Pergamon

Tetrahedron, Vol. 53, No. 49, pp. 16609-16644, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10305-2

TETRAHEDRON REPORT NUMBER 435

Synthesis of Nonracemic Phosphonates

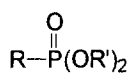
David F. Wiemer

Department of Chemistry, University of Iowa, Iowa City, Iowa 52245

Contents

1. Introduction.

Phosphonic acids and their phosphonate derivatives are common in the literature of organic chemistry where they are employed in synthetic operations leading to carbon-carbon bond formation,[1] sought for their potential contribution to biological activities,[2] and used as transition state analogues in production of antibodies catalytic for a wide variety of reactions.[3] As chemists' interests have focused on preparation of chiral compounds as single enantiomers,[4] interest in preparation of nonracemic phosphonates has followed suit. Thus a flurry of recent activity has expanded some of the traditional methods for phosphonate synthesis to allow preparation of nonracemic compounds and new synthetic methods have been developed. In turn, the increasing availability of nonracemic phosphonates should stimulate additional interest in their chemistry.



Without question, the best known synthetic application of phosphonates is their use in the Horner-Wadsworth-Emmons (HWE) condensation,[1] which often is used to prepare α,β-unsaturated carbonyl compounds from condensations of an aldehyde or ketone with an anion stabilized by both a phosphonate and a

E-mail: david-wiemer@uiowa.edu *FAX: 319-335-1270*

second electron withdrawing group. In condensations with phosphono acetates, which is arguably the most common expression of this strategy, both the need and the opportunity for obtaining nonracemic products may be limited, but with larger phosphono esters or phosphono ketones, issues of stereochemistry are more commonly encountered. Furthermore, phosphonates also can be employed in procedures that give access to other functional groups, including nonconjugated olefins[5] and cyclopropanes.[6]

Interest in the biological activity of phosphonates has grown tremendously in recent years. If phosphate esters represent the currency of metabolism, then the analogous phosphonates can be viewed as exquisite counterfeits: perhaps passable in many transactions but ultimately forgeries nonetheless. When the oxygen of a natural phosphate ester is formally replaced by a methylene group, the resulting phosphonate can be viewed as an isosteric analogue of the original phosphate with greatly enhanced metabolic stability. However, the formal substitution also affects the phosphorus acid pK_a's (with the second pK_a of the phosphonic acid about 0.5-1.5 pK_a units less acidic than that of the phosphate monoester)[7] and eliminates the possibility of enzymatic interaction with non-bonded electrons at this site. Addition of electron withdrawing substituents such as fluorine[8] or oxygen[9] to the α-carbon can address both of these issues and enhance biological activity. When an amino group is positioned on the α-carbon, α-amino phosphonates that are clear analogues of α-amino acids can be constructed. Introduction of a geminal difluoromethylene group does not produce stereochemical considerations, but preparations of most α-hydroxy and α-amino phosphonates will require consideration of the stereochemistry of the α-carbon if biological activity is a goal. Various α-hydroxy phosphonates already have established activity as inhibitors of renin,[10] enolpyruvylshikimate-3-phosphate (EPSP) synthase,[11] farnesyl protein transferase,[12] and HIV protease,[13] while α-amino phosphonates have been studied as inhibitors of a variety of enzymes, either directly or after they have been incorporated into peptide analogues.[14]

A relatively recent stimulus for interest in synthesis of phosphonates stems from their application in the preparation of catalytic antibodies.[3] In their mono ester mono anionic forms, phosphonates are believed to present a shape and charge distribution that mimics a high energy intermediate in acyl transfer reactions such as ester or amide hydrolysis.[3,15] When used to stimulate an immune response, phosphonates can serve as transition state analogues leading to formation of antibodies that stabilize reaction intermediates and express catalytic activity. Applications of phosphonate haptens are not limited to formation of antibodies for catalysis of acyl transfer reactions.[3] For example, phosphonates have been used to generate antibodies that complex with some ketones, providing a chiral environment that allows stereoselective reduction of a prochiral ketone by $NaBH_3CN$.[16] To maximize the potential for stereoselectivity inherent in enzyme catalyzed reactions and minimize antibody screening, use of nonracemic phosphonates for preparation of the catalytic antibodies can be viewed as advantageous,[17] although in some cases racemic haptens have been used deliberately to simultaneously prepare antibodies that selectively bind to either substrate enantiomer.[18]

This report will survey recent strategies employed to prepare nonracemic phosphonates. A consideration of preparations of α-hydroxy phosphonates may be the most appropriate point to begin. On one hand, α-hydroxy phosphonates can be converted to many other functionalized phosphonates, providing convenient access to other structural types.[19] On the other hand, there are many different approaches to α-hydroxy phosphonates, including a recent combinatorial strategy,[20] which together offer a great deal of flexibility to their synthesis. Keto phosphonates and phosphono esters also will be considered. Because there have been extensive commentaries on α-amino phosphonates,[14] they will not be considered here.

2. Hydroxy Phosphonates.

2.1 α-Hydroxy Phosphonates.

Prominent among the early routes to α-hydroxy phosphonates are the additions of dialkyl phosphites (Pudovic reaction)[21] and trialkyl phosphites (Abramov reaction)[22] to aldehydes and ketones, and it is not surprising that parallel reactions have been explored to provide access to nonracemic α-hydroxy phosphonates. In principle, nonracemic α-hydroxy phosphonates could be obtained from addition of achiral phosphites to nonracemic aldehydes and ketones, from reactions of optically active phosphorus (III) reagents with a carbonyl compound, or from condensation of an achiral phosphite with an aldehyde or prochiral ketone if mediated by a nonracemic catalyst. Examples of all three approaches are known.

At least in theory, nonracemic α-hydroxy phosphonates can be obtained from phosphite additions to any aldehyde or ketone drawn from the chiral pool. Several early examples involving phosphite additions to aldehydes (including glyceraldehyde, erythrose, xylose and arbinose derivatives[23]) and ketones (including preparation of ribose and glucose derivatives[24]) in protected carbohydrates illustrate this strategy. As might be expected, limited diastereoselectivity generally is observed for additions to aldoses, but the greater conformational definition of cyclic ketones usually results in greater diastereoselectivity.[23,24] In a nice comparison of diastereoselectivity under both Pudovic and Abramov conditions, an aldehyde (**1**) derived from methyl lactate was reported to give the greatest erythro/threo ratio (ca. 3:1 **2**:**3**) from an Abramov reaction with diisopropyl trimethylsilyl phosphite (Figure 1).[25a]

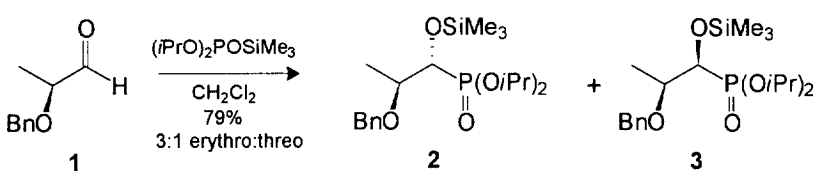


Figure 1. Synthesis of α-Hydroxy Phosphonates from O-Benzyl Lactaldehyde.[25]

More recent research has extended this approach to carbonyl compounds derived from amino acids. For example, the Boc amino aldehyde **4** derived from L-phenylalanine, undergoes diastereoselective addition of dimethyl phosphite to give α-hydroxy phosphonates **5** and **6** with diastereomeric excess (de) as high as 12:1 (Figure 2).[10] Even greater de's (up to >98:2) were observed in formation of the α-hydroxy phosphonates **8** and **9** through use of *t*-butyldimethylsilyl diethyl phosphite in a $TiCl_4$ catalyzed condensation with an α-dibenzylamino aldehyde (7) derived from L-phenylalanine.[26] Furthermore, a reversal of the addition stereochemistry was observed when diethyl phosphite was employed in place of the *t*-BDMS phosphite, which was explained on the basis of the lessened nucleophilicity of diethyl phosphite and the assumption of chelation controlled addition. In both studies, removal of the amine protecting groups gave β-amino α-hydroxy phosphonates valued as components of peptidomimetics.

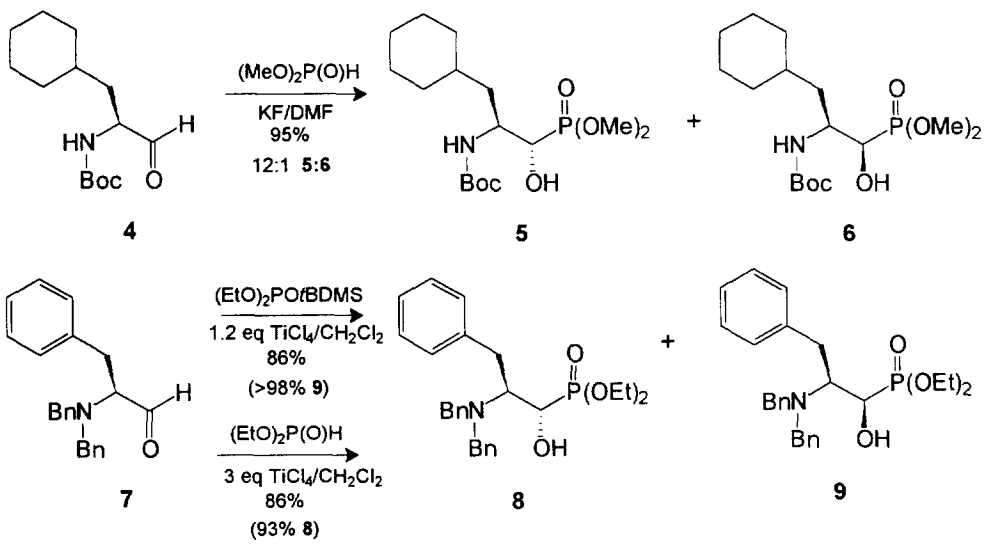


Figure 2. Stereoselective Phosphite Additions to Phenylalanine Derivatives.[10,26]

Phosphite condensations with nonracemic ketones have been used to prepare nucleoside 3'-phosphonic acids (**10**) via two complementary strategies (Figure 3). One[27] involved preparation of a ribose α-hydroxy phosphonate (**12**) through phosphite addition to the ribose-derived ketone **11**. Phosphonate **12** was converted to different nucleosides through reaction with various heterocyclic bases. Although this strategy allows incorporation of non-natural bases into the nucleoside derivatives, control of the stereochemistry of the glycosidic linkage can be problematic in some cases. The complementary approach[28] involves an initial preparation of the nucleoside ketones (**13**) and subsequent condensation with phosphite to obtain the hydroxy phosphonates **14**. While the latter strategy avoids issues of stereocontrol during ribosylation, it is limited to cases where the parent nucleosides are readily available.

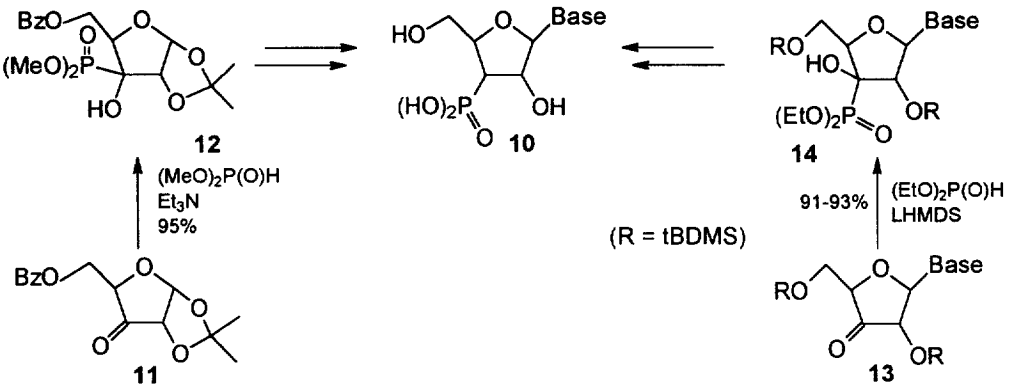


Figure 3. Syntheses of Nucleoside 3'-Phosphonates.[27,28]

Stereoselective additions of phosphorus acid derivatives to achiral aldehydes have been investigated under both Pudovic and Abramov reaction conditions. A number of nonracemic alcohols are readily available and could be employed in preparation of nonracemic dialkyl or trialkyl phosphites, but attention has been focused instead on the chemistry of mono- and diamide derivatives of phosphorus acid. The initial observation that oxazaphosphite **15a** reacted with benzaldehyde to afford a 3:1 mixture of the diastereomeric α-hydroxy phosphonates **17** and **18** prompted a study of BF_3 promoted additions of the methyl derivative **15b** to a variety of aldehydes (Figure 4). Diastereoselectivity was anticipated on the assumption that steric interactions between the isopropyl group of compound **15b** and the larger substituent of the aldehyde would hinder one approach. Unfortunately, only modest de (32%) was observed in the latter reactions.[29]

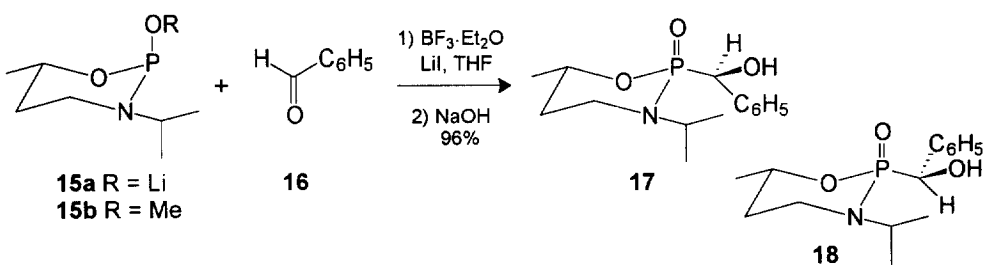
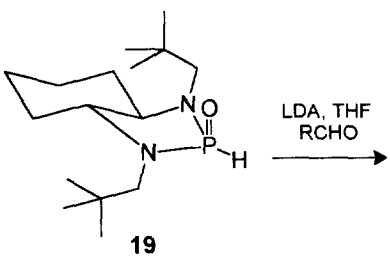


Figure 4. Oxazaphosphite Additions to Aldehydes.[29]

Phosphorus acid diamides have been reported to provide very attractive stereoselectivity in their condensations with a number of aldehydes.[30] Several N,N'-dialkyl derivatives of diaminocyclohexane have been used to prepare nonracemic phosphorus acid diamides, and condensations of these amides with various aldehydes have been explored (Figure 5). In the best cases, condensations of diamide **19** with benzaldehyde and β-naphthaldehyde gave product ratios of 25 and 29:1 by ^{31}P NMR (**20e** and **20d**). With aliphatic

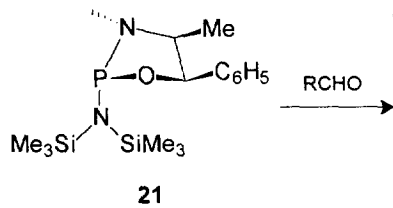
aldehydes where more modest ratios were observed (from 3.4 to 7.9:1), one or more recrystallizations usually gave a single diastereomer. Diffraction analyses established that major diastereomers produced from the *R,R*-diamide **19** and crotonaldehyde (**20b**) and isovaleraldehyde (**20f**) were S at the new stereogenic center. Conformational analysis suggested that *si* face addition of a tricoordinate phosphorus nucleophile to the carbonyl minimizes steric interactions of the aldehyde substituent with the methyl groups of the neopentyl substituent. Representative products were cleaved to the α-hydroxy phosphonic acids through reaction with aqueous HCl, and esterified to the corresponding dimethyl esters through reaction with ethereal diazomethane.



aldehyde	%	ratio
a cinnamaldehyde	68	7.9:1
b crotonaldehyde	91	6.9:1
c α-naphthaldehyde	58	14:1
d β-naphthaldehyde	91	29:1
e benzaldehyde	49	25:1
f isovaleraldehyde	82	3.4:1
g heptaldehyde	80	4:1

Figure 5. Diastereoselective Additions of Diamide **19**.[30]

Nonracemic phosphorus acid derivatives also have been employed in Abramov reactions. After an initial report[31a] demonstrating the viability of trialkylsilyl transfer from 2-bis(trimethylsilyl)amido-1,3,2-diazaphospholidine and a detailed study of the Abramov reaction mechanism,[31b] (1*R*, 2*S*)-ephedrine was used to prepare the nonracemic reagent **21** (Figure 6).[31c] Good to excellent diastereoselectivities were observed upon reaction of compound **21** with various carbonyl compounds to afford α-hydroxy phosphoryl compounds. While these studies have illuminated many details of the mechanism and stereochemical course of the Abramov reaction, conversion of the products to α-hydroxy phosphonates has not yet been reported.



aldehyde	%	de
a α-naphthaldehyde	62	32
b β-naphthaldehyde	86	82
c benzaldehyde	83	84
d butyraldehyde	---	62

Figure 6. Diastereoselective Additions of an Ephedrine Derivative.[31]

Diastereoselective additions of nonracemic P(III) derivatives to aldehydes have provided access to a number of chiral α-hydroxy phosphoryl compounds, but these strategies necessarily require stoichiometric amounts of a chiral reagent. It has been recognized for some time that phosphite condensations catalyzed by nonracemic materials might allow use of sub-stoichiometric quantities of the chiral, and generally most expensive, component. The first demonstration of this strategy employed quinine as the base,[32] and gave α-

hydroxy phosphonates from *o*-nitrobenzaldehyde (**23**) with ee's ranging from 28% for dimethyl phosphite to 80-85% for the more hindered di-*tert*-butyl phosphite[33] (Figure 7). Furthermore, it proved possible to convert the nitro group to other substituents (**24b-d**) via diazonium ion chemistry without racemization of the benzylic position.[33] A flurry of more recent publications has reported enantioselective catalysis of a variety of similar reactions with different nonracemic Lewis acid catalysts.[34-37] Rather modest ee's were obtained with complex **25,** which was derived from diisopropyl tartrate and $Ti(O\text{-}iPr)_4$.[34] Two research groups independently investigated the effect of catalytic amounts of the lanthanide binaphthol complex **26** on Pudovic reactions.[35,36] Both found ee's in the range of 20-28% for phosphite condensations with benzaldehyde, but more attractive de's were found with *p*-methoxy and *p*-methylbenzaldehyde.[35] The best results reported thus far employed a Li-Al-binaphthol complex (**27**).[37] With this catalyst, both good chemical yields and ee's in the range of 70-90% were observed with several aromatic and unsaturated aldehydes (Figure 7). Although saturated aldehydes such as hexanal and cyclohexanecarboxaldehyde also gave good chemical yields of the expected α-hydroxy phosphonates, only low ee's were observed in these cases. Nevertheless, these results should spur interest in exploration of other reagents for catalytic formation of nonracemic α-hydroxy phosphonates.[38]

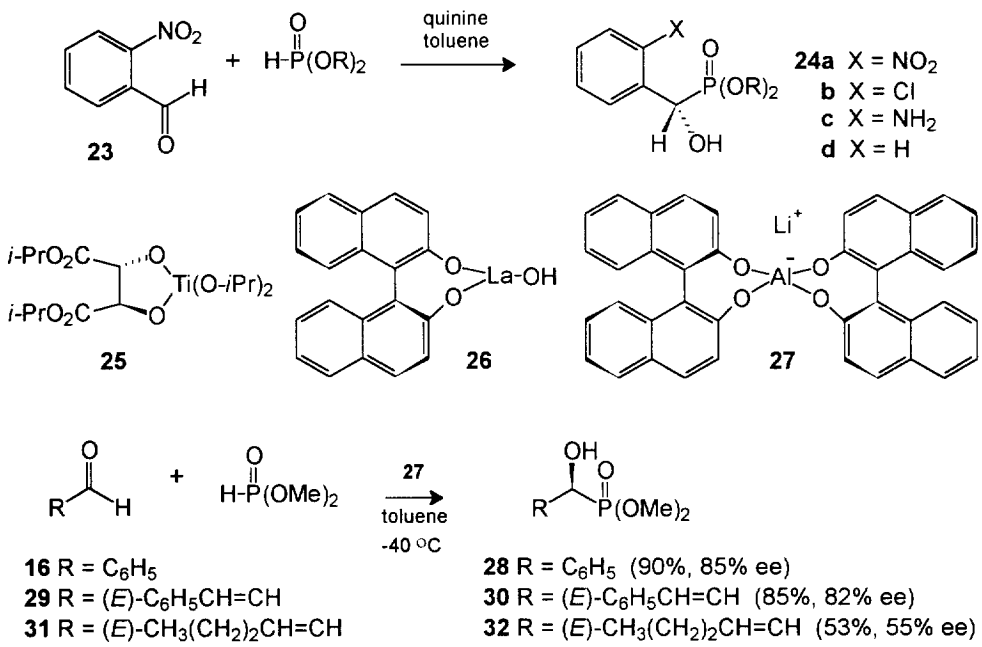


Figure 7. Enantioselective Additions of Dialkyl Phosphites to Aldehydes.[32-37]

There are a number of procedures known for introducing stereochemistry to phosphonates without formation of a carbon-phosphorus bond. The initial report describing asymmetric reduction of diethyl

benzoylphosphonate employed a stoichiometric amount of a nonracemic borohydride derived from pinene and 9-borabicyclononane.[39] Neither the ee nor the absolute configuration of the product were determined at that time, because the product (**24d**) was intended for solvolysis studies where that information was not required. Based on the reported rotation and more recent information, reaction with the borohydride derived from (+)-α-pinene gave the R enantiomer of α-hydroxy phosphonate **24d** in approximately 20% ee. A catalytic procedure that employed 5 mol% of the B-butyloxazaborolidine **33** as catalyst was subsequently reported (Figure 8).[40] Modest yields but good ee's were observed with the representative α-keto phosphonates that were examined. In a more recent study,[41] use of catechol borane or the borane-dimethyl sulfide complex provided better yields and higher ee's, parallel to improvements noted in other ketone reductions with these borane reagents.[42] In addition to reductions of α-keto phosphonates, the later study reported enantioselective reductions of both β-keto and γ-keto phosphonates to the corresponding β-hydroxy and γ-hydroxy phosphonates.[41] However, for

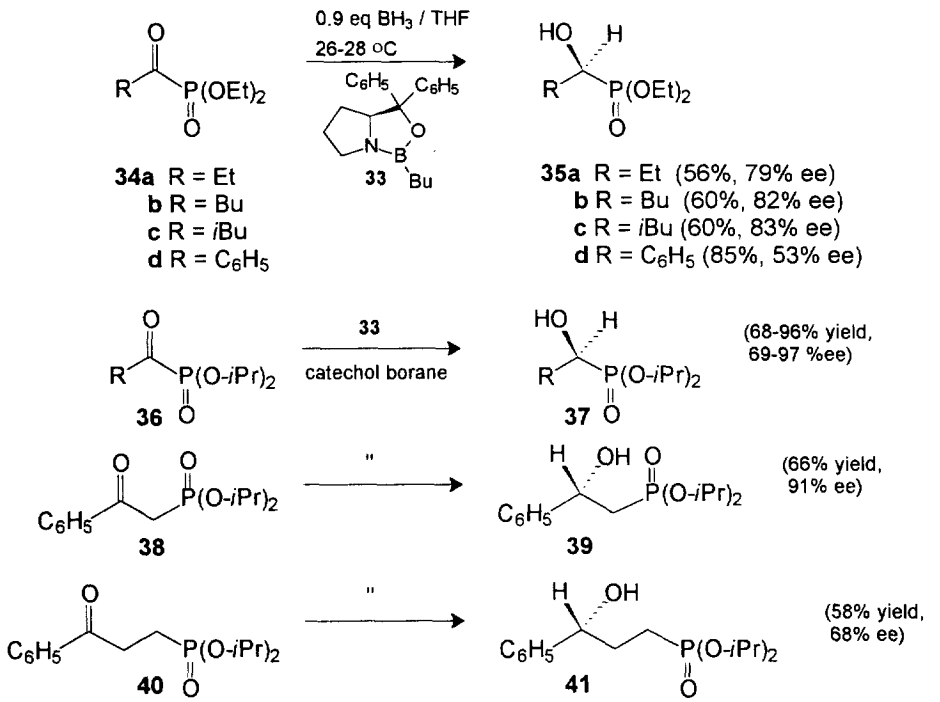
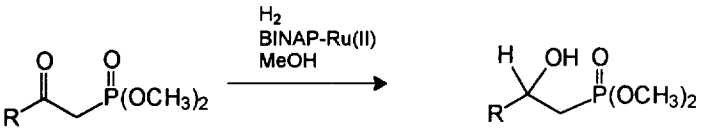


Figure 8. Enantioselective Borane Reductions of Keto Phosphonates.[40-41]

enantioselective reduction of β-keto phosphonates, a ruthenium-BINAP catalyst employed by Noyori and coworkers[43] has given nearly quantitative yields and ee's in the range of 94-98% (Figure 9). The excellent stereoselectivity of these reductions was explained on the basis of complexation of the catalyst with the phosphoryl oxygen, followed by intramolecular hydride delivery.[44]

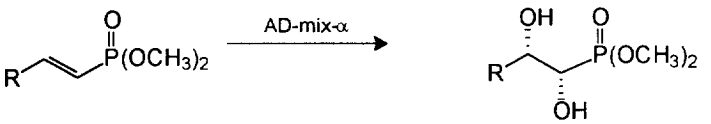


42a R = CH_3
b R = n-C_5H_{11}
c R = $(CH_3)_2CH$
d R = C_6H_5
e R = 

43a R = CH_3 (99%, 98% ee, *R*-BINAP, *R*)
b R = n-C_5H_{11} (98%, 94% ee, *S*-BINAP, *S*)
c R = $(CH_3)_2CH$ (96%, 96% ee, *S*-BINAP, *S*)
d R = C_6H_5 (96%, 95% ee, *R*-BINAP, *R*)
e R =  (100%, 94% ee, *S*-BINAP, *R*)

Figure 9. Enantioselective BINAP-Ru(II) Reductions of β-Keto Phosphonates.[43a,44]

In comparison to reductive routes to nonracemic phosphonates, oxidative routes have been less studied. One exception involves the synthesis of α,β-dihydroxy phosphonates via an enantioselective oxidation of vinyl phosphonates. Condensation of tetraalkyl methylene-bis-phosphonates with aldehydes provides ready access to vinyl phosphonates,[1] and subsequent oxidation with the AD-mix reagents[45] has been reported.[46] AD-mix oxidations of vinyl phosphonates with alkyl substituents at the β-position proceeded in modest yield and enantioselectivity. In contrast, phenyl and *p*-methoxyphenyl substituents resulted in much improved ee's (Figure 10). Comparable results were observed in an independent study.[46b] Even though a rationale for this observation has not been offered, the high ee and the synthetic transformations demonstrated with the *p*-methoxyphenyl product should attract more interest to this approach.



44a R = CH_3
b R = $C_6H_5CH_2OCH_2CH_2$
c R = C_6H_5
d R = *p*-$MeOC_6H_4$

45a R = CH_3 (48%, 33% ee)
b R = $C_6H_5CH_2OCH_2CH_2$ (30%, 44% ee)
c R = C_6H_5 (42%, 91% ee)
d R = *p*-$MeOC_6H_4$ (71%, >95% ee)

Figure 10. Enantioselective Oxidation of Vinyl Phosphonates.[46]

Vinyl phosphonates also can be converted to nonracemic α-hydroxy phosphonates via hydroboration/oxidation. One early report describes the reaction of vinyl phosphonate **46** with borane in THF.[47] Upon treatment with H_2O_2 and sodium hydroxide, oxidation and partial hydrolysis resulted in formation of the α-hydroxy phosphonate **47** as a 1:1 mixture of diastereomers (Figure 11). While the individual diastereomers were not separated or assigned stereochemistry, they did show different reactivity with several enzymes involved in processing of AMP. A later study[7] examined hydroboration/oxidation of vinyl phosphonate **48** with (-)- and (+)-diisopinocamphenylborane. A single diastereomer, assigned the 1*R*, 3*S*-

stereochemistry of compound **49**, was obtained from reaction of the nonracemic olefin **48** with the (-)-borane reagent. The other diastereomer (**50**) was obtained from the parallel reaction with the (+)-borane. This selectivity was explained on the assumption that the steric bulk of the phosphoryl group controlled approach of the chiral borane reagent. Given these demonstrations of vinyl phosphonate hydroboration/oxidation, and the number of chiral hydroboration reagents available, it is surprising that preparation of nonracemic α-hydroxy phosphonates via this approach has not been explored more extensively.[48]

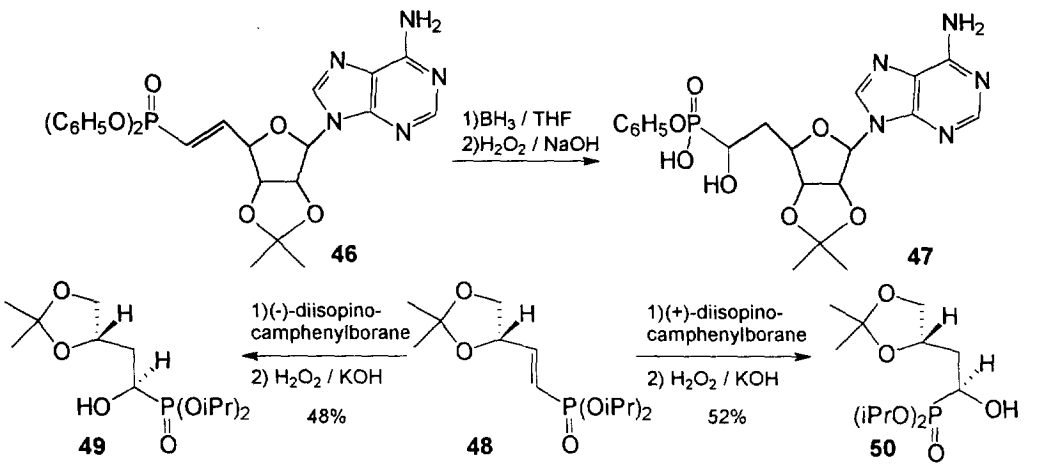


Figure 11. Hydroboration/Oxidation of Vinyl Phosphonates.[47,7]

An alternate strategy for oxidation of achiral phosphonates to nonracemic α-hydroxy phosphonates could be based on reaction of a phosphoryl stabilized anion with a nonracemic oxidant such as a (camphorsulfonyl)oxaziridine (e.g. **51**, a Davis reagent).[49] A preliminary report of this strategy described oxidation of phosphonates **52** to the corresponding α-hydroxy phosphonates **53** (Figure 12).[50] Good chemical yields have been observed along with some very attractive ee's, suggesting that further studies to better delineate the scope of this approach would be well worthwhile.

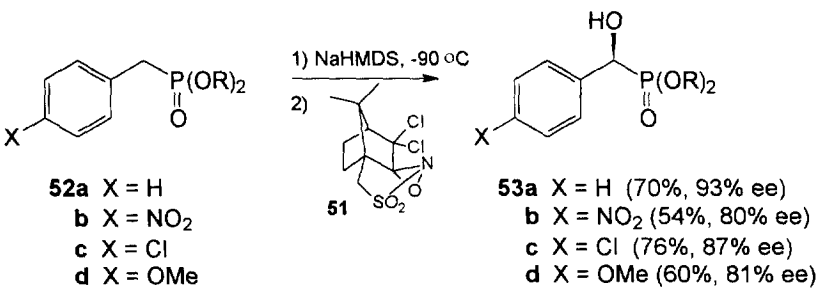


Figure 12. Enantioselective Oxidation of Phosphoryl-Stabilized Anions.[50]

Phosphoryl-stabilized anions also can be used to prepare nonracemic α-hydroxy phosphonates through sigmatropic rearrangements. For example, reaction of (-)- or (+)-menthol with PCl_3 followed by condensation of the dialkyl phosphite with formaldehyde and reaction with allyl bromide can be used to prepare the dimenthol phosphonate **54** (Figure 13).[51] Upon treatment of phosphonate **54** with *n*-BuLi, the α-hydroxy phosphonate **55** was obtained in excellent yield and very high de via a [2,3]-Wittig rearrangement. Formation of the *R*-phosphonate was favored when (-)-menthol was used, while use of (+)-menthol favored the *S*-phosphonate. An independent study appearing simultaneously employed the amino alcohol **56** as a chiral auxiliary incorporated in the cyclic compound **57**, and obtained phosphonate **58** in comparable yields and even greater de through a parallel rearrangement.[52] This later study also demonstrated that the configuration at phosphorus controls the rearrangement stereochemistry, ultimately allowing preparation of either C-1' stereoisomer from a single enantiomer of the amino alcohol **56**.

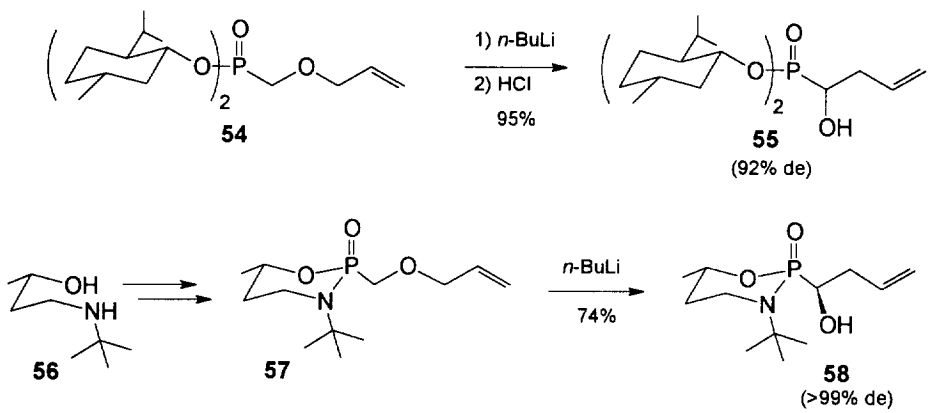


Figure 13. Diastereoselective [2,3]-Rearrangements of Phosphoryl Stabilized Anions.[51,52]

Preparation of an α-hydroxy phosphonate through diastereoselective alkylation of phosphoryl stabilized anions bearing an α-methoxy substituent has been demonstrated.[53] Only modest de was observed in alkylation of the phosphonamidate **59** by reaction with *t*-BuLi and methyl iodide to give compound **60** (Figure 14). In contrast, a single enantiomer of the sulfur analogue **61** allows selective access to either 1' stereochemistry by choice of reaction conditions, and does so in good de. The resulting thiophosphoryl products (**62** and **63**) were converted to the corresponding phosphonamidates in quantitative yield through reaction with mCPBA. Efficient cleavage of the chiral auxiliary occurs upon standard reaction with TMSI, and subsequent reaction with diazomethane provides the dimethyl ester. Unfortunately, only limited conversion of the α-methoxy compound to the α-hydroxy phosphonate was obtained through this sequence. The generality of this process must still be established, and further refinements in methods for the ether hydrolysis will be necessary before this approach is competitive with other routes to nonracemic α-hydroxy phosphonates.

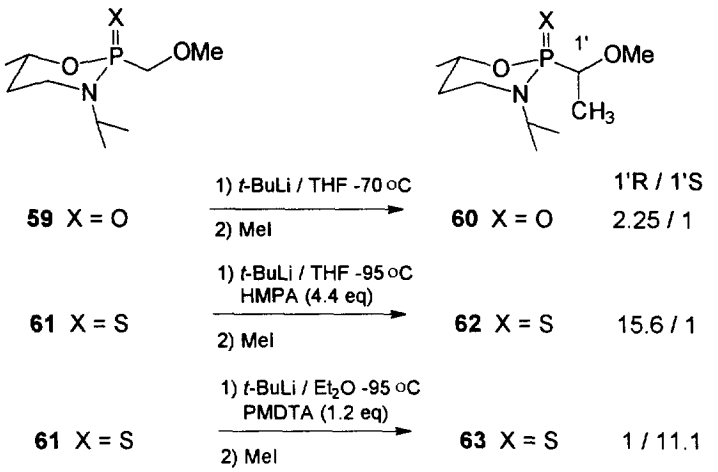
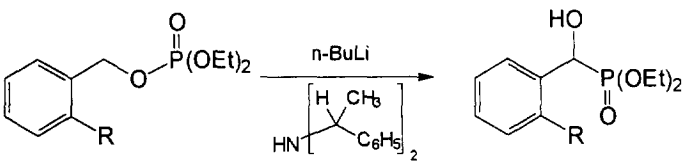


Figure 14. Diastereoselective Alkylation of Phosphoryl Stabilized Anions.[53]

In a study that may be of even greater significance because it forgoes use of nonracemic phosphonate substituents in favor of a nonracemic base, several dialkyl benzyl phosphates were isomerized to the expected α-hydroxy phosphonates in modest ee (Figure 15).[54] The amide bases derived from (*R,R*)- and (*S,S*)-bis(1-phenylethyl)amine (**66**) gave better yields and higher ee than the base derived from (*S*)-isopropyl(1-phenylethyl)amine. The origin of the stereoselectivity was shown to arise from enantioselective removal of a benzylic hydrogen, yielding a carbanion of high configurational stability which quickly rearranges to an enantiomerically enriched phosphonate with retention of configuration.



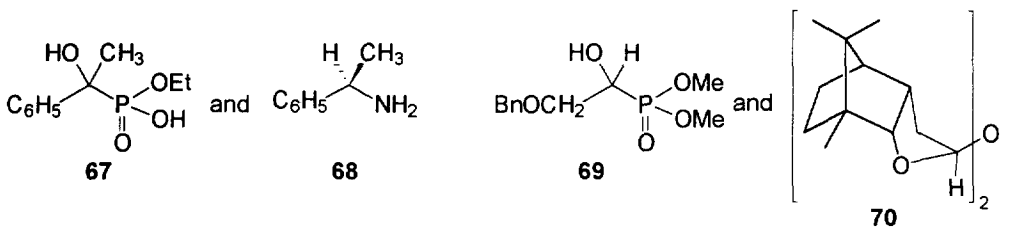
64a R = H
b R = CH_3
c R = OMe

65a R = H (64%, 41% ee, (*R, R*)-**66**, *R* product)
b R = CH_3 (57%, 24% ee, (*S, S*)-**66**, *S* product)
c X = OMe (48%, 63% ee, (*S, S*)-**66**, *S* product)

Figure 15. Enantioselective Rearrangement of Dialkyl Benzyl Phosphates.[54]

Given the extent of interest in α-hydroxy phosphonates, it is not surprising that some have been prepared in nonracemic form by resolution. Both the phosphonate group and the hydroxyl group provide opportunities for formation of diastereomers. For example, the α-hydroxy phosphonate **67** (Figure 16) was resolved[55]

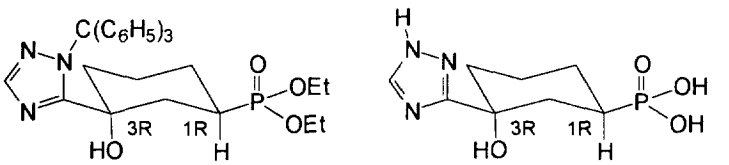
through reaction with (*R*)-(+)-phenethylamine (**68**), which gave a crystalline salt of the (-)-enantiomer. After neutralization of the mother liquors, addition of (*S*)-(-)-phenethylamine gave a crystalline salt of the (+)-enantiomer. In a complementary strategy involving derivatization of the hydroxyl group, compound **69** was converted to a pair diastereomeric acetals through reaction with the camphor derivative **70** (Figure 16).[56] The readily separated diastereomers undergo hydrolysis upon treatment with p-TsOH, providing both enantiomers of compound **69** in >98% ee. These enantiomers were then converted to phosphonic acid analogues of serine through Mitsunobu reaction with azide and catalytic hydrogenation.



67 68 69 70

Figure 16. Resolution of α-Hydroxy Phosphonates.[55,56]

Resolution of hydroxy phosphonates also is possible on chiral chromatographic supports. The racemic form of γ-hydroxy phosphonate **71**, designed as an inhibitor of imidazole glycerol phosphate (IGP) dehydratase, was resolved on a commercial HPLC column.[57] The phosphonic acids derived from the two enantiomers differed significantly in their ability to inhibit this enzyme, with the *R,R*-isomer **72** more active by about 100-fold (Figure 17), demonstrating again the significance of stereochemistry in biologically active phosphonates.



71 72

Figure 17. Chromatographic Resolution of a γ-Hydroxy Phosphonate.[57]

An alternate strategy for resolution of α-hydroxy phosphonates is based on enzyme mediated reactions, either hydrolysis of α-acyloxy derivatives or acylation of the hydroxyl group. In the first report on this approach,[58] racemic substrates were prepared by a standard Pudovic reaction followed by acylation of the resulting α-hydroxy phosphonates with acetic anhydride or an acyl chloride. Hydrolysis of the α-acyloxy group was examined with several different enzymes, including Lipases F-AP 15 and AP 6. In some trials, this procedure gave an optically pure S alcohol product and left the ester of R configuration virtually unreacted. For example (Figure 18), phosphonate **73** gave the *S*-α-hydroxy phosphonate **74** in 31% yield and >99% ee,

while the R enantiomer was obtained in 35% yield and 90% ee by chemical hydrolysis of recovered ester 75. In most other trials much lower yields or ee's were observed, suggesting that each substrate may require examination of a series of enzymes. This strategy was recently extended to preparation of the phosphorus analogues of phenylalanine and tyrosine,[59] where again the R ester was recovered while the S enantiomer was obtained as the alcohol with Lipase AP 6. The complementary strategy, i.e. enzyme catalyzed acylation of the α-hydroxy phosphonate also has been reported.[60,61] In a particularly attractive case, α-hydroxy phosphonate **76** gave >99% ee's for both the alcohol **77** (41% yield) and the ester **78** (unspecified yield).

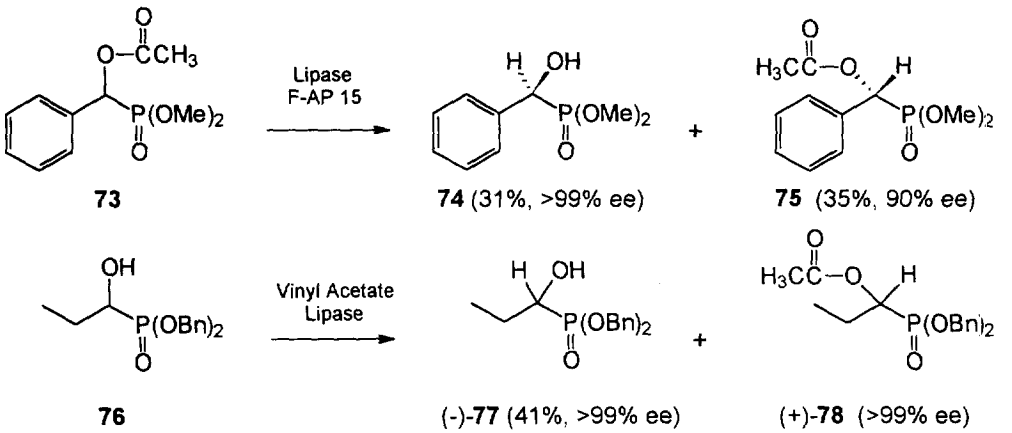


Figure 18. Enzymatic Resolutions of α-Hydroxy Phosphonates.[58,60]

In summary, nonracemic α-hydroxy phosphonates have been obtained by resolution and prepared through stereoselective formation of each of the four bonds to a tertiary carbon, as shown in Figure 19. Many of the synthetic methods have been, or could be, applied to form quaternary centers, although good stereoselectivity may be harder to obtain if the two alkyl substituents are similar in size and other control elements are absent.

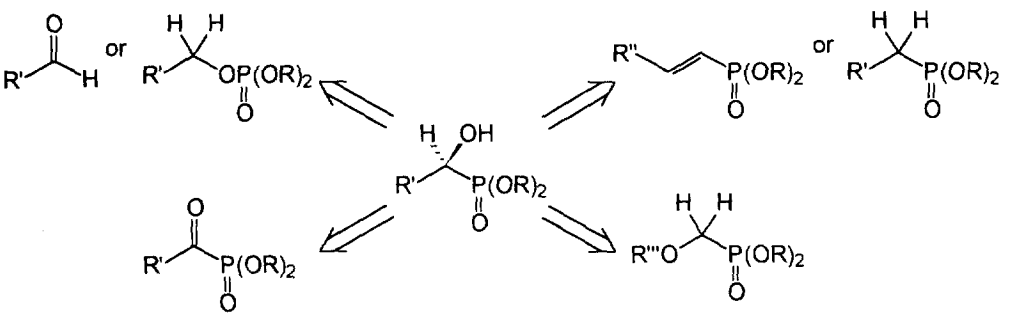


Figure 19. Known Disconnections to Nonracemic α-Hydroxy Phosphonates.[58,60]

2.2 β- and γ-Hydroxy Phosphonates.

Although not studied as extensively, synthesis of nonracemic β- and γ-hydroxy phosphonates also has been demonstrated. One attractive pathway involves stereoselective reductions of β- and γ-keto phosphonates as described above (e.g. Figure 8). An attractive alternative involves use of phosphite to open nonracemic epoxides to β-hydroxy phosphonates, or use of an alkylphosphonate anion to obtain γ-hydroxy phosphonates from nonracemic epoxides (Figure 20). For example, epoxide **79** is converted to the corresponding β-hydroxy phosphonate **80** in quantitative yield upon reaction with diethyl phosphite, *n*-BuLi, and BF_3.[62] Treatment of epoxide **79** with the diethyl methylphosphonate anion and BF_3 gave the γ-hydroxy phosphonate **81**.

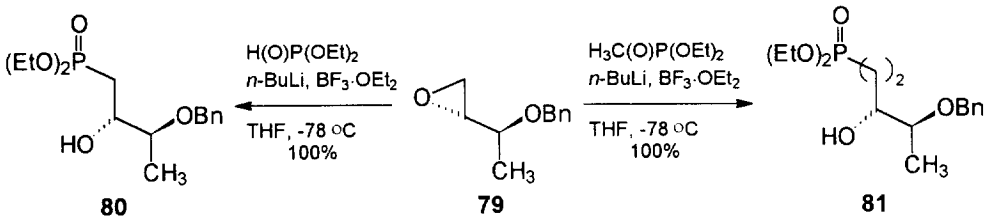


Figure 20. Conversion of Epoxides to β- and γ-Hydroxy Phosphonates.[62]

3. Keto Phosphonates.

3.1 Acyl (or α-Keto) Phosphonates.

The Arbuzov reaction of an acid chloride with a trialkyl phosphite provides general access to acyl (α-keto) phosphonates[63] and, at least in principle, if the acid chloride were derived from a nonracemic acid a nonracemic acyl phosphonate would result. Systematic studies have probed the physical properties and chemical reactivity of representative acyl phosphonates,[64] and suggested behavior hybrid between that of secondary amides and ketones.[65] However by comparison with α-hydroxy phosphonates, nonracemic acyl phosphonates remain relatively unexplored. One exception involved preparation of acyl phosphonates from *S*-alanine and *S*-leucine (Figure 21).[66] In this case, reaction of the phthalimide protected acid chlorides **82** with triethyl phosphite gave the phosphonates **83** in good yield and without racemization. Reduction of compounds **83**, first with $NaBH_3CN$ and then by free radical deoxygenation, followed by removal of the phthalimido group and ethyl esters, provided the β-amino phosphonic acids **84** in greater than 99% ee.

α-Keto phosphonates nonracemic by virtue of stereogenic centers incorporated into alkoxy or amino substituents on phosphorus may still be unknown. Recent studies have reported disastereoselective aldol[67a] and Mukaiyama-Michael[67b] condensations of α-keto phosphonates. Because these condensations might be

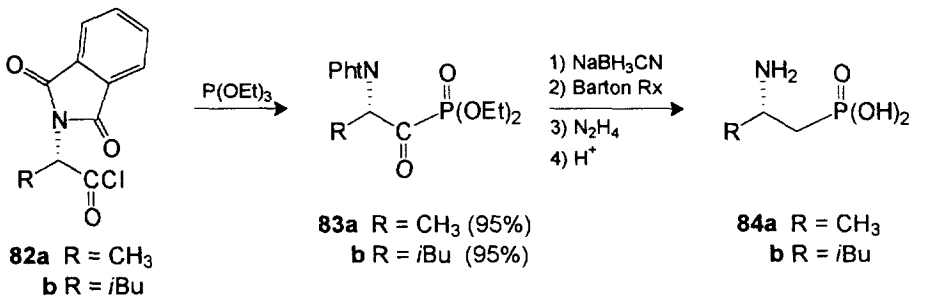


Figure 21. Synthesis of Nonracemic α-Keto Phosphonates.[66]

made enantioselective if chiral ligands were placed on the phosphorus, preparation of α-keto phosphonates with nonracemic substituents would appear to be a promising area for future research.

3.2 β-Keto Phosphonates.

Interest in the preparation of β-keto phosphonates has been much more pervasive, primarily because of their proven utility in reactions such as the HWE condensation.[1] Many methods have been used to prepare specific β-keto phosphonates, but only a few have been generally useful.[1, 68] In fact, only two routes to β-keto phosphonates are widely used, the Arbuzov synthesis and acylation of alkylphosphonates. Both of these approaches rely upon use of nucleophilic phosphorus reagents, which imposes a fundamental restriction in the variety of possible products; each method suffers from some individual limitations as well.

The classical Arbuzov synthesis (Figure 22),[69] which involves reaction of a trialkylphosphite with an α-halo ketone, may be the most commonly used route to β-keto phosphonates. This reaction works best with

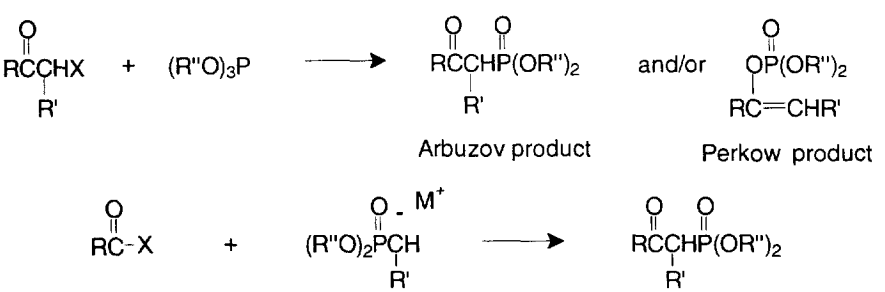


Figure 22. Common Syntheses of β-Keto Phosphonates.[1,69-73]

nucleophilic phosphites[70] and α-iodo ketones that readily undergo substitution reactions. Primary α-bromo- or α-chloroketones, and the α-halo derivatives of cyclic ketones, often undergo a competitive Perkow process to afford the isomeric vinyl phosphates.[71] Because substitution reactions are difficult for many secondary halides, the usefulness of Arbuzov reactions with any secondary halides is limited.[1] Even though the Arbuzov

reaction could be employed to prepare nonracemic β-keto phosphonates (e.g. if a stereogenic center were embedded in the second substituent of a halomethyl ketone), it is difficult to find examples of such reactions.[72]

The most common alternative to the Arbuzov synthesis of β-keto phosphonates has been the acylation of an alkylphosphonate anion.[73] This strategy (Figure 22) can be employed to prepare α-substituted phosphono ketones, although stereocontrol is not likely at the α position because the β-keto phosphonate anion is readily formed under the reaction conditions. However, nonracemic acid derivatives often have been used in this process, providing β-keto phosphonates with stereogenic centers at the γ position or beyond. For example, the prochiral anhydride **85** has been converted to the optically active β-keto phosphonate **87** (Figure 23) for use in synthesis of compactin and compactin analogues. Reaction of the anhydride first with a nonracemic alcohol or amine and then with diazomethane gave access to nonracemic diesters or amide/ester (**86**). These compounds were converted to the corresponding β-keto phosphonates **87** by reaction with the lithium anion of dimethyl methylphosphonate.[74] Yields were modest in the first two examples primarily because of competing elimination reactions which were minimized by use of the ester acid **86c**.

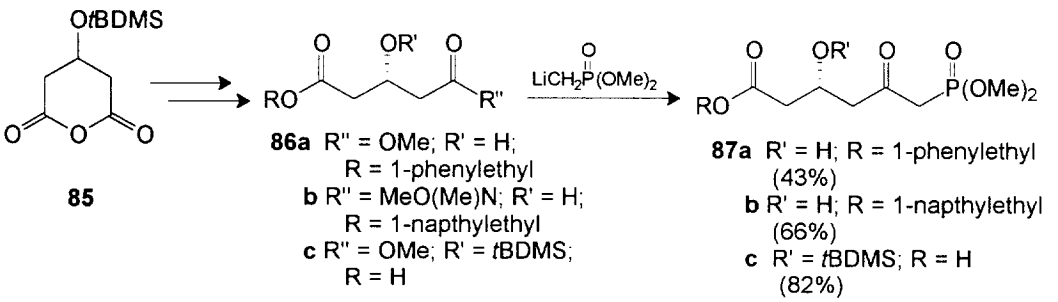


Figure 23. Synthesis of Nonracemic β-Keto Phosphonates from Prochiral Anhydride **85**.[74]

In a related case which involves acylation with a diester, a protected derivative of diethyl tartrate (**88**) was treated with the methylphosphonate anion (Figure 24).[75] The nonracemic phosphonate **90** was the major product of this reaction, presumably formed via a HWE condensation of the intermediate bisphosphonate. A second condensation of phosphonate **90** with acetaldehyde was used to complete a clever synthesis of the natural product (-)-terrein (**91**).

Methyl esters derived from carbohydrates and amino acids also have been used to prepare nonracemic phosphonates, and isomerization adjacent to the ester carbonyl under the basic reaction conditions does not appear to be a significant problem. For example, a synthetic sequence involving acylation of a methylphosphonate anion followed by HWE condensation has been examined as a strategy for obtaining higher sugars by homologation of smaller carbohydrates.[76] In a representative case, the glucose derivative **92** was

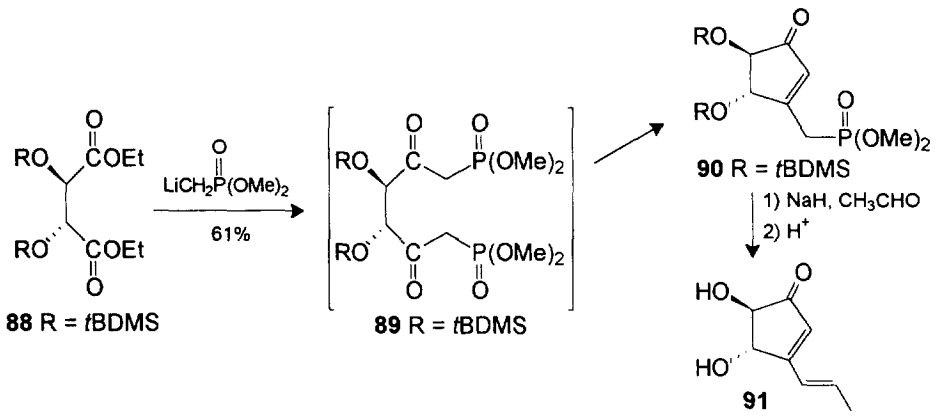


Figure 24. Conversion of Diethyl Tartrate to a Nonracemic β-Keto Phosphonate.[77]

converted to the phosphonate **93** in quantitative yield (Figure 25), and the resulting phosphonate was condensed with a variety of aldehydes, including some derived from other carbohydrates. A similar strategy has been used to convert the amino acid serine into sphingosine derivatives.[77] In the key step, the protected serine methyl ester *S*-**94** was allowed to react with the dimethyl methylphosphonate anion, to obtain the nonracemic β-keto phosphonate **95**. In a parallel reaction conducted with compound *R*-**94**, the α,α-difluoro phosphonate **96** was obtained by reaction with the dimethyl (difluoroethyl)phosphonate anion.[78]

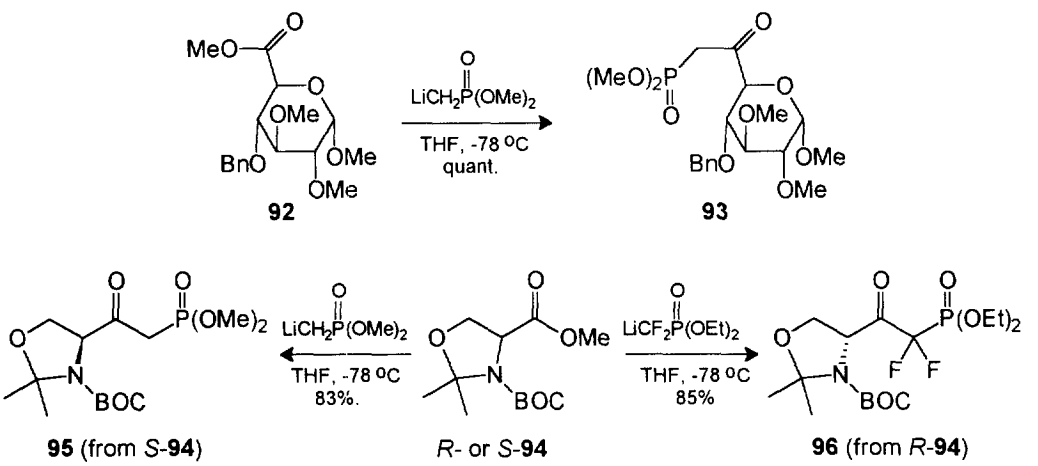


Figure 25. Acylation of Alkylphosphonate Anions.[76-78]

As might be expected on the basis of the preceding examples, methyl esters derived from nonracemic terpenes also can be employed for acylation of phosphonate anions. For example, methyl citronellate (**98**) reacts smoothly with the dimethyl methylphosphonate anion to afford the β-keto phosphonate **99** (Figure 26).[79] However, because nonracemic methyl citronellate is derived from pulegone hydrochloride (**97**) and the yield

may not be high, an interesting variation was examined. Pulegone hydrochloride itself was treated with the alkylphosphonate anion, resulting in direct formation of the β-keto phosphonate **99** in 71% yield.

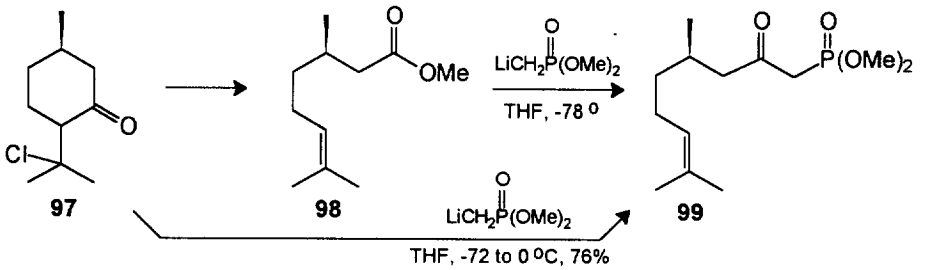


Figure 26. Reaction of Pulegone Hydrochloride with an Alkylphosphonate Anion.[79]

The previous examples, and numerous others,[80] demonstrate that acylation of alkylphosphonate anions often can be conducted without racemization at the α-position of the acylating agent. In cases where racemization may be a concern, an alternate strategy is available based on the addition of an alkylphosphonate anion to an aldehyde to give the β-hydroxy phosphonate followed by oxidation to the corresponding β-keto phosphonate. For example, conversion of α-D-glucose to aldehyde **100** was followed by condensation with the lithium anion of methyl dimethylphosphonate and oxidation to the β-keto phosphonate **101** with PCC (Figure 27).[81] This reaction proceeds in high overall yield but, because the starting aldehyde was prepared as a mixture

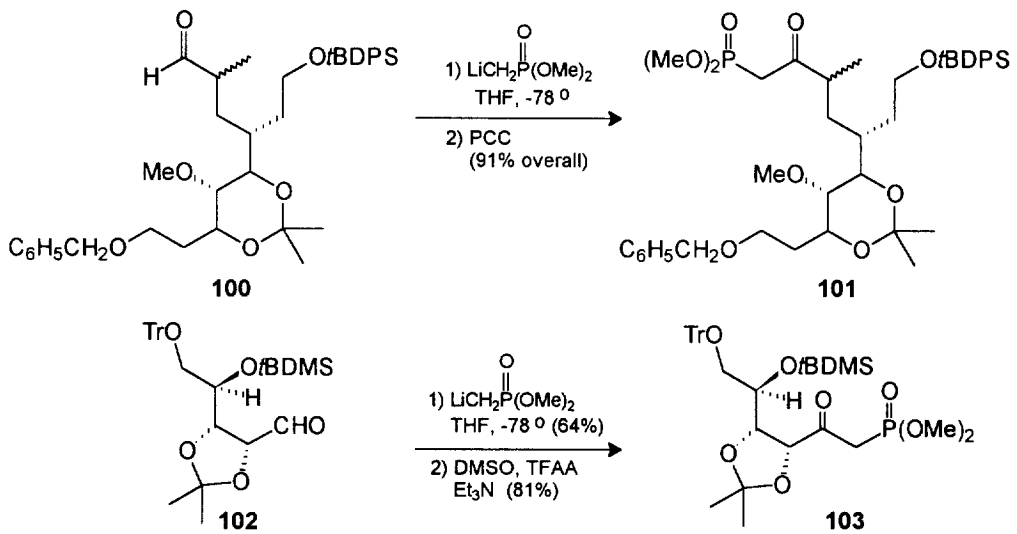
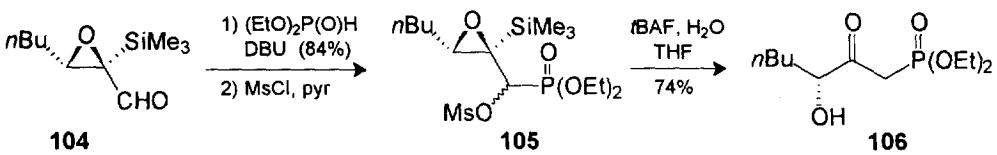


Figure 27. Aldehyde Addition/Oxidation Synthesis of β-Keto Phosphonates.[81,82]

of diastereomers, no information was given on the stability of this stereogenic center to the reaction sequence. A similar strategy was employed to convert the ribose-derived aldehyde **102** to the β-keto phosphonate **103**,

although in this case Swern conditions were employed for the oxidation.[82] Finally, a comparison of direct acylation versus aldehyde addition followed by oxidation with sodium dichromate suggested that acylation gave a better yield.[83]

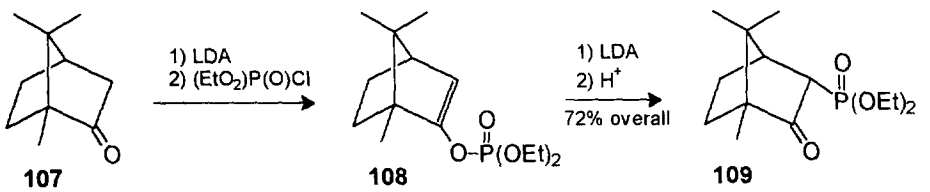
An interesting route to a nonracemic γ-hydroxy β-keto phosphonate draws upon Sharpless epoxidation for access to the aldehyde **104** (Figure 28).[84] After nucleophilic addition of the diethyl phosphite anion to the aldehyde and preparation of the corresponding mesylate (**105**), reaction with *t*BAF and water provides the γ-hydroxy β-keto phosphonate **106** via an allene oxide intermediate. While the generality of this route must still be established, the interface with Sharpless methodology suggests that a variety of appropriate substrates could be prepared.



104 **105** **106**

Figure 28. Synthesis of a γ-Hydroxy β-Keto Phosphonate via an Allene Oxide.[84]

Among the more recently reported strategies for synthesis of nonracemic β-keto phosphonates are several which employ electrophilic phosphorus reagents. Such strategies are inherently complementary to the more classical reactions based on phosphorus nucleophiles, and thus offer access to nonracemic β-keto phosphonates that would otherwise be very difficult to prepare. For example, reaction of the camphor (**107**) enolate with diethyl phosphorochloridate gives the corresponding vinyl phosphate (**108**) in good yield (Figure 29).[85] If this vinyl phosphate is treated with LDA, rearrangement to the corresponding β-keto phosphonate **109** proceeds smoothly, providing the first synthesis of this nonracemic camphor derivative. The entire reaction sequence can be carried out in a single flask, which improves both the synthetic ease and the overall yields.[85] While complete mechanistic details are not yet available for this reaction, when compound **108** was treated with LDA in the presence of TMS-Cl, a vinyl silane vinyl phosphate was obtained.[85d] This reaction documents abstraction of the



107 **108** **109**

Figure 29. Vinyl Phosphate/β-Keto Phosphonate Rearrangement.[85a]

vinylic hydrogen and supports formation of an intermediate vinyl anion in the rearrangement of vinyl phosphate **108** to phosphonate **109**. However in cases where the cyclic vinyl phosphate bears an acidic allylic hydrogen,

rearrangement proceeds through formation of an intermediate allyl anion. This has been verified for the vinyl phosphate derived from cyclohexanone by a deuterium labeling study.[85a]

Rearrangements of vinyl phosphates to β-keto phosphonates (or α-phosphono esters) have been demonstrated only with cyclic ketones,[85,86] lactones,[87] and esters,[87a] but this approach nonetheless offers a number of opportunities for preparation of nonracemic compounds. For example, ketones of the general structure **110** (Figure 30) give diastereomeric vinyl phosphates (**111a** and **111b**) when treated with LDA and a

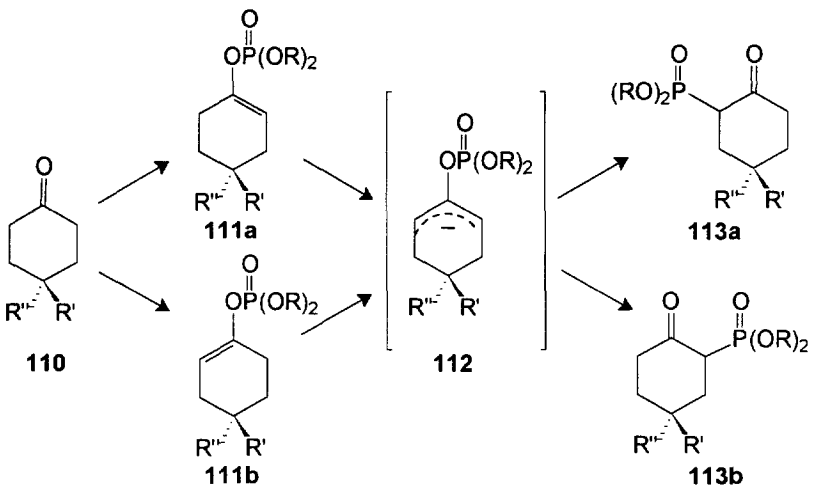


Figure 30. Diastereoselective Vinyl Phosphate/β-Keto Phosphonate Rearrangement.[88]

nonracemic phosphorochloridate.[88] If subsequent reaction with LDA generates a delocalized allylic anion (**112**), rearrangement to the β-keto phosphonate proceeds through diastereomeric transition states, potentially giving products **113a** and **113b** in unequal amounts. Modest stereoselectivity has been observed (Figure 31)

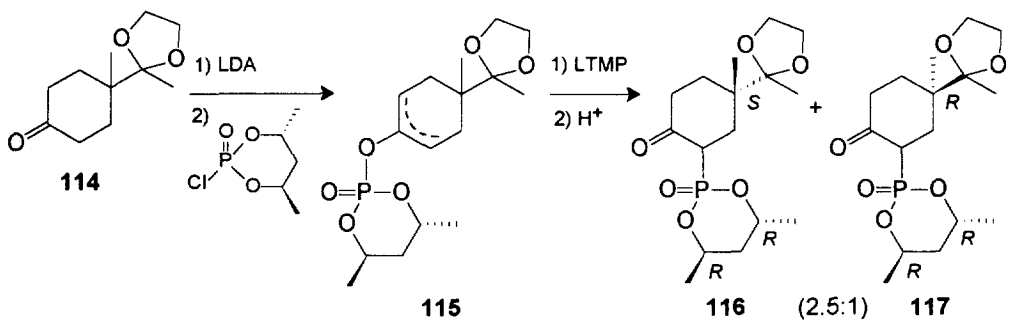


Figure 31. Diastereoselective Rearrangement of Vinyl Phosphate **115**.[88]

in several cases. One of the most interesting involved the prochiral ketone **114**. Treatment of the isomeric vinyl phosphates **115**, derived from ketone **114** and (2*R*, 4*R*)-pentane-2,4-diol, with LiTMP gave a 2.5:1 ratio

of the diastereomeric phosphonates **116** and **117**, and the stereochemistry of compound **117** was secured by crystallography. While the use of other phosphorus substituents may improve the yield and/or de of this process, the crystalline nature of the *R, R, R*-diastereomer in this series allowed preparation of useful quantities of the β-keto phosphonates.[89]

Because the reaction of ketone enolates with dialkyl phosphorochloridates gives only the vinyl phosphate product, a number of less direct strategies have been examined to generate β-keto phosphonates with phosphorus electrophiles. One such approach involves initial reaction of the ketone enolate with a dialkyl phosphorochloridite followed by oxidation of the products to the P(V) oxidation state. This strategy was used to prepare the nonracemic camphor phosphonate from camphor itself (Figure 32), although the reported yield is less attractive than that obtained via the rearrangement of the camphor vinyl phosphate described above.[90]

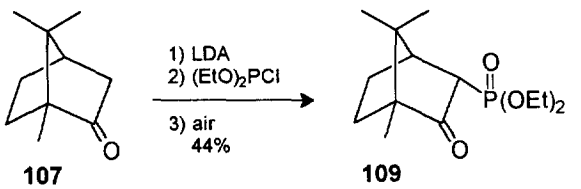


Figure 32. Reaction of Camphor with Diethyl Phosphorochloridite.[90]

When a β-keto phosphonate bearing a stereogenic center at the δ position or beyond is the target, alkylation of a β-keto phosphonate dianion may be a feasible strategy. It has been known for some time that formation of such dianions is feasible,[91] given the appropriate structural motif. While formation of a dianion precludes maintaining stereocenters at the α and γ positions, preparation of a nonracemic β-keto phosphonate (e.g. compound **120**) can be accomplished[92] by reaction of a nonracemic alkyl halide (**118**) with the achiral phosphonate **119**, as shown in Figure 33.

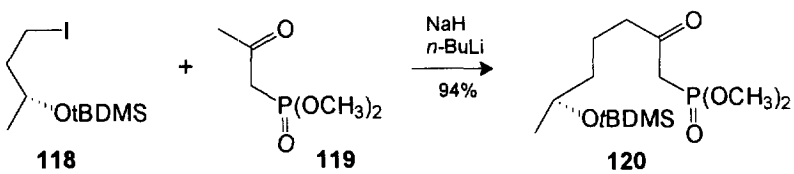


Figure 33. Alkylation of a β-Keto Phosphonate Dianion.[92]

Indirect phosphonylation of a ketone also has been accomplished through reaction of a ketone methylhydrazone with PCl_5 followed by reaction with an alcohol (Figure 34).[93] While only applied to achiral ketones in this initial report (e.g. compound **121**), this strategy for carbon-phosphorus bond formation would certainly appear to be compatible with the presence of stereogenic centers on the hydrazone. Furthermore, it allows

access to aromatic phosphonate esters (**123c**) which have shown promise for Z-stereocontrol in HWE condensations.[94]

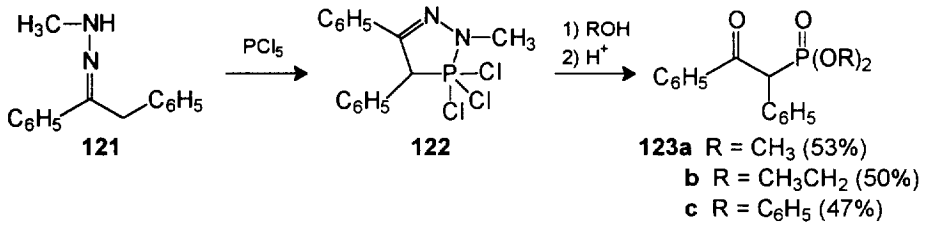


Figure 34. Synthesis of β-Keto Phosphonates from Ketone Hydrazones.[93]

Vinyl phosphonates are known to be substrates for conjugate addition reactions,[95] and have been used to prepare a variety of nonracemic phosphonates. For example (Figure 35), anions derived from SAMP hydrazones (**124**) have been shown to undergo conjugate addition to vinyl phosphonates (**125**) giving nonracemic δ-keto phosphonates (**127**) in good ee and reasonable yield.[96] In a related reaction, conjugate addition of lithiated Schollkopf's bislactim ether to vinyl phosphonates has been used to prepare nonracemic amino phosphonic acids.[97] The attractive de's should assure further exploration of this strategy for preparation of nonracemic keto phosphonates.

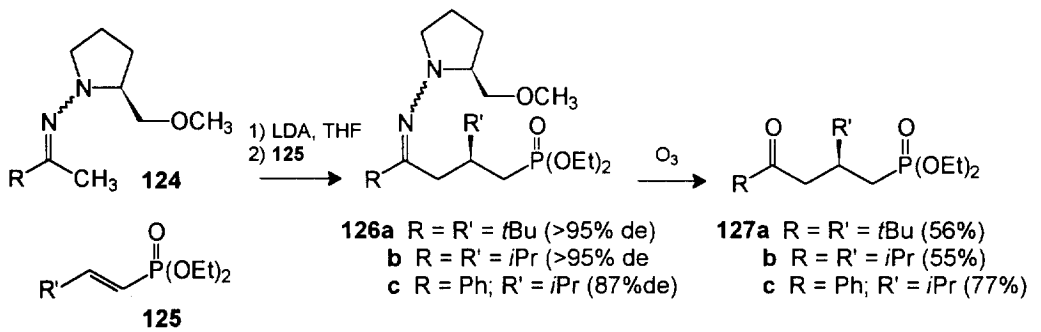


Figure 35. Conjugate Addition of SAMP Hydrazones to Vinyl Phosphonates.[96]

In summary, while nonracemic α-keto phosphonates (acyl phosphonates) are prepared primarily from acid chlorides, a variety of routes have been described for synthesis of nonracemic β-keto phosphonates (Figure 36). The classical routes pair nucleophilic phosphorus reagents with carbonyl electrophiles, e.g. trialkyl phosphites with α-halo ketones or alkylphosphonate anions with esters. More recent methods that employ electrophilic phosphorus reagents, such as the rearrangement of vinyl phosphates or the reaction of enolates with a dialkyl phosphorochloridite, are complementary and offer access to new types of nonracemic β-keto phosphonates including those based on cyclic systems.

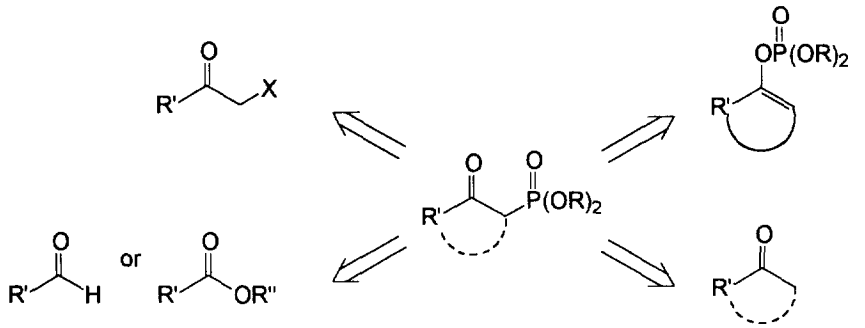


Figure 36. Known Disconnections to Nonracemic β-Keto Phosphonates.

4. Phosphono Esters.

4.1 α-Phosphono Acetates

The utility of α-phosphono esters in the HWE reaction has drawn significant attention to preparation of nonracemic phosphonates for use in asymmetric condensations.[98] The most commonly employed reagents are phosphono acetates, which may incorporate chirality in either the carboxylate (Figure 37) or phosphonate esters. The earliest example based on a nonracemic carboxylic acid ester[99] incorporated the natural product menthol (**129**), but recent investigations have more often employed the 8-phenylmenthol group (**130**).[100] Nonracemic acetates of this type have been prepared by reaction of the chiral alcohol with bromo- or chloroacetyl chloride followed by an Arbuzov reaction,[99,101] by direct reaction of phosphonoacetyl chloride with the alcohol,[102] or by a Mitsunobu reaction of the alcohol and phosphonoacetic acid.[103] An ester exchange process that begins with the methyl ester **128** and is catalyzed by DMAP also has been reported to give good yields with a variety of substrates.[100]

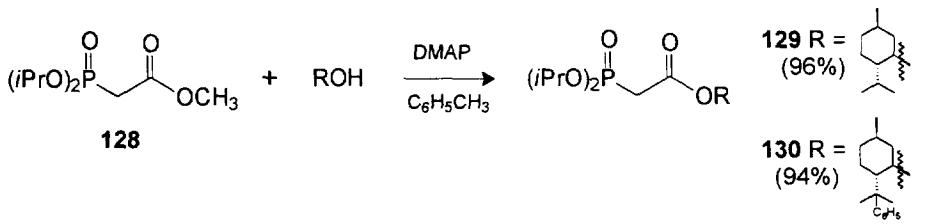
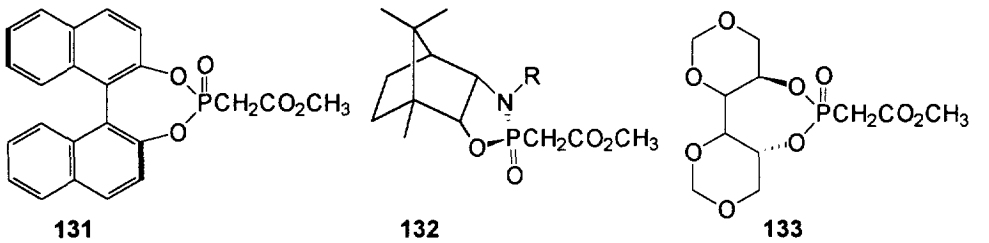


Figure 37. Synthesis of Nonracemic Phosphono Acetates by Ester Exchange.[100]

Similar strategies have been used to prepare nonracemic phosphono acetates containing chirality within the phosphonate esters (Figure 38). The binaphthol derivative **131** was prepared by reaction of methyl dichlorophosphite with the parent diol, followed by an Arbuzov reaction of the resulting phosphite with methyl

bromoacetate.[104] The camphor derivative **132** was prepared via a similar sequence with ethyl dichlorophosphite.[105] In contrast, the manitol derivative **133** was prepared by reaction of ethyl (dichlorophosphoryl)acetate with the parent diol.[106] Both strategies have proven to be efficient.

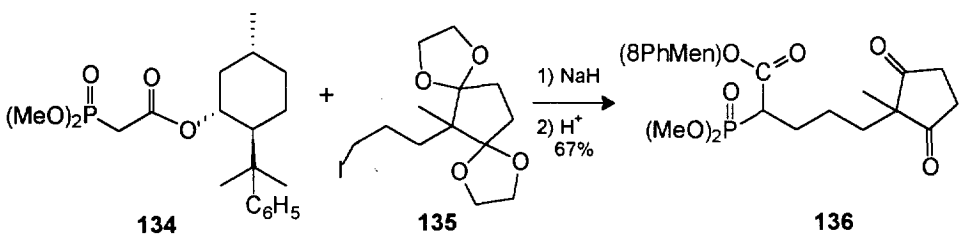


131 **132** **133**

Figure 38. Nonracemic Phosphono Acetates with Chiral Phosphorus Substituents.[104-106]

4.2 α-Phosphono Esters and Lactones

Synthesis of nonracemic phosphono esters derived from larger carboxylic acids has not been studied as extensively. However, in addition to extensions of the reactions described above, at least three additional routes are known. One is based on elaboration of a nonracemic phosphono acetate through alkylation, and is nicely demonstrated in a recent synthesis of the Vitamin D_3 synthon **136** from the acetate derivative **134** and the alkyl iodide **135** (Figure 39).[107] While stereocontrol at the α position of compound **136** was not obtained, this is unimportant given use of the resulting phosphonate in a diastereoselective HWE condensation to the corresponding hydrindenone.



134 **135** **136**

Figure 39. Alkylation of a Nonracemic Phosphono Acetate.[107]

Direct reaction of an ester enolate with diethyl phosphorochloridate results in clean formation of the vinyl phosphate rather than the phosphonate, but vinyl phosphate derivatives of esters can undergo rearrangement to the corresponding α-phosphono esters if treated with strong base.[87a] For example, the camphor lactone **137** was converted to the corresponding α-phosphono lactone **138** by this sequence (Figure 40). Direct C-P bond formation is possible through reaction of the ester enolate with diethyl phosphorochloridite,[108,90] rather than the phosphorochloridate, and if this reaction is followed by oxidation the phosphonate can be obtained. For

example, reaction of the anion derived from methyl citronellate (**139**) with diethyl phosphorochloridite followed by air oxidation was used to prepare the nonracemic phosphono ester **140** (Figure 40).[109] Even though it was conducted on a racemic substrate, conversion of lactone **141** to the α-phosphono lactone **142** provides a useful comparison of phosphonate synthesis by these two strategies.[87b]

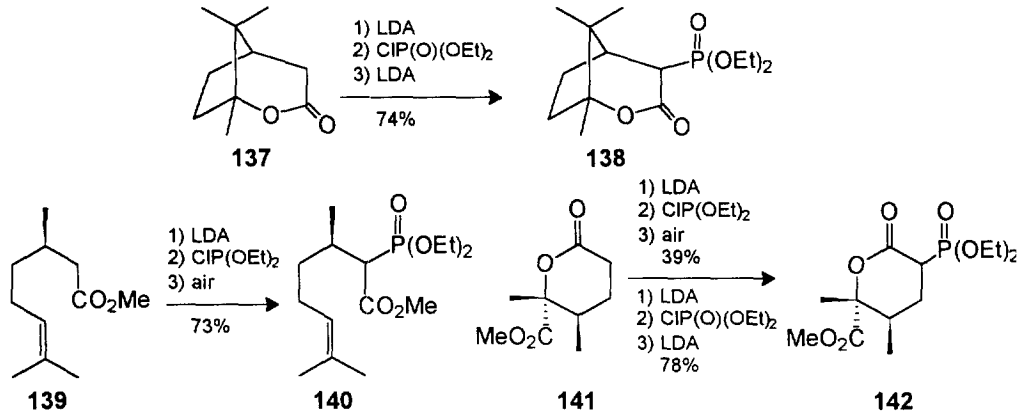


Figure 40. C-P Bond Formation with Esters and Lactones.[109,87]

In some cases, use of an ester equivalent can circumvent the reaction of diethyl phosphorochloridate with the oxygen of an ester enolate.[110] As applied in a synthesis of (+)-cleomeolide, the nitrile **143** (Figure 41) was converted to the phosphonate **144** by reaction with LDA and diethyl phosphorochloridate in good yield.[111] In this sequence, hydrolysis of the acetal and a HWE condensation were conducted before the cyano group was converted to the corresponding methyl ester.

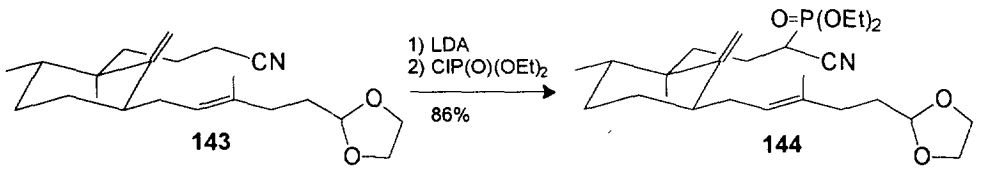


Figure 41. Synthesis of a Nonracemic α-Phosphono Nitrile.[111]

In summary, most attention to synthesis of nonracemic α-phosphono esters (Figure 42) has been devoted to acetate derivatives. Known syntheses of nonracemic phosphono acetates include procedures for incorporation of chirality within the carboxylate ester and the phosphonate esters, as well as alkylation at the α position. Studies on preparation of nonracemic phosphonates from larger esters and lactones have been reported, but their limited numbers suggest that this is an area that would profit from further exploration.

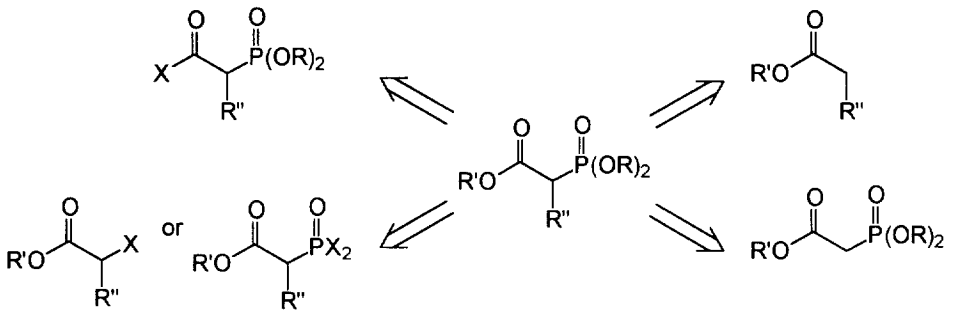
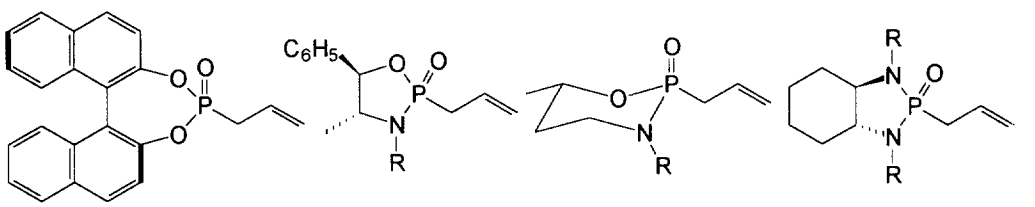


Figure 42. Known Disconnections to Nonracemic α-Phosphono Esters.

5. Miscellaneous.

Numerous other strategies can be envisioned for preparation of specific nonracemic phosphonates, and there are many nonracemic phosphonates in addition to the few selected examples displayed above. Three strategies of special promise are shown below.

A number of nonracemic alkylphosphonates have been prepared to exploit the possibility of chirality transfer from phosphorus to carbon through reactions of phosphoryl-stabilized anions. Phosphorus chirality is attained by incorporation of nonracemic substituents as phosphonate esters[112] or phosphonamides,[113-115] and the phosphoryl-stabilized anions have been used in diastereoselective additions to various electrophiles. One theme studied in several laboratories has been the conjugate addition of anions derived from nonracemic allyl phosphonates (Figure 43) to enones or α,β-unsaturated esters, because these additions generally result in the formation of at least one stereocenter in the adduct. After conjugate addition, the phosphorus auxiliary can be removed by oxidative cleavage of the double bond. This strategy already has been applied in natural product synthesis,[116] and further applications appear very likely as other variations on these reactions are developed.[117]



145 **146** **147** **148**

Figure 43. Nonracemic Alkylphosphonates.[112-115]

Routes to phosphonates based on free radical chemistry have been known for many years,[118] but examples that yield nonracemic products are still limited. Either addition of a phosphorus radical to a chiral

olefin or addition of a radical containing a stereogenic center to a phosphonate could be used to prepare nonracemic products. As an illustration of the former option, reaction of dimethylphosphite with bicyclo[2.2.1]hept-2-ene (**149**) in the presence of benzoyl peroxide gives the exo isomer **150** in very good yield (Figure 44).[119] As an example of the second strategy, radicals derived from nucleoside derivatives of the general form **151** undergo addition to dimethyl vinylphosphonate to give extended phosphonates such as **152**.[120] Even though recent work has extended this synthesis to other nucleoside derivatives,[121] much of the potential of free radical methods for synthesis of nonracemic phosphonates may remain to be uncovered.

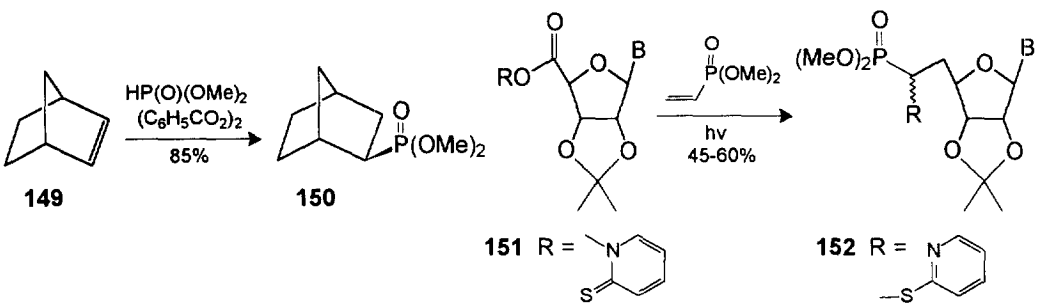


Figure 44. Free Radical Routes to Chiral Phosphonates.[119-120]

Finally, vinyl triflates have been reported to undergo palladium-catalyzed coupling with dimethyl phosphite to afford vinyl phosphonates in very good yield.[122] For example (Figure 45), the steroid derivative **153** undergoes coupling to afford the nonracemic vinyl phosphonate **154**. Even though this reaction does not produce a stereogenic center directly, it holds great promise for synthesis of nonracemic phosphonates because of the ubiquitous distribution of carbonyl groups and the ease with which they are converted to vinyl triflates.[123]

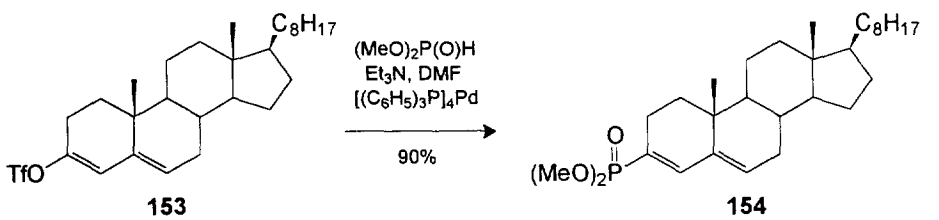


Figure 45. Palladium-Catalyzed Phosphonylation of Vinyl Triflates.[122]

6. Summary.

Recent years have witnessed a dramatic increase in interest in the preparation of nonracemic phosphonates. The result has been significant growth in the number and variety of strategies for stereocontrolled phosphonate synthesis. Much of this interest has stemmed from the potential biological

activity of phosphonates, their utility as intermediates for synthesis of other nonracemic compounds, and an increasing emphasis on preparation of chiral compounds in nonracemic form. But other ingenious applications of nonracemic phosphonates also continue to appear. Recent examples include use as nonracemic ligands for transition metal catalysts,[86] as nonracemic carbon acids for potentially enantioselective protonation of carbanions,[124] and as part of the functional group array of unnatural ionophores.[125] As these applications suggest, their increased availability combined with the boundless imagination of organic chemists will continue to spur growth in the chemistry of nonracemic phosphonates.

ACKNOWLEDGMENTS

Financial support from the National Institutes of Health (GM-44986) and the Roy J. Carver Charitable Trust is gratefully acknowledged.

REFERENCES AND NOTES

1. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.
2. Engel, R. *Chem. Rev.* **1977**, *77*, 349-367.
3. Lerner, R. A; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659-667.
4. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320-1367
5. Almeida, W. P.; Correia, C. R. D. *Tetrahedron Lett.* **1994**, *35*, 1367-1370 and references cited therein.
6. Jacks, T. E.; Nibbe , H.; Wiemer, D. F. *J. Org Chem.* **1993**, *58*, 4584-4588.
7. Lalinde, N.; Tropp, B. E.; Engle, R. *Tetrahedron* **1983,** *14*, 2369-2372.
8. Blackburn, G. M. *Chem. Ind. (London)* **1981**, 134-138.
9. Cooperman, B. S.; Chiu, N. Y. *Biochem.* **1973**, *12*, 1670-1676.
10. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587-5590. b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591-5594.
11. Sikorski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Font, J. L.; Gruys, K. J.; Han C. Y.; Lin, K. C.; Pansegrau, P. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. *Phosphorus, Sulfur, and Silicon* **1993**, *76*, 375-378.
12. Pompliano, D. L.; Rands, E.; Schaber, M. D.; Mosser, S. D.; Anthony, N. J.; Gibbs, J. B. *Biochemistry* **1992**, *31*, 3800-3807.
13. Stowasser, B.; Budt, K. H.; Li, J. Q.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625-6628.
14. a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, and Silicon* **1991**, *63*, 193-215. b) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879-10888.

15. Shokat, K. M.; Ko, M. K.; Scanlan, T. S.; Kochersperger, L.; Yonkovich, S.; Thaisrivongs, S.; Schultz, P. G. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1296-1303.
16. Nakayama, G. R.; Schultz, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 780-781.
17. a) Yager, K. M.; Taylor, C. M.; Smith, A. B., III *J. Am. Chem. Soc.* **1994**, *116*, 9377-9378. b) Wagner, J.; Lerner, R. A.; Barbas, C. F. III *Bioorg. Med. Chem.* **1996**, *4*, 901-916.
18. a) Janda, K. D.; Benkovic, S. J.; Lerner, R. A. *Science* **1989**, *244*, 437-439. b) Janda, K. D.; Ashley, J. A; Jones, T. M.; McLeod, D. A.; Schloeder, D. M.; Weinhouse, M. I.; Lerner, R. A.; Gibbs, R. A.; Benkovic, P. A.; Hilhorst, R.; Benkovic, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 291-297.
19. Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930-7933. b) Baraldi, P. G.; Guarneri, M.; Moroder, F.; Pollini, G. P.; Simoni, D. *Synthesis* **1982**, 653-655. c) Gouverneur, V.; Lalloz, M-N. *Tetrahedron Lett.* **1996**, *37*, 6331-34. d) Benayoud, F.; deMendonca, D. J.; Digits, C. A.; Moniz, G. A.; Sanders, T. C.; Hammond, G. B. *Org. Chem.* **1996**, *61*, 5159-5164. e) Öhler, E.; Zbiral, E.; *Synthesis* **1991**, 357-361. f) Öhler, E.; Kanzler, S. *Synthesis* **1995**, 539-543, and references therein.
20. Mjalli, M. M.; Cao, X. *Tetrahedron Lett.* **1996**, *37*, 6073-6076.
21. Pudovic, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81-96, and references cited therein.
22. Abramov, V. S.; *Dokl. Akad. Nauk. S. S. S. R.* **1950**, *73*, 487-489; *Chem. Abstr.* **1951**, *45*, 2855h. b) For an early application to steroids, cf: Benezra, C.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1967**, 624-632.
23. Paulsen, H.; Greve, W.; Kuhne, H. *Tetrahedron Lett.* **1971**, *12*, 2109-2112.
24. a) Evelyn, L.; Hall, L. D.; Steiner, P. R.; Stokes, D. H. *J. Chem. Soc., Chem Commun.* **1969**, 576-577. b) Evelyn, L.; Hall, L. D.; Lynn, L.; Steiner, P. R.; Stokes, D. H. *Carbohydrate Research* **1973**, *27*, 21-27.
25. a) Hammerschmidt, F. *Liebigs Ann. Chem.* **1991**, 469-475. b) The analogous TIPS aldehyde gives even better de: Bongini, A.; Camerini, R.; Panunzio, M.; *Tetrahedron: Asymmetry* **1996**, *7*, 1467-1476.
26. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1401-1404.
27. Serra, C.; Dewynter, G.; Montero, J. L.; Imbach, J. L. *Tetrahedron* **1994**, *50*, 8427-8444.
28. a) McEldoon, W. L.; Lee, K.; Wiemer, D. F. *Tetrahedron Lett.* **1993**, *34*, 5843-5846. b) McEldoon, W. L.; Wiemer, D. F. *Tetrahedron* **1995**, *51*, 7131-7148.
29. Gordon, N. J.; Evans, S. A., Jr. *J. Org. Chem.* **1993**, *58*, 5293-5294.
30. a) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *Tetrahedron: Asymmetry* **1994**, *5*, 499-502. b) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931-940.
31. a) Sum, V.; Kee, T. P. *J. Chem. Soc., Chem Commun.* **1993**, 1369-1370. b) Devitt, P. G.; Kee, T. P. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3169-3182. c) Sum, V.; Baird, C. A.; Kee, T. P.; Thornton-Pett, M. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3183-3200, and references cited therein.
32. Wynberg, H.; Smaardijk, Ab. A. *Tetrahedron Lett.* **1983**, *24*, 5899-5900.

33. Smaardijk, Ab. A.; Noorda, S.; van Bolhuis, F.; Wynberg, H.; *Tetrahedron Lett.* **1985,** *26*, 493-496.
34. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779-1782.
35. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783-1784.
36. Rath. N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227-230.
37. a) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926-2927. b) A binaphthoxide catalyst has also been reported: Sasai, H.; Bougauchi, M.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 2717-2720.
38. Mitchell, M. C.; Cawley, A.; Kee, T. P. *Tetrahedron Lett.* **1995**, *36*, 287-290.
39. Creary, X.; Geiger, C. C.; Hilton, K. *J. Am. Chem. Soc.* **1983**, *105*, 2851-2858.
40. Gajda, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965-1972.
41. a) Meier, C.; Laux, W. H. G. *Tetrahedron* **1996**, *52*, 589-598. b) Meier, C.; Laux, W. H. G.; Bats, J. W. *Liebigs Ann. Chem.* **1995**, 1963-1979.
42. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611-614.
43. a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931-2932. b) Kitamura. M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769-5772.
44. β-Keto thiophosphonates undergo a similar reduction with excellent ee's: Gautier, I.; Ratovelomanana-Vidal, V.; Savignac, P.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 7721-7724.
45. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H. L.; Morikawa, K.; Wang, Z. -M.; Xu, D.; Zhang, X. -L.; *J. Org. Chem.* **1992**, *57*, 2768-2771.
46. a) Yokomatsu, T.; Yoshida, Y.; Suemune, K.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 365-368. b) Lohray, B. B.; Maji, D. K.; Nandanan, E. *Indian J. Chem.* **1995**, *34B*, 1023-1025.
47. Hampton, A.; Perini, F.; Harper, P. J. *Biochemistry* **1973**, *12*, 1730-1736.
48. A recent study reported that hydroboration/oxidation of vinyl phosphonates is ~100% regioselective for the α-hydroxy phosphonate: Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 7424-7426.
49. a) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402-2404. b) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Thimma Reddy, R.; Chen, B. C. *J. Org. Chem.* **1992**, *57*, 7274-7285. c) Gala, D.; DiBenedetto, D. J.; Mergelsberg, I.; Kugelman, M. *Tetrahedron Lett.* **1996**, *37*, 8117-8120.
50. Pogatchnik, D. M.; Wiemer, D. F. *Tetrahedron Lett.* **1997**, *38*, 3495-3498.
51. Gulea-Purcarescu, M.; About-Jaudet, E.; Collignon, N.; *Tetrahedron Lett.* **1995**, *36*, 6635-6638.
52. Denmark, S. E.; Miller, P. C. *Tetrahedron Lett.* **1995**, *36*, 6631-6634.
53. Denmark, S. E.; Chen, C. T. *J. Am. Chem. Soc.* **1995**, *117*, 11879-11897.
54. Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 823-830.

55. a) Hammerschmidt, F.; Vollenkle, H. *Liebigs Ann. Chem.* **1986**, 2053-2064. b) (1-Naphthyl)ethylamine was used to resolve 1-hydroxyethylphosphinic acid, which was oxidized to the phosphonic acid: Sasaki, M. *Agric. Biol. Chem.* **1986**, *50*, 741-745.

56. Hammerschmidt, F.; Vollenkle, H. *Liebigs Ann. Chem.* **1989**, 577-583.

57. Mori, I.; Iwasaki, G.; Kimura, Y.: Matsunaga, S. I.; Ogawa, A.; Nakano, T.; Buser, H. P.; Hatano, M.; Tada, S.; Hayakawa, K. *J. Am. Chem. Soc.* **1995**, *117*, 4411-4412.

58. Li, Y. F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109-120.

59. Drescher, M.; Li,. Y. F.; Hammerschmidt, F.; *Tetrahedron* **1995**, *51*, 4933-4946.

60. Khushi, T.; O'Toole, K. J.; Sime, J. T. *Tetrahedron Lett.* **1993**, *34*, 2375-2378.

61. Heisler, A.; Rabiller, C.; Douillard, R.; Goalou, N.; Hagele, G.; Levayer, F. *Tetrahedron: Asymmetry* **1993**, *4*, 959-960.

62. a) Li, Z.; Racha, S.; Dan, L. El-Subbagh, H.; Abushanab, E. *J. Org. Chem.* **1993**, *58*, 5779-5783. b) Pragnacharyulu, P. V. P.; Abushanab, E. *Tetrahedron Lett.* **1995**, *36*, 5507-5510. c) Page, P.; Blonski, C.; Perie, J. *Tetrahedron Lett.* **1995**, *36*, 8027-8031.

63. a) Ackerman, B.; Jordan, T. A.; Eddy, C. R.; Swern, D. *J. Am. Chem. Soc.* **1956**, *78*, 4444-4447. b) Berlin, K. D.; Hellwege, D. M.; Nagabhushanam, M. *J. Org. Chem.* **1965**, *30*, 1265-1267. c) Zhdanov, Y. A.; Uzlova, L. A.; Glebova, Z. I. *Russ. Chem. Rev.* **1980**, *49*, 843-853.

64. Karaman, R.; Goldblum, A.; Breuer, E. *J. Chem. Soc. Perkin Trans. 1* **1989**, 765-774.

65. Afarinkia, K.; Echenique, J.; Nyburg, S. C. *Tetrahedron Lett.* **1997**, *38*, 1663-1666.

66. Oshikawa, T.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2728-2730.

67. a) Longmire, C. F.; Evans, S. A., Jr. *J. Chem. Soc. Chem. Commun.* **1990**, 922-923; b) Telan, L. A.; Poon, C. D.; Evans, S. A., Jr. *J. Org. Chem.* **1996**, *61*, 7455-7462.

68. Newer methods of β-keto phosphonate synthesis, not yet been applied to preparation of nonracemic compounds, include: a) Kim, D. Y.; Kong, M. S.; Kim, T. H.; *Synth. Commun.* **1996**, *26*, 2487. b) Lee, C. W.; Hong, J. E.; Oh, D. Y. *J. Org. Chem.* **1995**, *60*, 7027-7029. c) Kim, D. Y.; Kong, M. S. *J. Chem. Soc., Chem. Commun.* **1994**, 3359-3360. d) Koh, Y. J.; Oh, D. Y. *Tetrahedron Lett.* **1993**, *34*, 2147-2148. e) Hong, S.; Chang, K.; Ku, B.; Oh, D. Y. *Tetrahedron Lett.* **1989**, *30*, 3307-3308.

69. Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307-335.

70. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430

71. a) Perkow, W.; Ullerich, K; Meyer, F. *Naturwissenschaften* **1952**, *39*, 353. b) Bianchini, J.P.; Gaydou, E. M. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 1521-1523. c) Baroulare, M.; Sturtz, G. *Bull. Soc. Chim. Fr.* **1974**, *7-8*, 1585-1590.d) Gaydou, E.M.; Bianchini, J.P. *Chem. Commun.* **1975**, *14*, 541-542.

72. Where the Arbuzov reaction proves difficult, a Michaelis-Arbuzov reaction may be useful: Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685-4696. Both allylic (Falck, J. R.; Abdali, A.; Wittenberger, S. J. *J. Chem. Soc. Chem. Commun.* **1990**, 953-955) and propargylic (Kerdesky, F. A. J.; Schmidt, S. P.; Brooks, D. W. *J. Org. Chem.* **1993**, *58*, 3516-3520) halides have been used to prepare nonracemic phosphonates.

73. a) Corey, E. J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* **1966**, *88*, 5654-5656. b) Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649-654. c) Aboujaoude, E. E., Collignon, N.; Savignac, P. *J. Organomet. Chem.* **1984**, *264*, 9-17.

74. a) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731-3733. b) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *58*, 2374-2378. c) Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744-3747.

75. Altenbach, H. J.; Holzapfel, W. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 67-68.

76. Narkunan, K.; Nagarajan, M. *J. Org. Chem.* **1994**, *59*, 6386-6390.

77. Koskinen, A. M. P.; Krische, M. J. *Synlett* **1990**, 665-666.

78. Berkowitz, D. B.; Eggen, M.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61* 4666-4675.

79. Kojima, K.; Saito, S. *Synthesis* **1992**, 949-950.

80. a) Hanessian, S.; Rancourt, G.; Guidon, Y. *Can. J. Chem.* **1978**, 56, 1843-1846. b) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954-1957. c) Ditrich, K. Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325-6328. d) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, 25, 75-78. e) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461-1464. f) Yamanoi, T.; Akiyama, T.; Ishida, E., Abe, H.; Ameniya, M.; Inazu, T. *Chem. Lett.* **1989**, 335-336. g) Harre, M.; Trabandt, J.; Westermann, J. *Liebigs Ann. Chem.* **1989**, 1081-1083. h) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915-930. i) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692-7697. j) Delamarche, I.; Mosset, P. *J. Org. Chem.* **1994**, *59*, 5453-5457. k) Mulzer, J.; Martin, H. J.; List, B. *Tetrahedron Lett.* **1996**, *37*, 9177-9178. l) Knol, J.; Feringa, B. L. *Tetrahedron Lett.* **1997**, *38*, 2527-2530. m) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313-4320.

81. Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224-1226. b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011-4013. c) Paterson, I.; Yeung, K. S. *Tetrahedron Lett.* **1993**, *33*, 5347-5350.

82. Lim, M. I.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 4051-4054.

83. Mikolajczyk, M.; Balcewski, P. *Synthesis* **1984**, 691-694.

84. Kabat, M. M. *Tetrahedron Lett.* **1993**, *34*, 8543-8544.

85. a) Calogeropoulou, T.; Hammond, G.B.; Wiemer, D.F. *J. Org. Chem.* **1987**, *52*, 4185-4190. b) Gloer, K.B.; Calogeropoulou, T.; Jackson, J.A.; Wiemer, D.F. *J. Org. Chem.* **1990**, *55*, 2842-2846. c) An, Y. Z.; Wiemer, D.F. *J. Org. Chem.* **1992**, *57*, 317-321. d) Koerwitz, F. L.; Hammond, G. B.; Wiemer, D.F. *J. Org. Chem.* **1989**, *54*, 738-743.

86. Clarke, R. Gahagan, M.; Mackie, R. K.; Foster, D. F.; Cole-Hamilton, D. J.; Nicol, M.; Montford, A. W. *J. Chem. Soc. Dalton Trans. I* **1995**, 1221-1226.

87. a) Jackson, J.A.; Hammond, G.B.; Wiemer, D.F. *J. Org. Chem.* **1989**, *54*, 4750-4754. b) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967-5971.

88. a) An, Y. Z.; An, J. G.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 8197-8202. b) An, J.; Wilson, J. M.; An, Y. Z.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 4040-4045.

89. An, J. G.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775-8779.

90. Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556-5560.

91. Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071-3072.

92. Patterson, I.; Boddy, I. *Tetrahedron Lett.* **1988**, *29*, 5301-5304.

93. Baccolini, G.; Todesco, P. E.; Dalpozzo, R.; De Nino, A. *Gazz. Chim. Ital.* **1996**, *126*, 271-273.

94. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934-1939.

95. Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

96. Enders, D.; Wahl, H.; Papadopoulos, K. *Liebigs Ann.* **1995**, 1177-1184.

97. a) Ojea, V.; Fernandez, M. C.; Ruiz, M.; Quintela, J. M. *Tetrahedron Lett.* **1996**, *37*, 5801-5804. b) Ojea, V.; Ruiz, M.; Shapiro, G.; Pombo-Villar, E. *Tetrahedron Lett.* **1996**, *35*, 3273-3276.

98. Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369-379.

99. Tomoskozi, I.; Janzso, G. *Chem. Ind (London)* **1962**, 2085-2086.

100. Hatakeyama, S.; Sataoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713-2716 b) Hatakeyama, S.; Sataoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2717-2720.

101. a) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069-7071. b) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, 44, 4010-4011. c) Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885-5888. d) Franck-Neumann, M.; Briswalter, C.; Chemla, P.; Martina, D. *Synlett.* **1990**, 637-6640. e) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077-1080.

102. a) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732-4734. b) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104-7105.

103. Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896-906.

104. Tanaka, K.; Ohta, Y.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 4071-4074.
105. Narasaka, K.; Hidai, E.; Hayashi, Y.; Gras, J. L. *J. Chem. Soc., Chem Commun.* **1993**, 102-104.
106. Denmark, S. E.; Rivera, I. *J. Org. Chem.* **1994**, *59*, 6887-6889.
107. Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847-5849.
108. Boeckman, R. K., Jr.; Kamenecka, T. M.; Nelson, S. G.; Pruitt, J. R.; Barta, T. E. *Tetrahedron Lett.* **1991**, *32*, 2581-2584.
109. Lee, K.; Wiemer, D. F.; *Phosphorus, Sulfur, and Silicon* **1993**, *75*, 87-90.
110. Commins, D. L.; Jacobine, A. F.; Marshall, J. L.; Turnbull, M. M. *Synthesis* **1978**, 309-311.
111. Paquette, L. A.; Wang, T. Z.; Phillippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.
112. Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036-8043.
113. Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026-5029.
114. Denmark, S. E.; Kim, J. H. *J. Org. Chem.* **1995**, *60*, 7535-7547.
115. Hanessian, S.; Gomtsyan, A.; Payne, A.; Herve, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032-5034.
116. a) Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 4579-4582. b) Wang, T. Z.; Pinard, E.; Paquette, L. A. *J. Am. Chem. Soc.* **1995**, *118*, 1309-1318.
117. a) Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393-10394; b) Hanessian, S.; Cantin, L. D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103-1106.
118. Callot, H. J.; Benezra, C. *Can. J. Chem.* **1970**, *48*, 3382.
119. Peterson, A. C.; Levsen, S. M.; Cremer, S. E. *Phosphorus, Sulfur, and Silicon* **1996**, *115*, 241-254.
120. Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron* **1992**, *48*, 1627-1636.
121. Wnuk, S.; Robins, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2519-2520.
122. Holt, D. A.; Erb, J. M. *Tetrahedron Lett.* **1989**, *30*, 5393-5396.
123. Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630-4632.
124. Vedejs, E.; Garcia-Rivas, J. A. *J. Org. Chem.* **1994**, *59*, 6517-6518.
125. Burke, S. D.; O'Donnell, C. J.; Hans, J. J.; Moon, C. W.; Ng, R. A.; Adkins, T. W.; Packard, G. K. *Tetrahedron Lett.* **1997**, *38*, 2593-2596.

(*Received* 25 *June* 1997)

Biographical Sketch

David F. Wiemer was born and raised in southern Wisconsin. He received a B.S. degree from Marquette University in 1972, before moving to the University of Illinois at Champaign-Urbana to pursue graduate study in organic chemistry. He received the Ph.D. degree in 1976 for work in synthetic organic chemistry under the direction of Nelson J. Leonard, and then continued his career with postdoctoral study at Cornell University under the direction of Jerrold Meinwald. He joined the faculty in the Department of Chemistry at the University of Iowa in 1978, and now holds the rank of Professor. His research interests include the development of new methodology for synthesis of organophosphorus compounds, and the synthesis of various terpenoids with anti-viral, anti-leukemic, and anti-proliferative properties. He also is interested in the isolation, characterization, and synthesis of biologically active natural products.

David F. Wiemer