

Asymmetric Synthesis of 2-Alkyl-3-phosphonopropanoic Acids via P–C Bond Formation and Hydrogenation

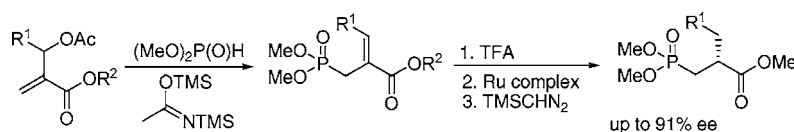
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ABSTRACT



Allylic acetates, formed by the acetylation of Baylis Hillman adducts, undergo addition of phosphorus nucleophiles to give stereoselectively the Z-unsaturated esters. TFA cleavage of the *tert*-butyl ester and asymmetric hydrogenation of the unsaturated acid yields the phosphono alkyl propanoic acid moiety, commonly found in phosphonate- and phosphinate-based enzyme inhibitors.

The tetracoordinate phosphoryl group is well recognized as an excellent mimic for the tetrahedral transition state of ester and amide hydrolysis.¹ Thus, phosphonates have become increasingly common in the development of tools for biological investigations, and in the generation of lead compounds for the pharmaceutical industry.² More recently, phosphinic acids [RR'²P(O)OH] have also become popular targets as mimics of tetrahedral transition states.³ Both phosphonate⁴ and phosphinate-based³ enzyme inhibitors commonly contain a 2-alkylpropanoic acid as the carbon substituent. The additional alkyl residue and resulting stereocenter complicates the synthesis of these molecules and often results in isomeric mixtures.⁵

In spite of the challenging syntheses, there are many examples of phosphonate and phosphinate enzyme inhibitors

(Figure 1) that show very potent activity.^{3,4} The phosphorus carbon bond in the 3-phosphono-2-alkylpropanoic acids is typically formed by alkylation of a phosphorus nucleophile with a Michael acceptor,^{3a,5} but although the chemical yields are good, there is generally little control of the newly formed

(1) (a) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654. (b) Sampson, N. S.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500. (c) Bartlett, P. A.; Hanson, J. E.; Giannousis, P. P. *J. Org. Chem.* **1990**, *55*, 6268. (d) Bartlett, P. A.; Giangordano, M. A. *J. Org. Chem.* **1996**, *61*, 3433.

(2) For examples, see: (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587. (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, Jr., E. W. *J. Med. Chem.* **1995**, *38*, 4557. (c) Wang, C.-L. J.; Taylor, T. L.; Mical, A. J.; Spitz, S.; Rielly, T. M. *Tetrahedron Lett.* **1992**, *33*, 7667. (d) Dellaria, J. F., Jr.; Maki, R. G. *Tetrahedron Lett.* **1986**, *27*, 3337. (e) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.

(3) For examples see: (a) Valiaeva, N.; Bartley, D.; Konno, T.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 5146. (b) Bartley, D.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757. (c) Chen, H.; Noble, F.; Roques, B. P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **2001**, *44*, 3523. (d) Jackson, P. F.; Tays, K. L.; Maclin, K. M.; Ko, Y.-S.; Li, W.; Vitharana, D.; Tsukamoto, T.; Stoermer, D.; Lu, X.-C. M.; Wozniak, K.; Slusher, B. S. *J. Med. Chem.* **2001**, *44*, 4170. (e) Vassiliou, S.; Mucha, A.; Cuniasse, P.; Georgiadis, D.; Lucet-Levannier, K.; Beau, F.; Kannan, R.; Murphy, G.; Knauper, V.; Rio, M.-C.; Basset, P.; Yiotakis, A.; Dive, V. *J. Med. Chem.* **1999**, *42*, 2610. (f) Bartlett, P. A.; Kezer, W. B. *J. Am. Chem. Soc.* **1984**, *106*, 4282. (g) Demange, L.; Dugave, C. *Tetrahedron Lett.* **2001**, *42*, 6295. (h) McDermott, A. E.; Creuzet, F.; Griffin, R. G.; Zawadzke, L. E.; Ye, Q.-Z.; Walsh, C. T. *Biochemistry* **1990**, *29*, 5767. (i) Hiratake, J.; Kato, H.; Oda, J. *J. Am. Chem. Soc.* **1994**, *116*, 12059. (j) Demange, L.; Dugave, C. *Tetrahedron Lett.* **2001**, *42*, 6295. (k) Matziari, M.; Beau, F.; Cuniasse, P.; Dive, V.; Yiotakis, A. *J. Med. Chem.* **2004**, *47*, 325.

(4) For examples, see: (a) Majer, P.; Hin, B.; Stoermer, D.; Adams, J.; Xu, W.; Duvall, B. R.; Delahanty, G.; Liu, Q.; Stathis, M. J.; Wozniak, K. M.; Slusher, B. S.; Tsukamoto, T. *J. Med. Chem.* **2006**, *49*, 2876. (b) Morphy, J. R.; Beeley, N. R. A.; Boyce, B. A.; Leonard, J.; Mason, B.; Millican, A.; Millar, K.; O'Connell, J. P.; Porter, J. *Biorg. Med. Chem. Lett.* **1994**, *4*, 2747.

(5) For examples, see: (a) Chen, H.; Noble, F.; Mothé, A.; Meudal, H.; Coric, P.; Danascimento, S.; Roques, B. P.; George, P.; Fournié-Zaluski, M. C. *J. Med. Chem.* **2000**, *43*, 1398. (b) Matziari, M.; Yiotakis, A. *Org. Lett.* **2005**, *7*, 4049.

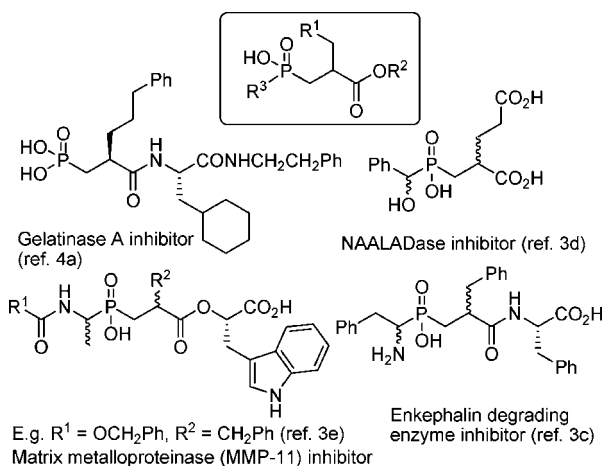


Figure 1. Examples of phosphonate and phosphinate enzyme inhibitors.

stereocenter. This problem has been addressed to some extent by using a chiral auxiliary on the Michael acceptor.^{3b,6} However, concern for the environment and a trend toward “green” chemistry has led to the need for catalytic transformations.

Catalytic asymmetric hydrogenation is a powerful tool for the introduction of stereocenters.⁷ Substituted itaconic acids have been successfully and selectively hydrogenated to give the corresponding 2-alkylsuccinates,⁸ which are structurally similar to the 3-phosphono-2-alkyl propanoic acids of interest. Therefore, it should be possible to form a phosphono analogue of itaconic acid as a substrate for asymmetric hydrogenation. Although we were concerned that the phosphoryl group might disrupt the appropriate coordination of the metal complex to the substrate leading to lower selectivity and slow reactions, successful examples of the hydrogenation of phosphonate analogs of commonly used acid substrates have been reported.⁹

Herein, we report a method to control the stereochemistry of the alkylpropanoic acid side chains found in phosphonate and phosphinate enzyme inhibitors via the asymmetric hydrogenation of unsaturated precursors. The unsaturated precursors are formed by the addition of a phosphorus nucleophile [P(O)H moiety] to acetylated Baylis–Hillman adducts.

Baylis–Hillman reaction of several aldehydes¹⁰ with methyl or *tert*-butyl acrylate followed by acetylation¹¹ of the

intermediate alcohol, gave the allylic acetates (**1**). Dialkyl phosphites were selected as the model for compounds containing the P(O)H group. Addition of dialkyl phosphites to the acetylated Baylis–Hillman adducts (**1**) in refluxing *N,O*-bis(trimethylsilyl)acetamide resulted in the formation of the phosphono unsaturated esters¹² (**2**) (Scheme 1, Table

Scheme 1. Synthesis of the Unsaturated Esters

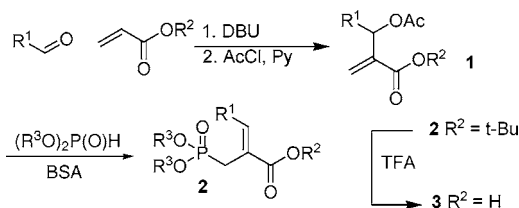


Table 1. Addition of Phosphites to Allylic Acetates (**1**)

no.	R ¹	R ²	R ³	yield (%) (2)	yield (%) (3)	Z/E ratio
2a	Ph	Me	Me	76		Z only
2b	Ph	<i>t</i> -Bu	Me	61	94	8:1
2c	Ph	<i>t</i> -Bu	Et	73		Z only
2d	Ph	<i>t</i> -Bu	Bn	27		Z only
2e	Ph	<i>t</i> -Bu	<i>i</i> -Pr	57		Z only
2f	2-furyl	<i>t</i> -Bu	Me	70	97	16:1
2g	<i>p</i> -MeO-C ₆ H ₄	<i>t</i> -Bu	Me	85	85	Z only
2h	<i>p</i> -Cl-C ₆ H ₄	<i>t</i> -Bu	Me	58	96	Z only
2i	<i>p</i> -F-C ₆ H ₄	<i>t</i> -Bu	Me	77	81	Z only
2j	<i>p</i> -Br-C ₆ H ₄	<i>t</i> -Bu	Me	65	91	Z only
2k	Me	<i>t</i> -Bu	Me	56	89	5:1

1). With the exception of benzyl phosphite, the yields for the addition–elimination reactions are generally good. The corresponding carboxylic acids (**3**) were obtained by cleaving the *tert*-butyl esters with TFA in CH₂Cl₂.

Phosphono esters (**2a**) was also prepared as mixture of *E* and *Z* isomers using a published method^{12a} (Scheme 2), as was the unsubstituted ester (**2l**). The *E* isomer showed a signal in the ¹H NMR spectrum for the alkene hydrogen at 6.95 ppm and the *Z* isomer showed a signal at 7.75 ppm. This

(6) Liu, X.; Hu, E.; Tian, X.; Mazur, A.; Ebetino, F. J. *Organomet. Chem.* **2002**, *646*, 212.

(7) For recent reviews of asymmetric hydrogenation, see: (a) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(8) (a) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421. (b) Boaz, N.; Mackenzie, E.; Debenham, S.; Large, S.; Ponasiak, J., Jr. *J. Org. Chem.* **2005**, *70*, 1872. (c) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205.

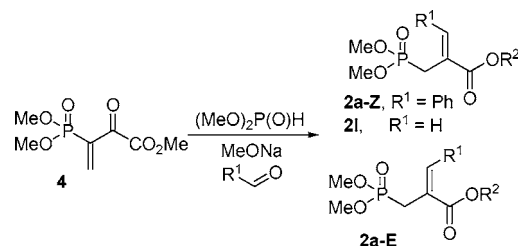
(9) (a) Schmidt, U.; Oehme, G.; Krause, H. *Synth. Commun.* **1996**, *26*, 777. (b) Gautier, I.; Ratovelomanana-Vidal, V.; Savignac, P.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 7721. (c) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387.

(10) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (c) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (d) Yu, C.; Liu, B.; Hu, L. J. *J. Org. Chem.* **2001**, *66*, 5413.

(11) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197.

(12) (a) Schoen, W. R.; Parsons, W. H. *Tetrahedron Lett.* **1988**, *29*, 5201. (b) Basavaiah, D.; Pandiaraju, S. *Tetrahedron* **1996**, *52*, 2261. (c) Kraïem, H.; Abdullah, M. I.; Amri, H. *Tetrahedron Lett.* **2003**, *44*, 553. (d) Muthiah, C.; Senthil Kumar, K.; Vittal, J. J.; Kumara Swamy, K. C. *Synlett* **2002**, *11*, 1787. (e) Oikawa, H.; Yagi, K.; Ohashi, S.; Watanabe, K.; Mie, T.; Ichihara, A.; Honma, M.; Kobayashi, K. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2368. (f) Fields, S. *Tetrahedron Lett.* **1998**, *39*, 6621. (g) Phillion, D.; Cleary, D. J. *J. Org. Chem.* **1992**, *57*, 2763. (h) Janecki, T.; Bodalski, R. *Synthesis* **1990**, *9*, 799. (i) Janecki, T.; Bodalski, R. *Synthesis* **1989**, *7*, 506. (j) Bentley, R.; Dingwall, J. *Synthesis* **1985**, *5*, 552. (k) Matziari, M.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Org. Lett.* **2001**, *3*, 659. (l) Gurulingappa, H.; Buckhaults, P.; Kumar, S. K.; Kinzler, K. W.; Vogelstein, B.; Khan, S. R. *Tetrahedron Lett.* **2003**, *44*, 1871.

Scheme 2. Synthesis of *E* and *Z* Unsaturated Esters

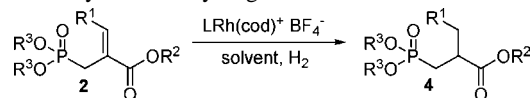


clearly identified the product of phosphite addition to the allylic acetate **2** as the *Z* isomer. The alkene geometries were assigned by NOE studies and confirmed in one example (**2j**) by single-crystal X-ray diffraction studies on the fully deprotected acid.¹³

In a 1995 patent, Talley reported the asymmetric hydrogenation of some (phosphono) unsaturated esters (**2**) with a rhodium dipamp complex. Hydrogenation of the parent compound (**2i**, $R^1 = H$, $R^2 = R^3 = Me$) gave the saturated ester with optical rotation ($[\alpha]_D$) of -8.8 ($c = 2.6$, MeOH). The absolute configuration of the chiral center in the product was assigned as *S*. No information in the levels of selectivity or the stereochemistry of the products was reported for the other examples given in the patent.¹⁴

The hydrogenation of the parent unsaturated ester **2i** with rhodium dipamp complex was repeated and the reported value of the optical rotation for the product was confirmed.¹⁴ However, in our hands hydrogenation of the substituted *Z* phosphono-unsaturated ester (**3a**) with rhodium dipamp gave low levels of selectivity (Table 2). Furthermore hydrogenation

Table 2. Asymmetric Hydrogenation of the Unsaturated Esters



no.	R ¹	R ²	R ³	solvent	ligand	% ee ^a
1	Ph	Me	Me	MeOH	Dipamp	7
2	Ph	Me	Me	MeOH	Duphos	0
3	Ph	Me	Me	CH ₂ Cl ₂	Duphos	34
4	Ph	Me	Me	PhMe	Duphos	15
5	Ph	Me	Me	THF	Duphos	35
6	Ph	<i>t</i> -Bu	Me	MeOH	Duphos	36
7	Ph	<i>t</i> -Bu	Me	THF	Duphos	42

^a Enantiomeric excess determined by HPLC.

tion of phosphonate (**3a**) ($R^1 = Ph$, $R^2 = R^3 = Me$) in THF with rhodium complexes^{8,15} derived from several other ligands, e.g., Bophos^{8a,b}, Mbpe,^{15a} Tangphos,^{8c,15d} and Me-Duphos,^{15a,b} gave saturated product with <3% enantiomeric excess (HPLC analysis). Only Et-Duphos^{15a,b} gave measur-

able levels of selectivity (Table 2). Neither changes in solvent or hydrogen pressure showed much effect on the reaction selectivity.

Since hydrogenation of unsaturated carboxylic acids is generally more selective than the corresponding esters,⁸ reaction of the phosphono unsaturated acids were examined. Unfortunately, hydrogenation of carboxylic acids (**3**) with various chiral rhodium catalysts also gave less than satisfactory results (Scheme 3, Table 3). The stereoselectivity of

Scheme 3

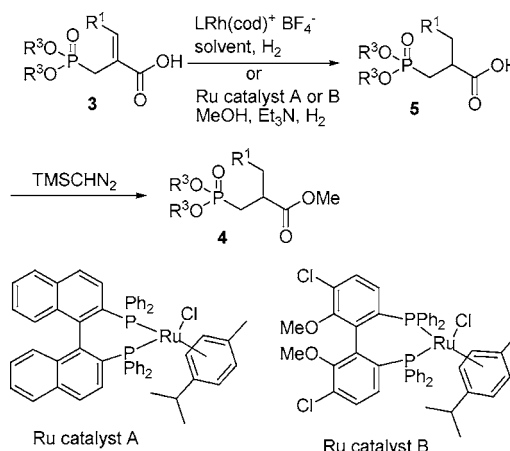


Table 3. Asymmetric Hydrogenation of the Unsaturated Carboxylic Acids Using Rh Catalyst

entry	R ¹	R ³	solvent	ligand	% ee ^a
1	Ph	Me	MeOH	Duphos	0
2	Ph	Me	MeOH, Bu ₃ N	Duphos	30
3	Ph	Me	MeOH	ferrotane	1
4	Ph	Me	MeOH, Bu ₃ N	ferrotane	4
5	Ph	Me	MeOH, Bu ₃ N	Tangphos	52

^a Enantiomeric excess determined by HPLC on the methyl ester **4**.

hydrogenation improved upon addition of tributylamine to the reaction mixture, but only to modest levels. After hydrogenation, the saturated acids (**5**) were converted to the corresponding methyl ester (**4**) by reaction with TMSCHN₂

(15) (a) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, 68, 37. Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, 64, 3290. (b) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, 120, 4345. (c) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, 117, 9375. (d) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, 41, 1612. (e) Hammadi, A.; Nuzillard, J. M.; Poulin, J. C.; Kagan, H. B. *Tetrahedron: Asymmetry* **1992**, 3, 1247.

(16) (a) Matteoli, U.; Frediani, P.; Bianchi, M.; Botteghi, C.; Gladiali, S. *J. Mol. Catal.* **1981**, 12, 265. (b) Genet, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Cano De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, 5, 675. (c) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, 102, 7932. (d) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, 52, 3174. (e) Drienben-Holscher, B.; Kralik, J.; Agel, F.; Steffens, C.; Hu, C. *Adv. Synth. Catal.* **2004**, 346, 979. (f) Laue, C.; Schroder, G.; Arlt, D. U.S. Patent 5-801,261, 1998.

(13) See the Supporting Information.

(14) Talley, J. U. S. Patent 5,473,092, 1995.

and the methyl esters were analyzed by HPLC to determine the selectivity.

Gratifyingly, hydrogenation of carboxylic acids (**3**) with the ruthenium catalysts¹⁶ (A or B) in methanol and triethylamine at 125 psi H₂ gave the saturated acids with good to high enantiomeric excess (Table 4, Scheme 3). The addition

Table 4. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Using Ru Catalyst

entry	R ¹	R ³	3, 4, 5	complex	% ee ^a
1	Ph	Me	a	A	71
2				B	91
3	2-furyl	Me	f	A	12
4				B	58
5	<i>p</i> -MeO-C ₆ H ₄	Me	g	A	65
6				B	83
7	<i>p</i> -Cl-C ₆ H ₄	Me	h	A	66
8				B	85
9	<i>p</i> -F-C ₆ H ₄	Me	i	A	71
10				B	81
11	<i>p</i> -Br-C ₆ H ₄	Me	j	A	62
12				B	80
13	Me	Me	k	B	89

^a Enantiomeric excess determined by HPLC on the methyl ester **4**.

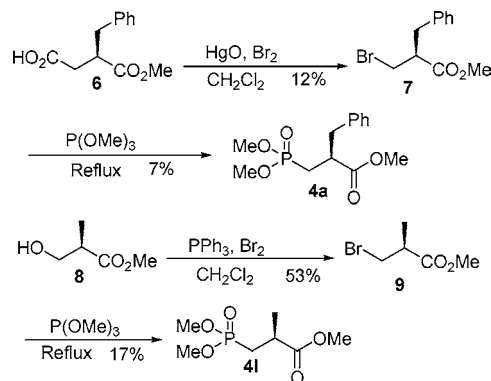
of a tertiary amine base was critical for high enantiomeric excess. The (*R*)-Cl-MeO-BIPHEP-Ru catalyst (complex B) was more selective than the Binap-Ru catalyst (complex A).

To determine the absolute stereochemistry of the saturated acids from hydrogenation, the commercially available optically pure (2*R*)-methyl 2-benzylsuccinic acid (**6**) was converted into the corresponding phosphonate (**4a**). Bromodecarboxylation (Hunsdiecker reaction) of the succinic acid (**6**) using bromine and red mercuric oxide in methylene chloride yielded the desired bromide **7**, albeit in very low yield.¹⁷ Arbuzov reaction of the bromide **7** with neat trimethyl phosphite led to the formation of the saturated ester (**4a**), again in low yield. This saturated ester had a positive rotation ([α]_D) and an 86% enantiomeric excess of the *S* isomer (HPLC). The saturated ester (**4a**) obtained by hydrogenation using the (*R*)-Cl-MeO-BIPHEP-Ru catalyst (complex B)

(17) (a) Arney, B. E., Jr.; Wilcox, K.; Campbell, E.; Gutierrez, M. O. *J. Org. Chem.* **1993**, 58, 6126. (b) Johnson, R.; Ingham, R. *Chem. Rev.* **1956**, 56, 219.

showed a negative rotation and an 87% enantiomeric excess of the opposite *R* isomer (Scheme 4).

Scheme 4. Determining the Absolute Configuration



Similarly, methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate (**8**) was converted to the corresponding bromide (**9**) using triphenylphosphine and bromine. Arbuzov reaction of the bromide (**9**) with trimethyl phosphite gave the saturated methyl ester (**4l**). This saturated ester had [α]_D = +8.19 (*c* 0.26, MeOH) which corresponded to the “*R*” isomer. The saturated ester (**4l**) obtained by the hydrogenation using the dipamap Rh-catalyst gave a negative rotation, which corresponded to the “*S*” isomer, confirming the early observations by Talley for this compound.

In conclusion, 2-alkyl-3-phosphonopropanoic acids are formed with high enantioselectivity by addition of phosphites to acetylated Baylis–Hillman adducts, cleavage of the *tert*-butyl ester and asymmetric hydrogenation with ruthenium complexes.

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Supporting Information Available: Typical experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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