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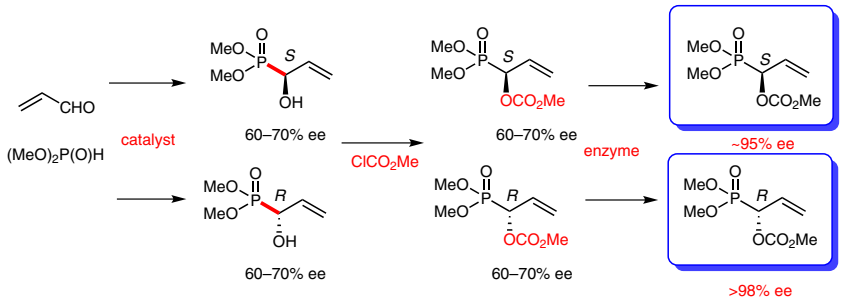
A Practical and Scalable Synthesis of (*S*)- and (*R*)-1-(Dimethoxyphosphoryl)allyl Methyl Carbonates

Sudeshna Roy
Nongnuch Sutivisedsak
Bruce C. Hamper
Alexander M. Lyss
Christopher D. Spilling*

Department of Chemistry and Biochemistry, University of Missouri–St. Louis, One University Boulevard, St. Louis, MO 63121, USA
cspill@umsl.edu



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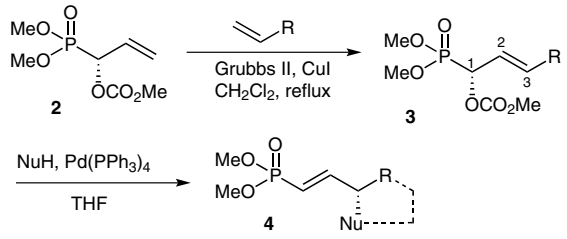
Abstract The preparation of (*S*)- and (*R*)-1-(dimethoxyphosphoryl)allyl methyl carbonates is achieved on multigram scale from commercially available dimethyl phosphite and acrolein in three steps. The key steps involve an asymmetric Pudovik reaction and enzyme-catalyzed kinetic resolution.

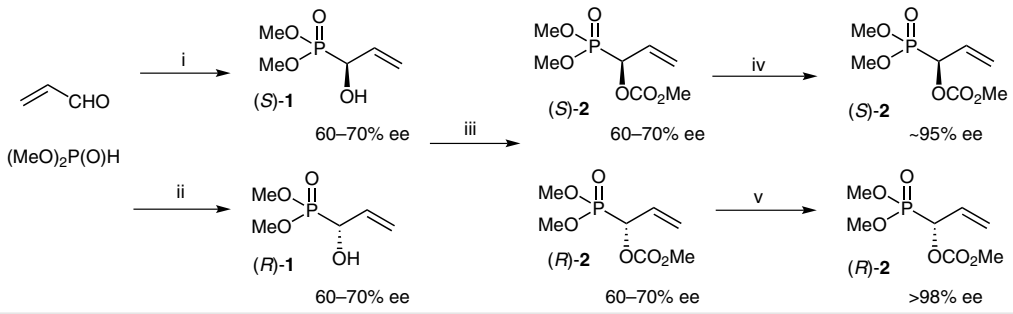
Key words cross-metathesis, enzymatic amplification, α-hydroxy phosphonates, natural products, phosphonoallylic carbonates



Scheme 2 Synthesis of phosphono allylic carbonates via alkene cross-metathesis and subsequent palladium-catalyzed substitution reactions

Allylic hydroxyphosphonates (**1**) and their carbonate derivatives (**2** and **3**) (Scheme 1 and Scheme 2) in particular, are useful building blocks for the synthesis of interesting biologically active molecules.[1–7] More complex phosphonate homologs (**3**) can be prepared (Scheme 2) by an alkene cross-metathesis reaction of the parent 1-(dimethoxyphosphoryl)allyl methyl carbonate (**2**) using the Grubbs second-generation catalyst.[8]

The substituted phosphono allylic carbonates (**3**) are useful substrates for palladium π-allyl chemistry (Scheme 2).[1–7,9] The steric and electronic influence of the phosphonate moiety dictates the stereochemical and regiochemical outcomes of the reaction. Addition of nucleophiles always takes place at the 3-position resulting in formation of a vinyl phosphonate (**4**), while relaying and preserving the chiral information from the starting material to the product.



Scheme 1 Synthesis of (*S*)-phosphono allylic carbonate (*S*)-**2** and (*R*)-phosphono allylic carbonate (*R*)-**2**. *Reagents and conditions*: (i) Ti(O*i*-Pr)$_4$, D-dimethyl tartrate, THF, –15 °C, 24 h (quant.); (ii) Ti(O*i*-Pr)$_4$, L-dimethyl tartrate, THF, –15 °C, 24 h (quant.); (iii) $ClCO_2Me$, DMAP, py, CH_2Cl_2, 0 °C to r.t., 18 h [(*S*)-**2**: 80%]; (iv) immobilized lipase AYS, MTBE, pH 7 phosphate buffer, r.t. (42%); (v) *Candida antarctica* lipase B (CALB), MTBE, pH 7 phosphate buffer, r.t. (62%).

Intramolecular reactions of pendent nucleophiles result in the formation of cyclic products.[4,5,7a]

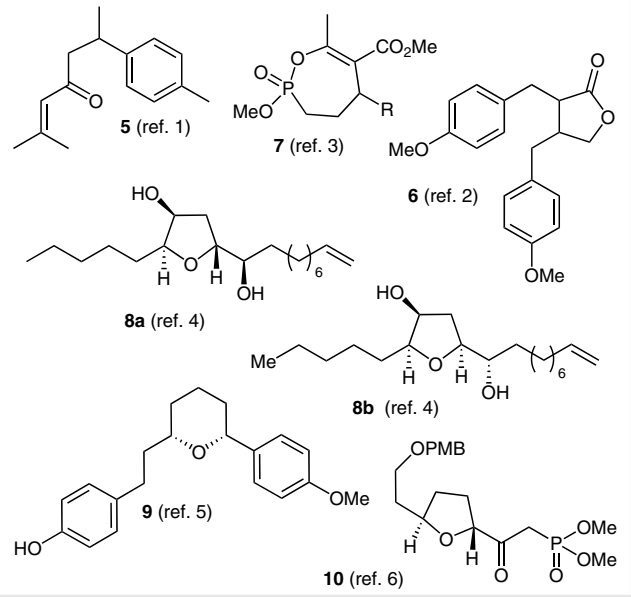
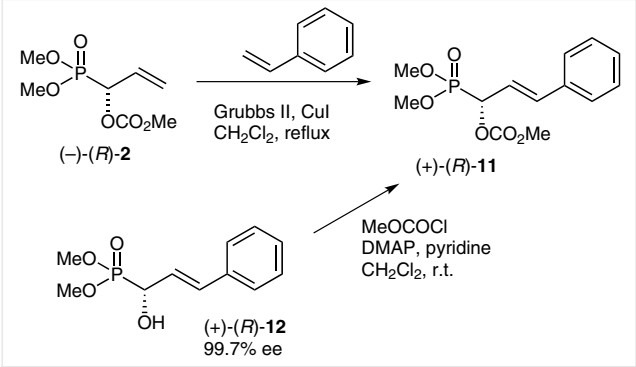


Figure 1 Examples of natural and biologically active compounds prepared from phosphono allylic carbonates

Phosphono allylic carbonates have been used extensively by us as chiral building blocks for the syntheses of natural products and biologically active compounds (Figure 1). The reaction of phosphono allylic carbonates with various nucleophiles has been used for the synthesis of tumerone (**5**) (aryl stannane),[1] enterolactone (**6**) (malonate),[2] cyclic enolphosphonate lipase inhibitors (**7**) (acetoacetate),[3] the tetrahydrofuran containing diastereoisomeric oxylipids (**8a** and **8b**),[4] centrolobine (**9**),[5] and the tetrahydrofuran-containing fragment of amphidinolides C and F (**10**) (intramolecular hydroxy),[6] amongst others.[7] Consequently, methods for obtaining both the (*R*)-**2** and (*S*)-**2** enantiomers of phosphono allylic carbonates are particularly useful.

The α-hydroxy phosphonates (*R*)-**1** and (*S*)-**1** (Scheme 1) were prepared by catalytic asymmetric phosphonylation using dimethyl tartrate and titanium(IV) isopropoxide [Ti(O*i*-Pr)$_4$] as the catalyst.[10] The enantiomeric excess of the non-racemic hydroxy phosphonates was determined by ^{31}P NMR spectroscopy with quinine as a shift reagent.[11] L-Dimethyl tartrate and D-dimethyl tartrate delivered the (*R*)- and (*S*)-hydroxy phosphonate enantiomers, respectively, typically with modest enantiomeric excess (60–70% ee). The hydroxy phosphonates were treated with methyl chloroformate and pyridine to give the corresponding carbonates (*R*)-**2** and (*S*)-**2**. At this point, high enantiopurities of the phosphono allylic carbonates were desired because of their envisaged application in palladium π-allyl chemistry. An increase in the enantiopurity was achieved by enzyme-mediated kinetic resolution of carbonates of moderate enantiopurity.[12] The minor carbonate enantiomer was hydrolyzed, leaving the major enantiomer with increased enantiomeric excess. Amongst the different lipases that were screened, *R*-selective Amano lipase AYS and *S*-selective *Candida antarctica* lipase B (CALB) gave excellent enantioselectivity. In fact, treatment of the *S*- and *R*-carbonates of 60–70% ee with immobilized lipase AYS[13] and CALB, respectively, in a biphasic solution of methyl *tert*-butyl ether (MTBE) and pH 7 phosphate buffer yielded the respective carbonates in very high enantiomeric excess (usually ≥95%). The hydroxy phosphonate (**1**) is formed in low enantiomeric excess (see ref. 12 for details) and is usually discarded.

The enantiomeric purity of the carbonates **2** was determined directly by HPLC with an amylose-based AD-H chiral stationary phase. Carbonates **2** lack a sufficient chromophore for UV detection even at lower than 205 nm wavelengths, however, the enantiomers can be detected using a combination of polarimetric and refractive index detectors.[14] Alternatively, the enantiomeric excess can be determined indirectly by conversion of **2** into UV-absorbing phosphono cinnamyl carbonate (**11**) via alkene cross-metathesis with an excess of styrene using Grubbs' second-generation catalyst (Scheme 3).[8] The enantiomers of **11** can be resolved by HPLC using either an AD-H or Whelk-O 1[2] chiral stationary phase. The absolute configurations of the carbonates (*R*)-**2** and (*S*)-**2** were unambiguously assigned by conversion of the (–)-(*R*)-**2** enantiomer (~95% ee by HPLC) into (*R*)-**11**-(+). The rotation and HPLC elution order were in agreement with a sample of (+)-(*R*)-**11** prepared from configurationally known α-hydroxy phenylallyl phosphonate (+)-(*R*)-**12**.[15]



Scheme 3 Conversion of carbonate (–)-(*R*)-**2** into the configurationally known (+)-(*R*)-**11** derivative via alkene cross-metathesis

In summary, we have developed an efficient and reliable three-step procedure for the production of multigram quantities of (*R*)- and (*S*)-phosphono allylic carbonates **2**. The key transformations include an asymmetric Pudovik reaction, formation of the carbonate, and enzyme-mediated kinetic resolution. The individual steps are high yielding, highly reproducible, and overall have wide application in

the synthesis of biologically active natural products and could be useful in medicinal chemistry for the synthesis of heterocyclic compounds.

All reactions were carried out in oven-dried glassware under an atmosphere of argon unless otherwise noted. Tetrahydrofuran (THF) was dried by passing through activated alumina columns and then heated at reflux over Na/benzophenone and distilled. Dichloromethane (CH_2Cl_2) was dried over calcium hydride (CaH_2). Commercial reagents of high purity were purchased and used without further purification, unless otherwise noted. Ti(O*i*-Pr)$_4$ and dimethyl phosphite were distilled before use. Dimethyl tartrate was dried by azeotropic removal of water by toluene, followed by drying under vacuum. Lipase AYS was obtained from Amano and CALB was purchased from Sigma Aldrich. Reactions were monitored by thin-layer chromatography (TLC) using TLC silica gel plates (60 Å 254 nM) and visualizing with UV light or $KMnO_4$ stain. Silica gel (Natland International Corp, 230–400 mesh) was used for flash column chromatography. Optical rotations were recorded using a Jasco P-1010 polarimeter. IR spectra were obtained using a Thermo Nicolet Avatar 360 FT-IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ at 300 or 500 (^{1}H), 75 or 125 (^{13}C) and 121 (^{31}P) MHz, respectively. ^{1}H NMR spectra were referenced to residual $CHCl_3$ (7.27 ppm), ^{13}C NMR spectra were referenced to the center line of $CDCl_3$ (77.23 ppm), and ^{31}P NMR spectra were referenced to external 85% H_3PO_4 (0 ppm). Coupling constants, *J*, are reported in Hz.

Dimethyl (*S*)-(1-Hydroxyallyl)phosphonate [(*S*)-1]

To a solution of dry D-dimethyl tartrate (3.18 g, 89.3 mmol, 20 mol%) in anhydrous THF (135 mL) at –15 °C was added freshly distilled Ti(O*i*-Pr)$_4$ (5.23 mL, 17.8 mmol, 20 mol%), and the resulting mixture was stirred for 0.5 h. Freshly distilled dimethyl phosphite (16.36 mL, 178.6 mmol, 2 equiv) was added followed, after 10 min, by the addition of acrolein (5.95 mL, 89.3 mmol, 1 equiv). The flask containing the reaction mixture was placed in a freezer at a temperature of –15 °C for a period of 24 h. The reaction was quenched by dropwise addition of H_2O to precipitate the TiO_2, which was removed by filtration through Celite. The organic solution was washed with brine (50 mL) and the aq layer re-extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc–hexanes) to give the hydroxy phosphonate (*S*)-**1**.

Yield: 10.15 g (100%); colorless oil; R_f = 0.25 (100% EtOAc); 70% ee (measured by ^{31}P NMR spectroscopy after the addition of quinine as a chemical shift reagent).

IR (neat, NaCl): 3298, 2959, 2855, 1638 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09–5.92 (m, 1 H), 5.68–5.46 (m, 1 H), 5.41–5.30 (m, 1 H), 4.60–4.50 (m, 1 H), 3.82 (d, J_{H-P} = 11.3 Hz, 6 H).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 24.2.

(*S*)-1-(Dimethoxyphosphoryl)allyl Methyl Carbonate [(*S*)-2]

To a solution of hydroxy phosphonate (*S*)-**1** (1.86 g, 16.05 mmol, 1 equiv) in CH_2Cl_2 (15.6 mL) was added DMAP (0.392 g, 3.21 mmol, 20 mol%) followed by py (1.94 mL, 24.1 mmol, 1.5 equiv) and then $ClCO_2Me$ (3.3 g, 2.47 mL, 2 equiv) at 0 °C. The reaction mixture was allowed to warm to r.t. and was stirred for 16 h. The reaction was quenched with HCl (1 M) and the aq layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc–hexanes) to give the carbonate (*S*)-**2**.

Yield: 2.87 g (80%); colorless oil; R_f = 0.58 (100% EtOAc).

IR (neat, NaCl): 2960, 2856, 1757, 1642 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04–5.88 (m, 1 H), 5.57–5.45 (m, 2 H), 5.43–5.38 (m, 1 H), 3.85 (s, 3 H), 3.83 (d, J_{H-P} = 10.5 Hz, 6 H).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 19.48.

To the *S*-carbonate (*S*)-**2** (3.09 g, 70% ee) was added MTBE (61 mL) and pH 7.0 phosphate buffer (61 mL), followed by the immobilized lipase AYS (4.43 g). The reaction mixture was agitated using a rotary shaker for 24 h, after which another batch of immobilized lipase AYS (4.43 g) was added. The mixture was stirred for an additional 48 h and then filtered through a pad of Celite. After the addition of brine, the aq mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc–hexanes) to give the carbonate (*S*)-**2**.

Yield: 1.29 g (42%); a colorless oil; 95% ee; $[\alpha]_D$ +16.7 (*c* 1, $CHCl_3$).

The enantiomeric excess was measured either directly or indirectly by HPLC (see the Supporting Information).

Dimethyl (*R*)-1-Hydroxyallylphosphonate [(*R*)-1]

The title compound was prepared using the same procedure as that described for the synthesis of (*S*)-hydroxy phosphonate (*S*)-**1**, using L-dimethyl tartrate instead of D-dimethyl tartrate.

(*R*)-1-(Dimethoxyphosphoryl)allyl Methyl Carbonate [(*R*)-2]

A solution of the *R*-carbonate (*R*)-**2** (0.5 g, 72% ee) in MTBE (5 mL) was added to a solution of CALB (0.6 g) in pH 7.0 phosphate buffer (5 mL). The flask containing the mixture was placed in an oil bath set to 40 °C and the contents stirred. The progress of the reaction was monitored by taking an aliquot from the organic and aq layers (0.1 mL from each layer). The aliquot was drawn out from the mixture by syringe and evaporated in vacuo before checking by ^{31}P NMR spectroscopy. The reaction was stopped at 24% conversion and the CALB was removed by filtration. The CALB was washed several times with MTBE to rinse off the reaction mixture which was coated on the enzyme-polymer surface. The CALB was dried in air and kept in a freezer for subsequent reuse. The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the carbonate (*R*)-**2**.

Yield: 0.26 g (68%); colorless oil; >98% ee.

Enzyme Recycling

The CALB can be used up to five times in the hydrolysis of the *R*-carbonate (*R*)-**2** under the same reaction conditions to give products with similar ee values, but with diminishing reaction rates. Recycling of the immobilized lipase AYS was not examined.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560487.

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