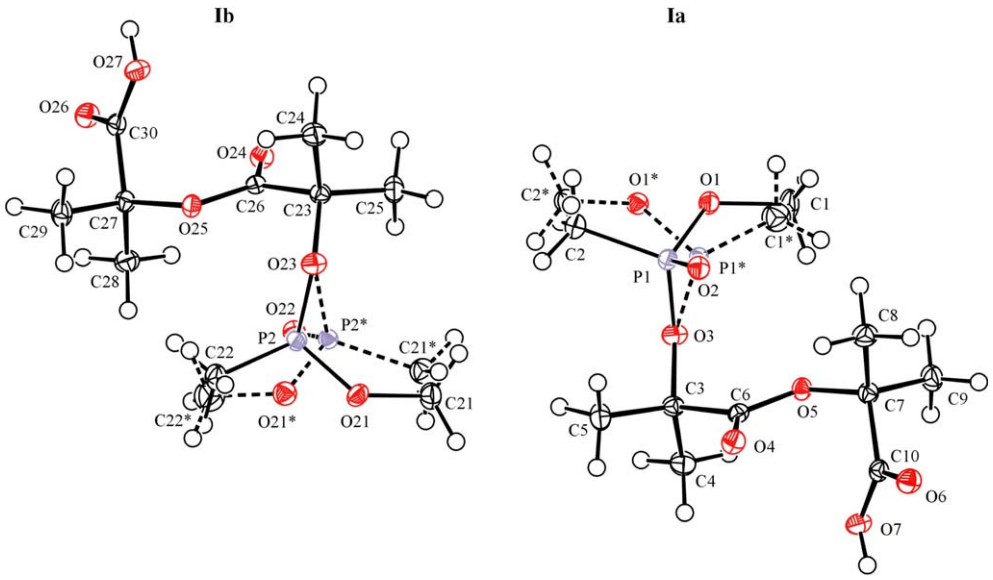


Figure 2. A perspective view of the two independent molecules (**Ia** and **Ib**). The major disorder component is shown with solid bonds and the minor component with dashed bonds.

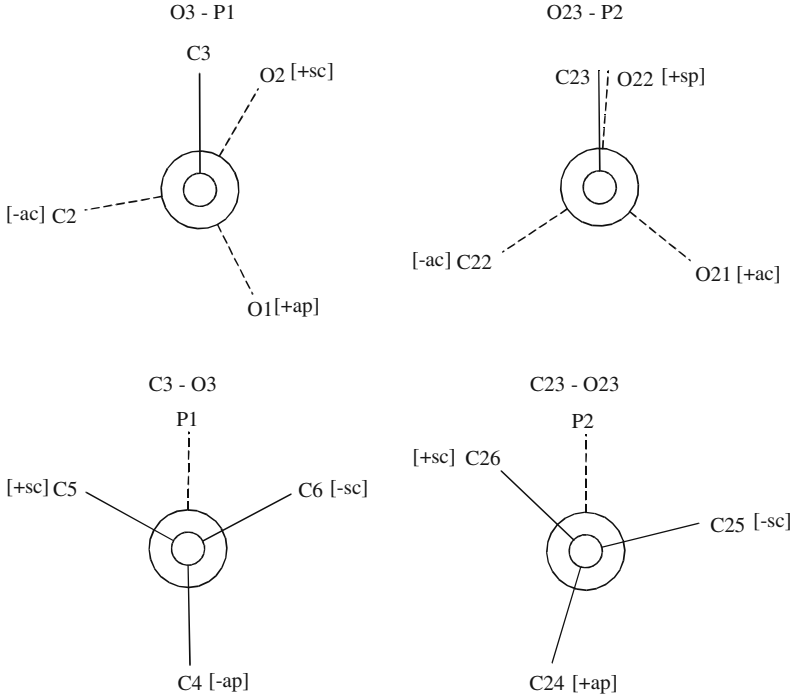


Figure 3. Four Newman projections showing the difference in torsion angles of the major disorder component of the two independent molecules.

This can be seen from the following torsion angles: C5–C3–C6–O5 = −166.7(1), C3–C6–O5–C7 = 180.0(1), C6–O5–C7–C9 = 168.1(1), C25–C23–C26–O25 = 164.7(1), C23–C26–O25–C27 = −179.0(1), C26–O25–C27–C29 = −168.2(1). On the other hand, the molecules **Ia** and **Ib** differ considerably in the fragment O1, O2, P1, O3, C3, C4 (O21, O22, P2, O23, C23, C24). Figure 3 shows four Newman projections (created with PLATON[12]) along the P1–O3 (P2–O23) and O3–C3 (O23–C23) bonds in the major component of the twofold disorder of the P1, O1 and P2, O21 atoms. In the unit cell, the molecules are connected by two intermolecular hydrogen bonds: O7–H7···O2 ($0.5 + x$, $0.5 - y$, $2 - z$) and O22–H27···O22 ($0.5 + x$, $1.5 - y$, $2 - z$), 1.79 Å (H7···O2) and 1.82 Å (H27···O22) with the angles O7–H7···O2 and O27–H27···O22 of 179.1 and 176.3°, respectively; distances O7···O2 and O27···O22 of 2.633(1) and 2.658(1) Å (Fig. 4).

3. Conclusion

In a summary, we have presented a new approach to the synthesis of both R_P and S_P enantiomers of the methylphosphonate derivative **3** immobilized separately on the ArgoGel®–OH solid support, utilizing one of P-ester arms terminated with the carboxylic acid function for a classical resolution of racemic mixture via diastereomeric salts with alkaloid bases. Unexpected formation of **3** containing two α-hydroxyacid moieties was rationalized via the proposed nucleophilic attack of **1** (Z = Y = Li) onto the intermediate anhydride **4**. Finally, the condensation of **2** with α-hydroxyacid methyl esters led to the formation of ca. 1:1 adducts **6a–d** which, in contrast to literature reports, underwent under basic hydrolytic conditions either P–OMe or simultaneous C(O)OMe and P–OMe cleavages.

Hitherto, optically active P-chiral phosphonates have been synthesized in stereocontrolled reactions of nucleophilic substitution at the phosphorus atom and oxidation of P^{III} or P^{IV}=S to P=O bonds. The P–Me function in racemic **3** is usually further functionalized with carbanionic or radical methods and used in synthesis.[13–17] The same methods may be used for optically active **3**. Alternatively, our new approach may be also applied for other α-substituted phosphonates.

4. Experimental

4.1. General remarks

The ^{1}H NMR (200 and 500 MHz) and ^{13}C NMR (50 and 125 MHz) spectra were recorded using a Bruker AC-200 and a Bruker DRX-500 spectrometers, respectively. The IR spectra were recorded using an ATI Mattson Infinity FTIR 60 spectrometer. The mass spectra of pure compounds were obtained using a Finnigan Mat 95 spectrometer. Column chromatography was done using Merck silica gel (F_{254} 60, 70–230 and 270–400 mesh). Organic solvents were purified by standard procedures. Auxiliary numbering of carbon atoms is depicted in structures **3** and **6**. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

4.2. Methyl methylphosphonochloridate 2

This compound was obtained according to the literature procedures.[7–9]

Yield 71–79%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.96$ (d, 3H, $^2J_{H-P} = 17.6$ Hz, P–CH_3), 3.87 (d, 3H, $^3J_{H-P} =$

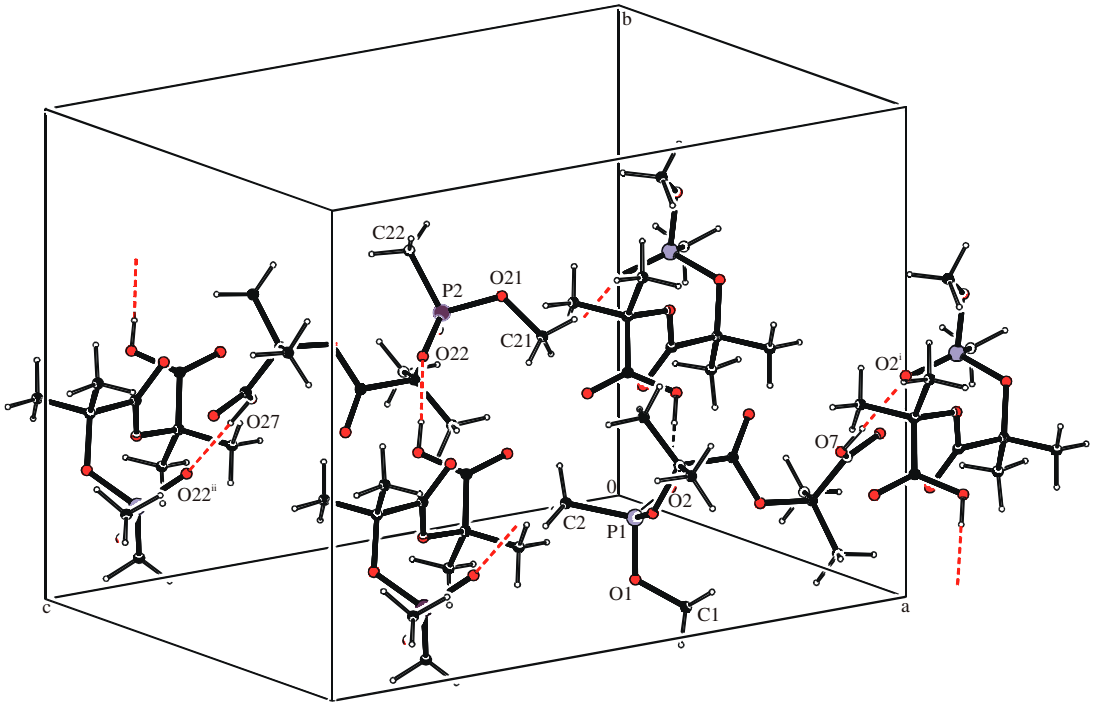
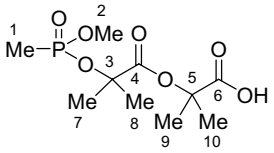


Figure 4. Diagram showing hydrogen bonds of the major disorder component of the two independent molecules.

13.6 Hz, P–OCH_3); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 42.6$ ppm.

4.3. Synthesis of racemic (R_P+S_P)-2-(2-(methoxy(methyl)-phosphoryloxy)-2-methylpropanoyloxy)-2-methylpropanoic acid 3

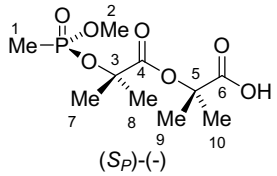


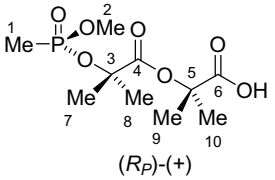
To a stirred solution of 2-methyllactic acid (500 mg, 4.8 mmol) in THF (50 mL), *n*-BuLi (2 mL, 4.8 mmol, 2.4 M solution in *n*-hexane) was added at −50 °C under argon atmosphere and after 15 min the same quantity of *n*-BuLi was added again. The ice-bath was removed, the temperature was increased to 0 °C and a stoichiometric amount of methyl methylphosphonochloridate **2** (617 mg, 4.8 mmol) was added. The resulting mixture was warmed to the room temperature and stirred for 2 h. Then 5% HCl aqueous solution was added, the solvent was evaporated and the residue was extracted with chloroform (3 × 20 mL). The combined chloroform solutions were washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product which was further purified by column chromatography over silica gel using chloroform/methanol in a gradient as the eluent.

Yield 60%; white crystals, mp 117 °C; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 32.60$ ppm; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.57$ (d, 3H, $^2J_{H-P} = 17.9$ Hz, C^1H_3), 1.61, 1.62, 1.64, 1.65 (4 × s, 12H, C^7H_3, C^8H_3, C^9H_3, $C^{10}H_3$), 3.75 (d, 3H, $^3J_{H-P} = 11.5$ Hz, C^2H_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 12.41$ (d, $^1J_{C-P} = 148.4$ Hz, C^1H_3), 24.18, 24.82, 26.61, 26.70 (4 × s, C^7H_3, C^8H_3, C^9H_3, $C^{10}H_3$), 52.30 (d, $^2J_{C-P} = 6.5$ Hz, C^2H_3), 80.64, 80.80 (s, C^3, C^5), 171.17, 173.39 (s, C^4, C^6); IR (film): ν/cm^{-1} 2949, 2875, 2656, 2548, 1749, 1728, 1471, 1302, 1226, 1186, 1133, 1019, 992, 935, 758; MS-CI (isobutane): m/z (%) = 283 (M^++1, 100); MS-HR-CI: M^++1, found: 283.0946 for $C_{10}H_{20}O_7P$—calculated 283.0944.

4.4. Synthesis of (+)-(R_P)-3 and (−)-(S_P)-3 enantiomers via chromatographic resolution of diastereomeric salts

To a stirred solution of (R_P)-**3** and (S_P)-**3** racemic mixture (100 mg, 0.35 mmol) in chloroform (20 mL), a stoichiometric amount of quinine (115 mg, 0.35 mmol) or cinchonine (0.35 mmol) was added at room temperature. The resulting mixture was stirred overnight. The solvent was evaporated and the crude product containing two diastereomeric salts in a ratio 1:1 (for quinine, 1:1, $R_f = 0.37/0.55$, $\delta_{^{31}P} = 31.37/30.66$ ppm; for cinchonine, 1:1, $\delta_{^{31}P} = 32.1/28.5$ ppm) was separated on two fractions (eluent: chloroform/methanol, 10:1). Each fraction was dissolved in chloroform and acidified with 5% aqueous solution of HCl. Then the products were extracted with chloroform (3 × 20 mL). The combined chloroform solutions were dried separately over anhydrous $MgSO_4$, filtered and evaporated to give (based on the X-ray analysis) pure (+)-(R_P)-**3** [from the salt with $R_f = 0.37$] and (−)-(S_P)-**3** [from the salt with $R_f = 0.55$] enantiomers in 30–40% yields, respectively, with respect to (R_P,S_P)-**3**.





(−)-(S_P)-**3**: $[\alpha]_{589} = -12.0$ (c 0.46, $CHCl_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 32.60$ ppm; (+)-(R_P)-**3**: $[\alpha]_{589} = +12.3$ (c 0.46, $CHCl_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 32.60$ ppm.

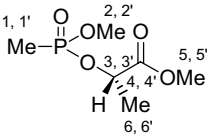
4.5. Immobilization of pure (R_P)-(+)-3 and (S_P)-(−)-3 on a solid support-ArgoGel®–OH (0.2–0.6 mmol/g)

To a suspension of ArgoGel®–OH (440 mg, 0.18 mmol) in dichloromethane under argon atmosphere, the enantiomer (+)-(R_P)-**3** or (−)-(S_P)-**3** (50 mg, 0.18 mmol), DCC (27 mg, 0.22 mmol) and 4-DMAP (3 mg, 0.02 mmol) were added at room temperature. The resulting mixtures were stirred for 12 h [both for the (R_P)-**3** or the (S_P)-**3**]. Then, the solid support was separated, washed with dichloromethane, ethyl acetate, methanol and dried under low pressure.[10] ^{31}P NMR (81 MHz, solid phase, without lock): $\delta = 29.80$ ppm.

4.6. General procedure for the synthesis of α-hydroxyacid methyl esters derivatives 6a–d

To a stirred solution of α-hydroxyacid methyl ester (4.8 mmol) and pyridine (5 mmol) in THF (50 mL) at 0 °C, a stoichiometric amount of methyl methylphosphonochloridate **2** (4.8 mmol) was added. The resulting mixture was stirred for 2 h. Then, the precipitate of pyridinium hydrochloride was separated and the residue was extracted with chloroform. The combined chloroform solutions were washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product **6** which was further purified by column chromatography over silica gel using chloroform/methanol in a gradient as the eluent.

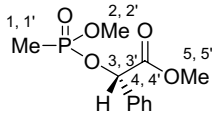
4.6.1. (S_C,R_P+S_P)-Methyl 2-(methoxy(methyl)phosphoryloxy)propanoate 6a.



Yield: 69%; a colourless liquid; $[\alpha]^{25}_{589} = -30.0$ (c 2.0, $CHCl_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 33.24$, 34.68 ppm, (1:1); ^1H NMR (500 MHz $CDCl_3$): $\delta = 1.47$ (d, 3H, $^2J_{H-P} = 12.1$ Hz, C^1H_3), 1.49 (m, 6H, C^6H_3, $C^{6'}H_3$), 1.53 (d, 3H, $^2J_{H-P} = 12.1$ Hz, $C^{1'}H_3$), 3.63 (d, 3H, $^3J_{H-P} = 11.2$ Hz, C^2H_3), 3.65 (d, 3H, $^3J_{H-P} = 11.5$ Hz, $C^{2'}H_3$), 3.71 (m, 6H, C^5H_3, $C^{5'}H_3$), 4.93 (m, 2H, C^3H,

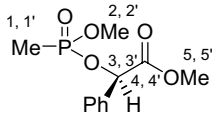
$C^{3'}H$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 11.21$ (d, $^1J_{C-P} = 145.7$ Hz, C^1H_3), 11.39 (d, $^1J_{C-P} = 146.8$ Hz, $C^{1'}H_3$), 19.05 (d, $^3J_{C-P} = 5.3$ Hz, C^6H_3), 19.35 (d, $^3J_{C-P} = 5.1$ Hz, $C^{6'}H_3$), 51.30 (d, $^3J_{C-P} = 6.8$ Hz, C^2H_3), 52.17 (d, $^3J_{C-P} = 6.8$ Hz, $C^{2'}H_3$), 52.29, 52.32 (2 × s, C^5H_3, $C^{5'}H_3$), 69.86 (d, $^2J_{C-P} = 6.2$ Hz, C^3H), 70.27 (d, $^2J_{C-P} = 5.8$ Hz, $C^{3'}H$), 171.32 (d, $^3J_{C-P} = 3.4$ Hz, C^4), 171.44 (d, $^3J_{C-P} = 3.5$ Hz, $C^{4'}$); IR (film): ν/cm^{-1} 2995, 2848, 1744, 1316, 1217, 1101, 1053, 1001, 900; MS-CI (isobutane): m/z (%) 197 (M^++1, 100); MS-HR-CI: M^++1, found: 197.0578 for $C_6H_{14}O_5P$—calculated 197.0573.

4.6.2. (S_C,R_P+S_P)-Methyl 2-(methoxy(methyl)phosphoryloxy)-2-phenylacetate 6b.



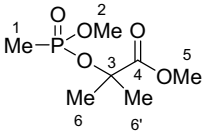
Yield: 63%; a colourless liquid; $[\alpha]_{589}^{25} = +91.2$ (c 2.0, $CHCl_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 33.85$, 33.73 ppm, (1:0.8); ^1H NMR (500 MHz $CDCl_3$): $\delta = 1.32$ (d, 3H, $^2J_{H-P} = 17.4$ Hz, C^1H_3), 1.61 (d, 3H, $^2J_{H-P} = 18.2$ Hz, $C^{1'}H_3$), 3.41 (d, 3H, $^3J_{H-P} = 11.3$ Hz, C^2H_3), 3.66, 3.67 (2 × s, 6H, C^5H_3, $C^{5'}H_3$), 3.76 (d, 3H, $^3J_{H-P} = 11.3$ Hz, $C^{2'}H_3$), 5.78 (d, 1H, $^3J_{H-P} = 8.9$ Hz, C^3H), 5.82 (d, 1H, $^3J_{H-P} = 8.7$ Hz, $C^{3'}H$), 7.31–7.43 (2 × m, 10H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.31$ (d, $^1J_{C-P} = 146.4$ Hz, C^1H_3), 11.41 (d, $^1J_{C-P} = 145.9$ Hz, $C^{1'}H_3$), 51.26 (d, $^3J_{C-P} = 7.1$ Hz, C^2H_3), 52.00 (d, $^3J_{C-P} = 6.8$ Hz, $C^{2'}H_3$), 52.45, 52.50 (2 × s, C^5H_3, $C^{5'}H_3$), 75.06 (d, $^2J_{C-P} = 4.9$ Hz, C^3H), 75.33 (d, $^2J_{C-P} = 5.5$ Hz, $C^{3'}H$), 127.02, 127.11, 128.60, 128.63, 129.03, 129.09 (C–Ph), 169.49 (d, $^3J_{C-P} = 4.7$ Hz, C^4), 169.65 (d, $^3J_{C-P} = 4.4$ Hz, $C^{4'}$); IR (film): ν/cm^{-1} 3010, 2955, 1757, 1455,1437, 1219, 1065, 992, 917, 757, 731; MS-CI (isobutane): m/z (%) 259 (M^++1, 100); MS-HR-CI: M^++1, found: 259.0735 for $C_{11}H_{16}O_5P$—calculated 259.0735.

4.6.3. (R_C,R_P+S_P)-Methyl 2-(methoxy(methyl)phosphoryloxy)-2-phenylacetate 6c.



Yield: 63%; a colourless liquid; $[\alpha]_{589}^{25} = -98.85$ (c 2.0, $CHCl_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 33.85$, 33.73 ppm, (1:0.8); ^1H NMR (500 MHz $CDCl_3$) $\delta = 1.34$ (d, 3H, $^2J_{H-P} = 18.3$ Hz, C^1H_3), 1.63 (d, 3H, $^2J_{H-P} = 18.3$ Hz, $C^{1'}H_3$), 3.43 (d, 3H, $^3J_{H-P} = 11.5$ Hz, C^2H_3), 3.69, 3.70 (2 × s, 6H, C^5H_3, $C^{5'}H_3$), 3.78 (d, 3H, $^3J_{H-P} = 11.6$ Hz, $C^{2'}H_3$), 5.80 (d, 1H, $^3J_{H-P} = 9.0$ Hz, C^3H), 5.84 (d, 1H, $^3J_{H-P} = 8.7$ Hz, $C^{3'}H$), 7.31–7.43 (2 × m, 10H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.40$ (d, $^1J_{C-P} = 146.5$ Hz, C^1H_3), 11.51 (d, $^1J_{C-P} = 145.7$ Hz, $C^{1'}H_3$), 51.35 (d, $^3J_{C-P} = 6.9$ Hz, C^2H_3), 52.10 (d, $^3J_{C-P} = 7.0$ Hz, $C^{2'}H_3$), 52.59, 52.59 (2 × s, C^5H_3, $C^{5'}H_3$), 75.16 (d, $^2J_{C-P} = 4.9$ Hz, C^3H), 75.43 (d, $^2J_{C-P} = 5.3$ Hz, $C^{3'}H$), 127.11, 127.20, 128.68, 128.71, 129.11, 129.16 (C–Ph), 169.58 (d, $^3J_{C-P} = 4.3$ Hz, C^4), 169.75 (d, $^3J_{C-P} = 4.4$ Hz, $C^{4'}$); IR (film): ν/cm^{-1} 3007, 2955, 1757, 1496, 1437, 1222, 1065, 1039, 989, 924, 730; MS-CI (isobutane): m/z (%) 259 (M^++1, 100); MS-HR-CI: M^++1, found: 259.0737 for $C_{11}H_{16}O_5P$—calculated 259.0735.

4.6.4. Methyl 2-(methoxy(methyl)phosphoryloxy)-2-methylpropanoate 6d.



Yield: 65%; a colourless liquid; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 31.8$ ppm; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.50$ (d, 3H, $^2J_{H-P} = 18.0$ Hz, C^1H_3), 1.58, 1.65, (2 × s, 6H, C^6H_3, $C^{6'}H_3$), 3.67 (d, 3H, $^3J_{H-P} = 11.3$ Hz, C^2H_3), 3.73 (s, 3H, C^5H_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.12$ (d, $^1J_{C-P} = 148.3$ Hz, C^1H_3), 26.84, 26.90 (2 × s, C^6H_3, $C^{6'}H_3$), 51.35 (d, $^2J_{C-P} = 6.5$ Hz, C^2H_3), 52.42 (s, C^5), 80.41 (s, C^3), 173.20 (s, C^4); IR (film): ν/cm^{-1} 2994, 2955, 1748, 1250, 1144, 1052, 1021, 809; MS-CI (isobutane): m/z (%) = 211 (M^++1, 100); MS-HR-CI: M^++1, found: 211.0735 for $C_7H_{16}O_5P$—calculated 211.0728.

4.7. (*S*)-Methyl 2-(diphenylphosphinooxy)propanoate 8

Methyl-(*S*)-lactate (2 g, 19.2 mmol, 1.8 mL) was dissolved in dry ether (50 mL) and to the resulting solution triethylamine (2.9 g, 28.9 mmol, 4 mL) was added at 0 °C under argon atmosphere. Then chlorodiphenylphosphine (4.3 g, 19.2 mmol, 3.6 mL) was added dropwise at this temperature. Next, the temperature was raised to 20 °C and after 30 min a white precipitate was filtered off. The filtrate was evaporated and the crude **8** was used in the next oxidation reaction to **9**.

Crude **8**. Purity: ca. 90% based on ^{31}P NMR; yellow oil; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 116.12$ ppm; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.54$ (d, 3H, $^3J_{H-H} = 6.9$ Hz, CH–CH_3), 3.68 (s, 3H, COOCH_3), 4.54 (dq, 1H, $^3J_{H-P} = 9.5$ Hz, $^3J_{H-H} = 6.9$ Hz, CH–CH$_3$), 7.2–7.7 (m, 10H, $(C_6H_5)_2P$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.94$ (s, CH–CH$_3$), 51.94 (s, COOCH$_3$), 74.74 (d, $^2J_{C-P} = 21.6$ Hz, CH–CH$_3$), 128–142 (many signals, $(C_6H_5)_2P$), 172.95 (s, C=O); MS-EI (70 eV): m/z (%) = 288 (M^+, 0.6), 273 (M^+−Me, 23), 201 ($Ph_2P{=}O^+$, 100); MS-HR-EI: M^+, found: 288.0918 for $C_{16}H_{17}O_3P$—calculated 288.0915.

4.8. (*S*)-Methyl 2-(diphenylphosphoryloxy)propanoate 9

The compound **8** (1.08 g, 3.75 mmol) was dissolved in methanol (10 mL) and to the resulting solution hydrogen peroxide (30%, 11.25 mmol, 1.15 mL) was added dropwise at −20 °C. After 1 h, the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated to afford 1.19 g of the crude product **9**.

Yield: 100% (crude product). Purity: 90% (based on ^{31}P NMR). Analytical sample was purified on a Merck silica gel plate (20 cm × 20 cm) using benzene/acetone (1:1) solvent system; Pale yellow oil; $[\alpha]_{589}^{22} = -7.4$ (*c* 2.79, CH_2Cl_2); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 33.14$ ppm; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.57$ (d, 3H, $^3J_{H-H} = 6.8$ Hz, CH–C*H*$_3$), 3.66 (s, 3H, COOC*H*$_3$), 4.95 (dq, 1H, $^3J_{H-P} = 9.7$ Hz, $^3J_{H-H} = 6.8$ Hz, C*H*–CH$_3$), 7.25–7.60, 7.70–8.00 (2 × m, 10H, $(C_6H_5)_2P$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.75$ (s, CH–*C*H$_3$), 52.13 (s, COO*C*H$_3$), 69.15 (d, $^3J_{C-P} = 5.4$ Hz, *C*H–CH$_3$), 128–133 (many signals, $(C_6H_5)_2P$), 171.09 (s, *C*=O); IR (film): ν/cm^{-1} 3055, 2987, 2952, 1754, 1435, 1212, 1123, 1096, 1050, 983, 742, 697; MS-EI (70 eV): m/z (%) = 304 (M^+, 4.5), 217 (M^+–COOMe, 22), 201 ($Ph_2P{=}O^+$, 100), 77 (Ph^+, 22); MS-HR-EI: M^+, found: 304.0865 for $C_{16}H_{17}O_4P$—calculated 304.0864.

4.9. Crystallographic data

Crystal data: $C_{10}H_{19}O_7P$; $M_r = 282.22$; orthorhombic, $P2_12_12_1$; $a = 12.3835(4)$ Å, $b = 12.7183(4)$ Å, $c = 17.6996(5)$ Å; $V = 2787.64(15)$ Å,[18] $Z = 8$; $D_x = 1.345$ Mg m^{-3}; Mo Kα radiation; cell parameters from 14,559 reflections; $\theta = 4.7$–$37.5°$; $\mu = 0.22$ mm^{-1}; $T = 100(2)$ K; plate, colourless; 0.57 × 0.44 × 0.10 mm; crystallization from methanol; (S_P)-(−).

Refinement: refinement on F^2, $R[F^2 > 2\sigma(F^2)] = 0.043$, $wR(F^2) = 0.098$, 14,559 reflections, 377 parameters; H atoms constrained to parent site; calculated weights $w = 1/[\sigma^2(F_o^2) + (0.047P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$; $(\Delta/\sigma)_{max} = 0.001$; $\Delta\rho_{max} = 0.42$ e Å^{-3}; $\Delta\rho_{min} = -0.33$ e Å^{-3}; extinction correction: none; absolute structure: Flack;[18] Flack parameter: −0.08(5).

Computer programs: data collection: CrysAlis CCD[19] (Oxford Diffraction, 1995–2003); cell refinement: CrysAlis RED[19] (Oxford Diffraction, 1995–2003); data reduction: CrysAlis RED[19] (Oxford Diffraction, 1995–2003); structure solution: SHELXS-97[20] (Sheldrick, 1990); structure refinement: SHELXL-97[20] (Sheldrick, 1997); molecular graphics: PLATON;[12] software for data elaboration: SHELXL-97[20] (Sheldrick, 1997).

Crystallographic data (excluding structure factors) for the structure **3** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC: 293503. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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References

1. Mikołajczyk, M.; Bałczewski, P. *Top. Curr. Chem.* **2002**, *223*, 161–214.
2. Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recueil* **1997**, 1283–1301.
3. Xiaodong, C.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 7489–7492.
4. Chengzhi, Z.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 5457–5460.
5. Johnson, Ch. R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253–9256.
6. Nicolau, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132–5133.
7. Balthazor, T. M.; Florez, R. A. *J. Org. Chem.* **1980**, *45*, 529–531.
8. Jacobsen, N. E.; Bartlett, N. E. *J. Am. Chem. Soc.* **1983**, *105*, 1613–1619.
9. Nakamura, M.; Sawasaki, K.; Okamoto, Y.; Takamuku, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 141–146.
10. Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174–2175.
11. Patel, D. V.; Gordon, E. M.; Schmidt, J. R.; Weller, H. N.; Young, M. G.; Zahler, R.; Barbacid, M.; Carboni, J. M.; Gullo-Brown, J. L.; Hunihan, L.; Ricca, C.; Robinson, S.; Seizinger, B. R.; Tuomari, A. V.; Manne, V. *J. Med. Chem.* **1995**, *38*, 435–442.
12. Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.
13. Bałczewski, P.; Mikołajczyk, M. *Rev. Heteroat. Chem.* **1998**, *18*, 37–59.
14. Bałczewski, P.; Szadowiak, A.; Białas, T. *Heteroat. Chem.* **2006**, *17*, 22–35.
15. Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253.
16. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
17. Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649–654.
18. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.
19. Oxford Diffraction. *CrysAlisCCD and CrysAlisRED*. Version 1.171. Oxford Diffraction Poland, Wrocław, Poland, 2003.
20. Sheldrick, G. M. SHELXS97 *and* SHELXL97; University of Göttingen: Germany, 1997.