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Synthesis of Natural Products Containing a C-P Bond

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1. Introduction

Most of the organic compounds in nature are composed of C-C bonds. Until 1959, all the organophosphorus compounds isolated from living things had been shown to have the carbon containing portion of the molecule attached to the phosphorus through a heteroatom (*e.g.* a phosphate). However, it has since been proven that compounds containing C-P bonds are not only also present, but stable.

Since the discovery of aminoethylphosphonic acid (AEP) in sheep rumen by Horiguchi and Kandatsu in 1959, many new types of related compounds have been found in hundreds of aquatic and terrestrial animals and microorganisms. These compounds are found both free and bound to structural components of cells such as lipids and proteins. Many of these compounds have attracted attention because of their antibacterial, antiviral, antibiotic, pesticidal, anti-cancer and enzyme inhibitory properties. Much of this activity has been attributed to the relatively inert nature of the C-P bond and to the physical and structural similarity of phosphonic and phosphinic acids to the biologically important phosphate ester and carboxylic acid functional

groups. These compounds can often act as substrate mimics and interfere with enzymatic processes. For example, the phosphonic acid analog of glycine is a plant-growth regulator[1] and the phosphonic acid analog of phenylalanine is a competitive inhibitor of phenylalanyl-5-RNA-synthase.[2]

Many reviews have appeared describing the natural occurrence,[3] biosynthesis,[4] metabolism,[5] and general study[6] of these compounds. The synthesis of aminophosphonic and aminophosphinic acid containing natural products has been summarized.[7] The purpose of this review is to complement the existing reviews by summarizing the available syntheses for naturally occurring C-P containing compounds. In keeping with the philosophy of *Tetrahedron*, this report is designed to be more illustrative rather than comprehensive. Natural products are listed in their approximate order of discovery, and syntheses for each natural product are grouped by synthetic strategy. In cases where multiple similar syntheses exist, the landmark synthesis is generally depicted rather than the most recent variation. Materials that have been isolated but not synthesized are noted as such; however, care must be taken with the structure assignments, as there is no substitute for independent synthesis.

2. Nomenclature

"Natural C-P compound" is the generic name for biological phosphorus compounds containing a carbon to phosphorus bond. The nomenclature for C-P compounds is derived from the seven inorganic parent compounds having a P-H bond, and in most cases named as substitution products resulting from replacement of H with an alkyl group, which is then attached as a prefix. A few representative examples are given below:

Derived Phosphorus Compounds		Seven Parent Phosphorus Compounds	
$HPMe_2$	dimethylphosphine	PH_3	phosphine
$HP(OH)(Me)$	methylphosphinous acid	$(HO)PH_2$	phosphinous acid
$MeP(OH)_2$	methylphosphonous acid	$(HO)_2PH$	phosphonous acid
$(MeO)_3P$	trimethylphosphite	$(HO)_3P$	phosphorous acid
$(MeO)_2P(O)H$	dimethylphosphite	$H_2P(O)(OH)$	phosphinic acid
$Me_2P(O)H$	dimethylphosphonite	$HP(O)(OH)_2$	phosphonic acid
$(MeO)_3P(O)$	trimethylphosphate	$P(O)(OH)_3$	phosphoric acid
$MeP(O)(OMe)_2$	dimethyl methylphosphonate		
$Me_2P(O)(OMe)$	methyl dimethylphosphinate	PH_5	phosphorane
$(MeO)_2P$-Cl	dimethyl phosphorochloridate	$P(O)Cl_3$	oxyphosphorus trichloride
$MeP(O)(NH_2)_2$	methylphosphoramidite	$H_3P(O)$	phosphine oxide

3. Conventions and Abbreviations

AEP	2-Aminoethylphosponic Acid
AHAPPA	3-(*N*-Acetyl-*N*-hydroxyamino)propylphosphonic Acid
AMPA	2-Aminomethylphosphonic Acid
APPA	2-amino-3-phosphonopropionic acid (3-Phosphonoalanine)
BAC	Bile Acid Conjugate
DM-AEP	2-(*N,N*-Dimethylamino)phosphonic acid (*N,N*-dimethyl-AEP)
ee	Enantiomeric excess
DCC	Dicyclohexylcarbodiimide
EPPA	Epoxypropylphosphonic acid
FC	Fosfonochlorin

FM	Fosfazinomycin
GPL	Glycerophosphonolipid
HO-AEP	1-Hydroxy-2-aminoethylphosphonic acid
IR	Infrared spectroscopy
MM-AEP	2-(*N*-Monomethylamino)phosphonic acid (*N*-methyl-AEP)
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance spectroscopy
PAA	Phosphonoacetaldehyde
PhThNH	Phthalimide
PL	Phosphonolipid
PPA	Phosphonopyruvic Acid
PTC	Phase transfer catalysis
PTX	Phosphonothrixin
rt	Room temperature
RZ	Rhizocticin
SPL	Sphingophosphonolipid
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TMAEP	2-(*N,N,N*-Trimethylamino)phosphonic acid (*N,N,N*-trimethyl-AEP)
TMS	Trimethylsilyl

4. C-P Bond Forming Reactions

The two primary challenges associated with the synthesis of C-P containing compounds are formation of the C-P bond itself and protecting group cleavage. The synthetic methods for producing the C-P bond have been extensively reviewed.[8] For the synthesis of natural products, C-P bond forming reactions generally fall into the following categories:

a) Michaelis-Arbusov reaction of trialkylphosphites with alkylhalides:

$$(RO)_3P + RX \rightarrow R\text{-}P(O)(OR)_2$$

b) Michaelis-Becker reaction of alkali salts of dialkylphosphonates with alkylhalides:

$$NaP(O)(OR)_2 + RX \rightarrow R\text{-}P(O)(OR)_2$$

c) Michael addition of either trialkylphosphites or dialkyl phosphonates to unsaturated C=C bonds:

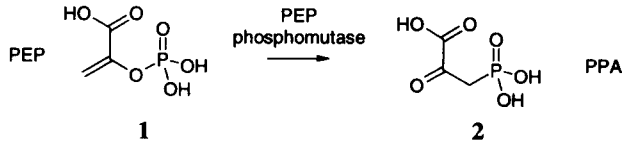
$$(RO)_3P \text{ or } H\text{-}P(O)(OR)_2 + R'\text{-}CH{=}CH_2 \rightarrow R'\text{-}CH_2CH_2\text{-}P(O)(OR)_2$$

d) Addition of trialkylphosphites or dialkyl phosphonates to open aziridines and epoxides:

$$(RO)_3P \text{ or } NaP(O)(OR)_2 + \text{3-ring heterocycle} \rightarrow X\text{-}CH_2CH_2\text{-}P(O)(OR)_2$$

X = heteroatom

In nature, the conversion of phosphoenolpyruvate (**1**, PEP) to phosphonopyruvate (**2**, PPA) is thought to be the crucial step in the biogenesis of C-P bonds.[6] The C-P bond forming enzyme phosphoenolpyruvate phosphomutase, responsible for this conversion, has recently been isolated and characterized from the protozoa *Tetrahymena pyriformis*[9] and *Pseudomonas gladiola* B-1.[10] The biosynthesis of phosphonates has been reviewed.[11]



1 **2**

5. Common Protecting Group Strategies

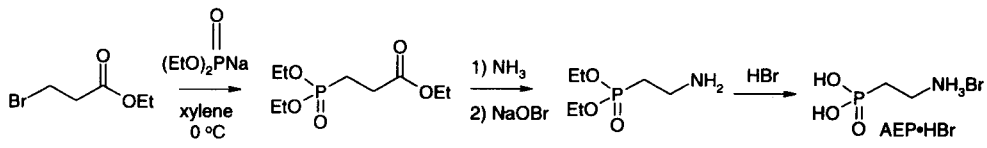
Cleavage of alkyl phosphonates and phosphinates has generally been performed as the last step and requires harsh mineral acid hydrolysis (e.g. 48% HBr, reflux for 5 hours or conc. HCl, reflux for 12 hours). An alternative mild method for dealkylation of phosphonate esters employs TMSCl/NaI/MeCN.[12] Deprotection of amine-protecting groups has usually invoked hydrogenation of *N*-benzyl groups or hydrazinolysis of phthalimides. Finally, propylene oxide is often used to remove HCl, and silver oxide used to remove HI from aminophosphonic acids.

6. Synthesis

6.1. 2-Aminoethylphosphonic Acid (AEP)

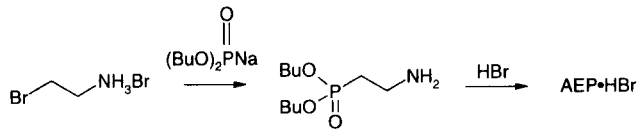
The first C-P containing natural product isolated was 2-aminoethylphosphonic acid (AEP), also known as ciliatine. It was isolated by Horiguchi and Kandatsu during the analyses of amino acids isolated from sheep rumen ciliate protozoa.[13] Kittredge *et al.* also isolated and identified AEP both in free form and esterified with glycerol in the sea anemone *Anthopleura elegantissima.*[14] AEP is one of the most abundant naturally occurring phosphonates, having since been isolated from many sources, including human brain, although it is mostly found in marine invertebrates and microorganisms.[15] AEP can be viewed as a phosphonic analog of taurine, β-alanine, or the *des*-oxy analog of ethanolamine phosphate. Being the first and oldest of the naturally occurring C-P containing natural products, AEP has been extensively studied and reviewed.[16] There have been many syntheses of AEP. The major distinctive methods are illustrated below:

6.1.1. Michaelis-Becker Reactions with β-Bromoethyl (Latent) Amines. Michaelis-Becker reaction of sodium diethylphosphonate with ethyl β-bromopropionate (**3**) gave β-carboxyethylphosphonate (**4**, 78% yield).[17] Conversion to diethyl β-carbamylethylphosphonate followed by Hofmann degradation and hydrolysis of the phosphonate esters gave AEP•HBr (**6**, 71% yield).



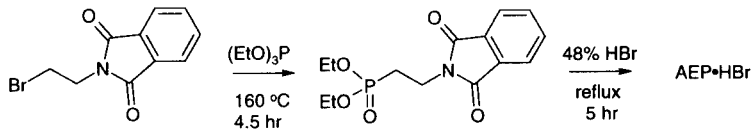
3 **4** **5** **6**

Reaction with β-bromoethylamine hydrobromide (**7**) with excess sodium dibutylphosphite gave dibutyl AEP (**10**) which was also hydrolyzed with HBr to AEP•HBr.[18]



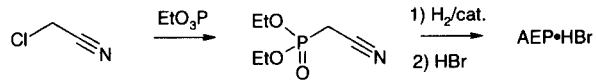
7 **8**

6.1.2. Michaelis-Arbusov Reactions with β-Bromoethyl (Latent) Amines. The first synthesis of AEP was accomplished more than a decade before its discovery as a natural product. Michaelis-Arbusov reaction of an equimolar amount of triethylphosphite with β-bromoethylphthalimide (**9**) followed by hydrolysis in 48% HBr gave AEP•HBr (50% overall yield).[19]



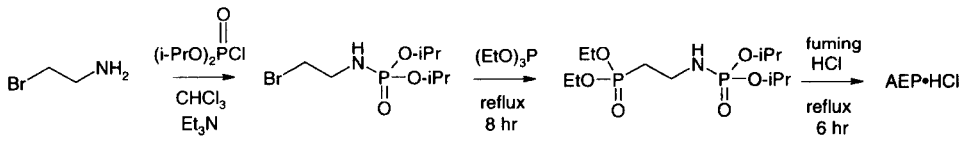
9 **10**

Michaelis-Arbusov reaction of a mixture of triethylphosphite and chloroacetonitrile (**11**) gave diethyl cyanomethylphosphonate **12** (92% yield).[20] Catalytic reduction of the nitrile followed by acidic hydrolysis gave AEP•HBr (47-86% yield).



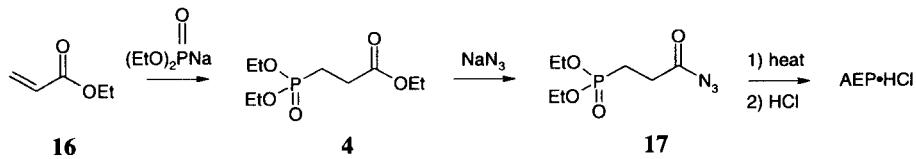
11 **12**

Michaelis-Arbusov reaction of triethylphosphite with diisopropyl β-bromoethylphosphoramide (**14**) followed by hydrolysis gave AEP•HCl (65-70% yield).[21]



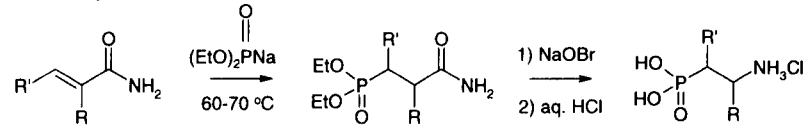
13 **14** **15**

6.1.3. Conjugate additions to Acrylates. Sodium diethylphosphonate was added to ethyl acrylate (**16**) to give 3-phosphonopropionate **4** (84% yield). Conversion to azide **17** followed by Curtius rearrangement then gave AEP•HCl. This method was extended by Wasielewski to prepare several simple analogs of AEP.[22]



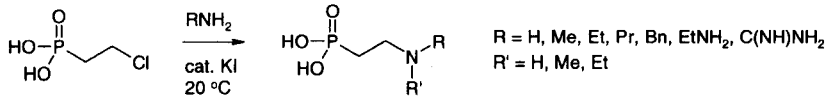
16 **4** **17**

By analogy to the above method, addition of diethyl hydrogen phosphonate to acrylamide **18** ($R^1 = R^2 =$ H, 75-81% yield) followed by Hofmann degradation of the resultant carbamoyl phosphonate **19** ($R^1 = R^2 = H$) and acidic hydrolysis gave AEP•HCl (75-85% yield).[23] Several analogs **20** (R^1 = H, Me, Ph R = H, Me) were also prepared in this way.



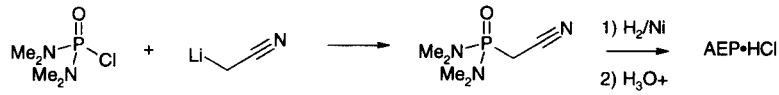
18 **19** **20**

6.1.4. Amination of β-Haloethylphosphonates. AEP and it's *N*-substituted derivatives were prepared in one step using chloroethylphosphonic acid **21** with amines in a dilute alkali solution accelerated by a catalytic amount of KI (78-82% yield).[24] This synthesis was similar to Kittredge's landmark synthesis of MM-AEP (Section 6.B.1).



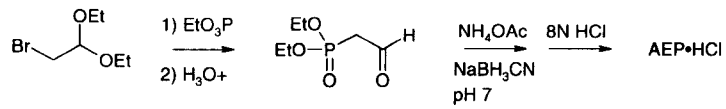
21 **22**

6.1.5.Additions to Halophosphorus Derivatives. Condensation of cyanomethyllithium (**24**) with *bis*-(dimethylamino)chlorophosphate **23** (51-95% yield) gave an intermediate, **25**, similar to Isbell's (**12**). Reduction of the nitrile (92-100% yield) followed by hydrolysis of the P-N bonds (34-76% yield) gave AEP•HCl (58% overall yield for AEP).[25]



23 **24** **25**

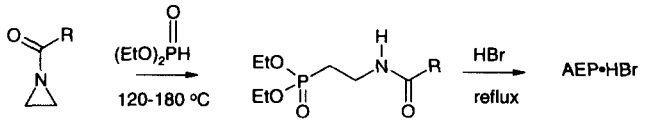
6.1.6. Imination/Enamine Reduction. Michaelis-Arbusov reaction of β-bromoacetaldehyde diethylacetal (**26**) with triethylphosphite gave 2-oxoethylphosphonate **27**. Reductive amination with ammonium acetate or alkyl amines (31-92% yield) followed by hydrolysis (51-81% yield) gave thirteen analogs of AEP (50% overall yield for AEP•HCl).[26]



26 **27**

In an analogous sequence,[27] the reaction of phosphonic aldehydes with benzylamine in the presence of reducing agents such as $NaBH_3CN$ yielded benzylaminoalkylphosphonates, which lead to phosphonic amino esters after catalytic hydrogenation. Hydrolysis with dilute HCl gave AEP•HCl. If the reducing agent was H_2/Pd, debenzylation occurred simultaneously with enamine reduction. Phosphonic ketones have also been employed to prepare analogs.[28]

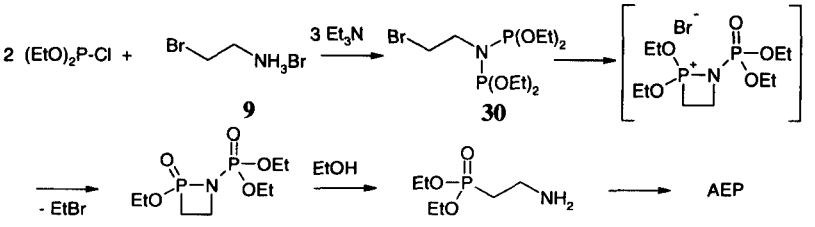
6.1.7. Aziridine Ring Opening with Phosphorus Nucleophiles. Heating diethylphosphite with *N*-acetylaziridine **28** (R = Me) gave aminoethylphosphonate **29** (42% yield) which was converted with boiling HBr to AEP. Use of triethylphosphite gave *N*-Ethyl AEP (65% yield).[29]



28 **29**

In a variation of this method, use of tris(trimethylsilyl)phosphite at 120-180 °C with 1-acylaziridines (R = CO_2Me, CO_2Et, $P(O)(OEt)_2$) gave the polysilylated aminoethylphosphonate analog of **29** (71-85% yield) which was readily hydrolyzed with 48% HBr to AEP•HBr (48-81% yield).[30]

6.1.8. 1,2-Azaphosphetidines. Reaction of two equivalents of diakyl phosphorochlorodite with β-bromoethylamine hydrobromide (**9**) in the presence of triethylamine gave *N,N*-bis(dialkoxyphosphino)-2-bromoethylamine (**30**), which upon thermolysis underwent intramolecular Arbusov rearrangement to give the 1,2-azaphosphetidine **31** as a stable compound.[31] Ethanolysis of the P-N bond gave the trialkylphosphite and diethylAEP (**5**) which could be hydrolyzed to AEP.

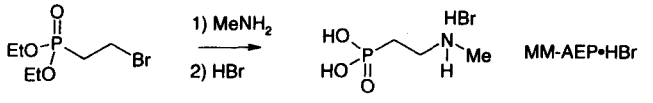


6.2. Synthesis of Labeled AEP. ^{14}C-labeled AEP was prepared by Michaelis-Becker addition to β-bromoethylphthalimide (Section 6.A.2, 5% overall yield).[32] ^{32}P-labeled material was prepared biosynthetically by growing *Tetrahymena pyriformis* in a ^{32}Pi-enriched medium (5-10% yield).[33]

6.3. *N*-Methyl-AEP Analogs

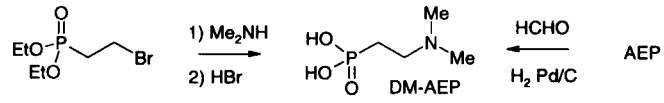
Three *N*-methyl analogs of AEP were isolated from the sea anemone *Anthopleura xanthogrammica* while attempting to isolate a phosphonic analog of phosphorylcholine.[34] These materials have all been synthesized.

6.3.1. Monomethyl-AEP (MM-AEP). Reaction of diethyl 2-bromoethylphosphonate with monomethylamine or dimethylamine gave monomethyl-AEP (MM-AEP, 50% yield).



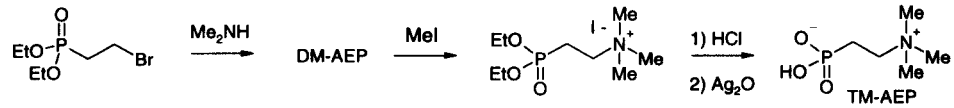
32 **33**

6.3.2. Dimethyl-AEP (DM-AEP). Reaction of diethyl β-bromoethylphosphonate with dimethylamine gave dimethyl-AEP (DM-AEP) in 50% yield. Alternatively, reductive methylation of AEP with formaldehyde under hydrogen also gave DM-AEP (40% yield). AEP can also be alkylated using formaldehyde in the presence of formic acid to give DM-AEP (81% yield).[35]



32 34

6.3.3. Trimethyl-AEP (TM-AEP). TM-AEP (**36**) was first synthesized by treating DM-AEP (**34**) with iodomethane followed by hydrolysis and iodide removal with silver oxide (29% overall yield from diethyl β-bromoethylphosphonate **9**).[36]



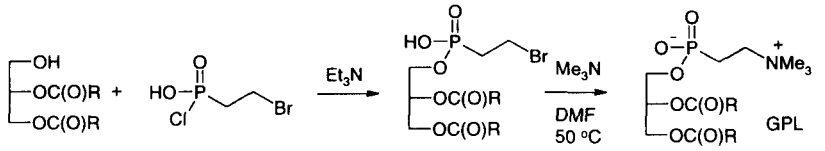
32 34 35 36

An alternative synthesis of TM-AEP was achieved by Michael addition of dimethylamine to diethyl vinylphosphonate to generate a β-dimethylaminoethylphosphonate followed by iodomethane alkylation and dehalogenation as above.[37] Primary and secondary aminoalkylphosphines were prepared by aminoalkylation of PH_3 with ω-chloroalkylamines in the basic medium DMSO/KOH.[38] Selective biphasic *N*-quaternization in CH_2Cl_2/H_2O followed by oxidation with hydrogen peroxide gave AEP derivatives. TMAEP can also be prepared by treating bromoethylphosphonic acid with trimethylamine (24% yield).

6.4. Phosphonolipids (PL).

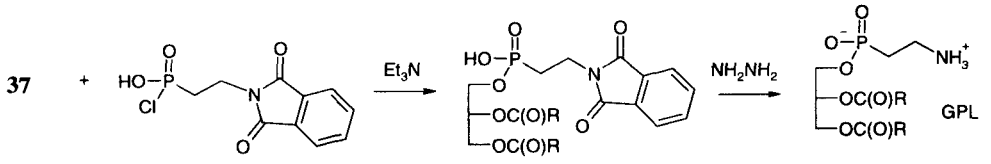
Phosphonolipids is the name given by Baer and Stanacev to the class of complex lipids comprising, in their structures, an additional molecule of AEP or one of the *N*-methylated analogs.[39] These materials have typically been isolated from invertebrates such as the sea hare *Aplysia kurodai*,[40] although they have also been found in many species of animals and plants, including vertebrate sources such as beef brain and human sperm. Thus far, only AEP analogs have been found in conjugates. However, the possibility exists for conjugation of a wide variety of C-P containing natural products with a wide array of glycerol derivatives. Because of this, synthesis of a variety of phosphonolipids has been achieved. As this work has been extensively reviewed,[41] only several representative examples will be given here.

6.4.1. Glycerophosphonolipids (GPL). There is some evidence for the natural occurrence of phosphonic acid analogs of L-α-lecithins in sea anemones, and such materials have therefore been synthesized.[42] β-Bromoethylchlorophosphonyl chloride (**38**) reacts with a diacylated glycerol derivative D-α,β-dipalmitin (**37**) to give the phosphonate **39** which is then further reacted - in this case, with trimethyl amine - to give the TMAEP conjugate **40**. Most phosphonolipid syntheses are variations of this theme.



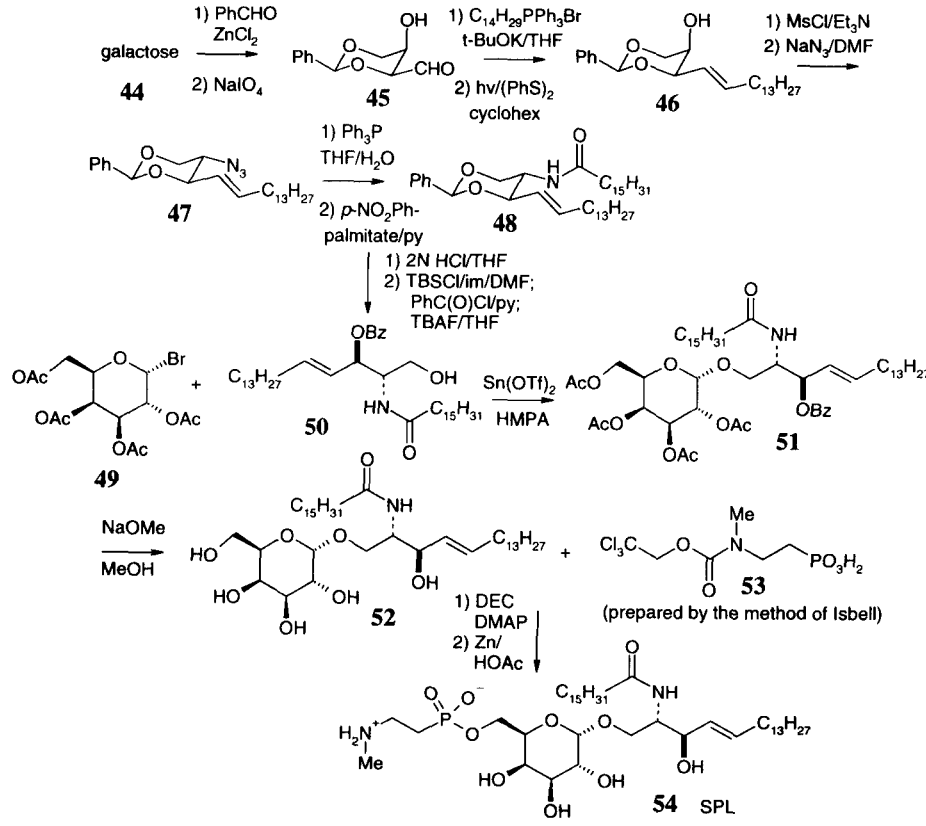
37 38 39 40

The L-α-cephalin dipalmitoyl-L-α-glyceryl -(2-aminoethyl) phosphonate (**43**) was isolated from *Anthopleura elegantissima*.[15] Phosphonylation of D-α,β-dipalmitin **37** with 2-phthalimidoethylphosphonic acid monochloride (**41**) and triethylamine followed by hydrazinolysis to remove the phthaloyl protecting group gave the cephalin **43**.[43]

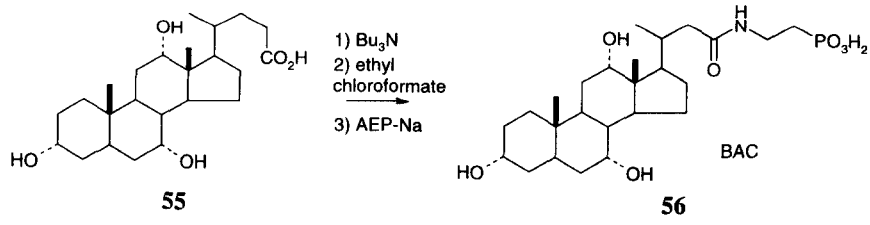


41 42 43

6.4.2. Sphingophosphonolipids (SPL). Ceramide-2-AEP (**54**), a sphingophosphonolipid, was isolated from the sea anemone *Anthopleura elegantissima*.[44] It was later found to be present in a wide variety of bivalves.[45] Many SPLs have been isolated from tissues of marine mollusca and marine Protostomia.[46] One of the simplest such compounds was isolated from the marine snail *Turbo cornutus*, and has been synthesized from galactose (**44**) as shown below.[47]



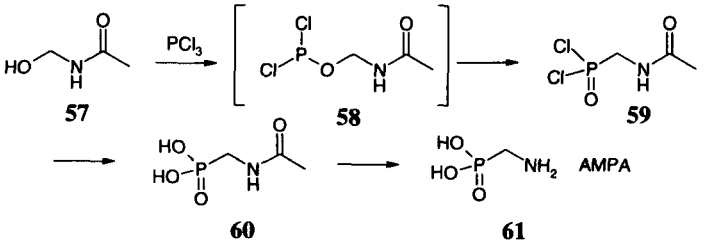
6.4.3. Bile Acid Conjugates (BAC). Citiacholic acid **56** and taurocholic acid are bile acid conjugates of AEP with cholic acid (**55**) isolated from bovine gall bladder bile.[48] Citiacholic acid was prepared by the carbonic-carboxylic acid anhydride method of Bergstrom and Norman used to prepare taurocholic and glycocholic acids.[49]



6.5. 2-Aminomethane Phosphonic Acid (AMPA).

2-Aminomethane phosphonic acid (**61**, AMPA), the phosphonic acid analog of glycine, is the primary metabolite in the degradation of the commercial herbicide Roundup® (glyphosate, or *N*-carboxymethylaminomethane phosphonic acid) and therefore has been isolated from plants and from soil which has been exposed to this material. It has been used to make pharmaceutical preparations which have

antibacterial activity. Introduction of an amino group to the same carbon as the phosphono group is generally accomplished either by ammonolysis of an α-halophosphonic acid obtained from reaction of PCl_3 with a carbonyl compound or reduction of α-keto derivative to hydroxy followed by conversion to halo, or by reduction of nitrogen derivatives of α-keto-phosphonates. A unique approach is shown below.[50]



57 58 59 60 61

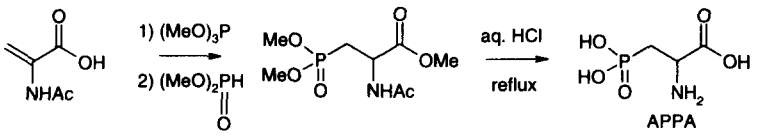
Variations of this reaction include use of *N*-benzoyl amide and a mixture of trimethylphosphite and phosphorus trichloride (73% yield),[51] or aminoalkylation of triphenylphosphite with *N*-BOC protected aminomethylacetate (48% yield), prepared from BOC-NH_2, acetic anhydride, and formaldehyde.[52]

Other preparations, many of which proceed through the same types of intermediates, include high temperature reaction with trialkylphosphites,[53] acid catalyzed thermal isobutylene elimination from *N*-*t*-butylaminomethylphosphonic acid (175 °C),[54] direct amination of chloromethylphosphonic acid with ammonia at 150 °C,[55] reduction of benzhydrylic Schiff's bases,[56] phosphite additions to hexahydrotriazines,[57] and treatment of acylaminomethanephosphonic acids with water at 300 °C,[58]

6.6. 2-Amino-3-phosphonopropionic acid (APPA).

2-Amino-3-phosphonopropionic acid (APPA, **64**) was first isolated by Kittredge and Hughes from *Zoanthus sociatus*.[59] Also called AP-3 and 3-phosphonoalanine, APPA is a biosynthetic precursor of AEP and has been found in humans, protozoa and marine organisms. It can be considered as the formal phosphono analog of aspartic acid or as the *des*-oxy analog of serine phosphate. APPA is a selective, potent modulator of the metabotropic excitatory amino acid receptor subtype.[60] Many syntheses of this material have been reported. The three main methods are illustrated here.

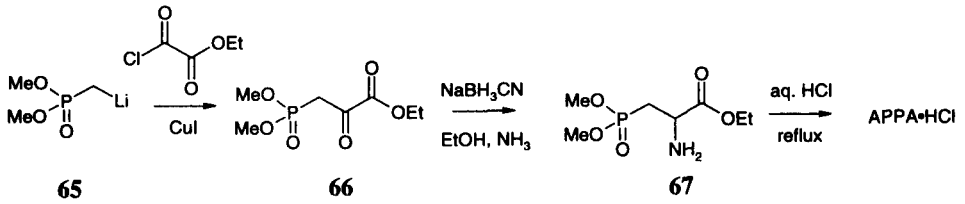
6.6.1. Michael Addition. APPA was first synthesized by addition of dimethyl phosphonate to methyl *N*-acetyl-2-aminoacrylate (50% yield), which was prepared by trimethylphosphite-mediated esterification of the corresponding acid (**62**), followed by acid hydrolysis.[61]



62 63 64

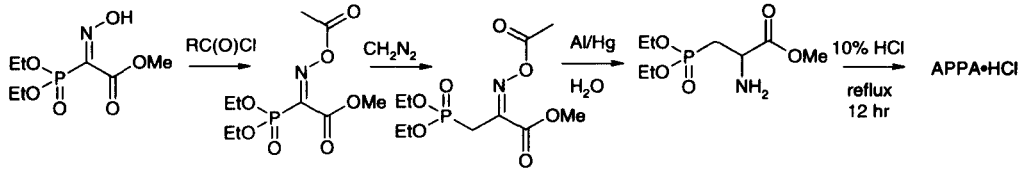
Analogs with a phosphinate in place of the phosphonate have been prepared analogously.[62]

6.6.2. Reductive Amination. Reductive amination of trialkylphosphonopyruvate **66**, prepared *via* Varlet's AEP synthesis, with sodium cyanoborohydride and ammonia in methanol followed by acidic hydrolysis gave APPA•HCl.[63]



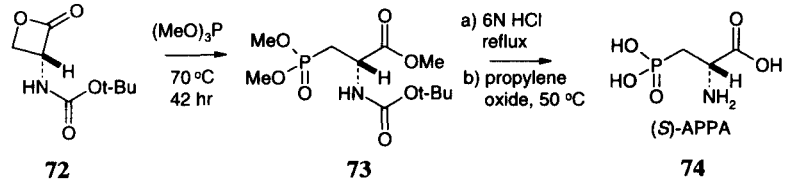
65 66 67

6.6.3. CH_2 Insertion into a C-P bond. *O*-Acyl oximes **69**, prepared by acylation of hydroxyiminophosphonate **68** with acetyl chloride or benzoyl chloride in the presence of triethylamine (83-95% yield), were homologated with diazomethane to give the 2-(acyloxyimino)-3-(diethoxyphosphinyl)propionic acid derivatives **70** (50-96% yield).[64] Reduction with aluminum amalgam gave the amine (64-83% yield), which was hydrolyzed with HCl to APPA•HCl.



68 69 70 71

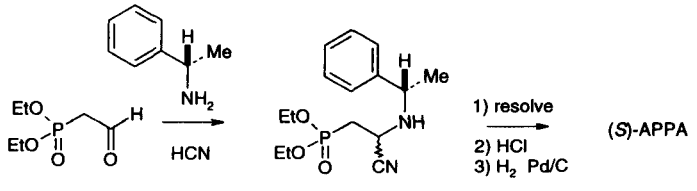
6.6.4. Enantioselective Syntheses. Several syntheses of the biologically active isomer (*S*)-APPA (**74**) exist. Nucleophilic addition of trimethylphosphite to enantiomerically pure 3-amino-2-oxetanone 72 followed by adventitious esterification gave (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate (**73**) in > 97% ee (82% yield).[65] Exhaustive acidic hydrolysis followed by treatment with propylene oxide afforded (*S*)-APPA (**74**) as its zwitterion. Enantiomeric purity was demonstrated to be > 97% by Mosher's method.



72 73 74

Hutchinson and Parkes executed an analogous synthesis using *N*-Fmoc and $TMSOP(OMe)_2$ as the nucleophile (39% yield).[66]

The optically active nitrile **76** was prepared by reaction of diethylphosphonoacetaldehyde with hydrogen cyanide and (*S*)-(-)-α-methylbenzylamine in 50% ee.[67] Acid hydrolysis, enrichment of the diastereomers by fractional crystallization, and debenzylation led to the isolation of (*S*)-APPA with 86% ee.



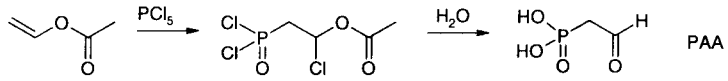
75 76

Enantiomerically pure material has also been obtained enzymatically *via* Lipase PS catalyzed enantioselective acetylation of prochiral 2-(ω-phosphono)alkyl-1,3-propanediol.[68]

6.6.5. Synthesis of Labeled APPA. ^{14}C-labeled APPA was prepared by analogy to the method of Chambers and Isbell (10% yield).[69] ^{3}H-labeled material was prepared by a catalytic exchange method.[70]

6.7. Phosphonoacetaldehyde (PAA)

A biosynthetic precursor of AEP, phosphonoacetaldehyde (**79**, PAA) was isolated by La Nauze and Rosenberg in 1967 while trying to elucidate the mechanism of breakdown of AEP in *Bacillus.* [7] Hydrolysis of 2-acetoxy-2-chloroethylphosphonyl dichloride (**78**), prepared by the addition of PCl_5 to vinyl acetate (**77**), at ambient temperature in aqueous THF gave PAA almost quantitatively.[71]

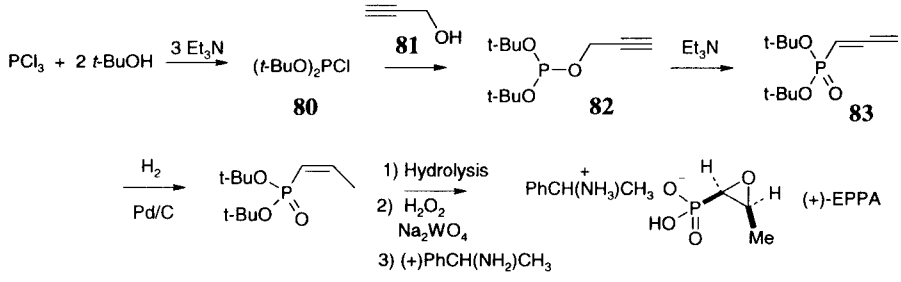


77 **78** **79**

6.8. Fosfomycin: (-) (1*R*,2*S*)-(*Z*)-1,2-epoxypropylphosphonic acid (EPPA)

(-) (1*R*,2*S*)-(*Z*)-1,2-Epoxypropylphosphonic acid (**85**, EPPA), also called fosfomycin or phosphonomycin, is a low molecular weight cell-wall active antibiotic found by Hendlin *et al.* in 1969 in a fermentation broth of *Streptomyces fradiae.*[72] This molecule, at the time, was the first example of biosynthesis of a C-P containing natural product by a prokaryotic organism. The first synthesis and chemical determination of its absolute configuration was described by Christensen *et. al.*[73] Since then a multitude of syntheses have been published. The syntheses generally fall into one of two categories: epoxidation of (*Z*)-1-propenylphosphonates or halohydrinphosphonate ring closure. The halohydrins are formed by one of three reactions: Darzens reaction, Michaelis-Becker reaction with α-haloketones, or hydrohalogenation of olefins. A recent example of each as well as a few classical examples are included here. For a recent comprehensive review, see Savignac *et. al.*[74]

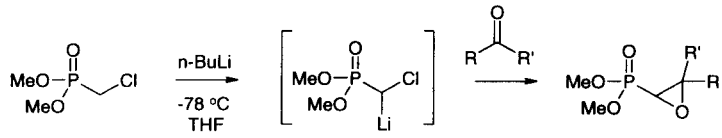
6.8.1. Epoxidation of (*Z*)-1-Propenylphosphonates. One of the first syntheses published utilized di-*t*-butyl 2-propynylphosphite (**82**), prepared from di-*t*-butyl phosphorochloridate (**80**) and propargyl alcohol (**81**).[75] This material was thermally rearranged to the propadienylphosphonate **83**. Selective hydrogenation to the *cis*-olefin **84** followed by hydrolysis (81% yield) and epoxidation gave racemic **85**. Optically pure material was obtained by resolution with (+)-phenethylamine (33% yield).



80 **82** **83** **84** **85**

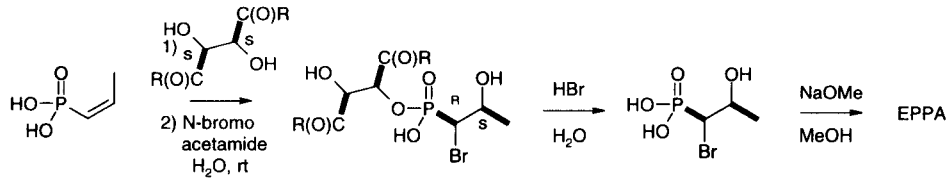
6.8.2. Base-Catalyzed Halohydrinphosphonate Ring Closure

Halohydrins *via* Darzens Reaction. Metallation of dialkyl chloromethylphosphonates **86** (*n*-BuLi, THF) followed by treatment with carbonyl compounds gives chlorohydrins, which on warming cyclize to epoxides **87** (50-90% yield).[76] The Darzens process generally proceeds without side reactions, but is not stereoselective or enantioselective.



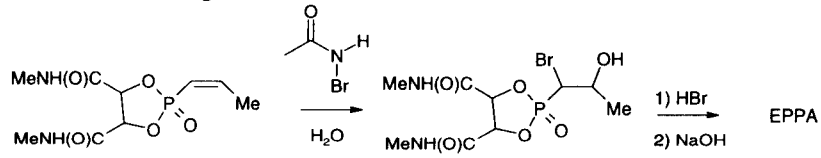
86 **87**

Halohydrins *via* Halohydroxylation of Olefins. The first non-microbial asymmetric synthesis uses tartaric acid as a chiral auxiliary to direct diastereoface selection in the bromohydroxylation of the prochiral (*Z*)-1-propenylphosphonic acid (**88**).[77] The bromohydroxylation occurs at ambient temperature in water to give (1*R*, 2*S*)-bromohydrins **89** (20-40% de, 90-95% yield) which are resolved *via* crystallization and converted to enantiomerically pure EPPA.



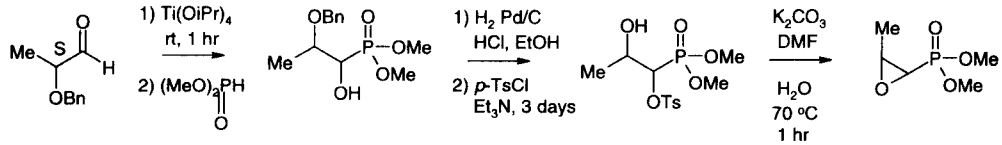
88 **89** **90**

In another synthesis by the same authors,[78] dioxolanes **91** (prepared by 3 different methods) were brominated to yield a 3:1 mixture of bromohydrins **92** (90% yield) which were deprotected with HBr and then cyclized with NaOH in MeOH to give EPPA.



91 **92**

Halohydrins *Via* Phosphonate Reaction With α-Halocarbonyls. Most examples utilize the hydroxyl generated from phosphonate addition to the carbonyl to displace a β-halogen. This example uses an α-tosylate rather than a β-halogen as the leaving group. Treatment of (*S*)-1-benzyloxypropanal (**93**) with phosphonic acid diesters (89% yield) followed by debenzylation, tosylation (92% yield), and then base-catalyzed conversion of the resulting tosylates to epoxides (95% yield) gave EPPA dimethyl ester (**96**).[79]



93 **94** **95** **96**

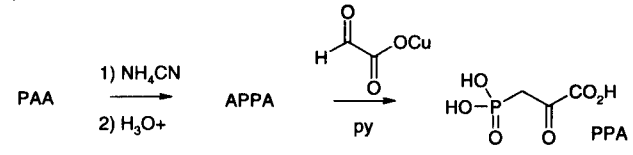
6.8.3. Enzymatic Syntheses. Four hundred and seventy strains of various microorganisms were tested for their ability to epoxidize *cis*-propenylphosphonate to (-)-EPPA. *Cellvibrio gilvus* KY 3412 was selected as the best strain. Conversion of 100% at less than 0.05% propene and of 40% at 0.5% propene were obtained after five days of cultivation.[80] EPPA was produced from *cis*-propenylphosphonic acid by fifteen strains of aerobic bacteria and two actinomycetes isolated from soils.[81]

6.8.4. Labeled EPPA. Stereospecific tritiation of dibutyl propargylphosphinate, hydrolysis, epoxidation, and resolution of the amine salt gave labeled EPPA.[82]

6.9. Phosphonopyruvic Acid (PPA)

Phosphonopyruvic Acid (**2**, PPA) was produced by blocked mutants of *Streptomyces hygroscopicus* SF-1293 during studies of the biosynthesis of bialaphos (section 6.10).[83]

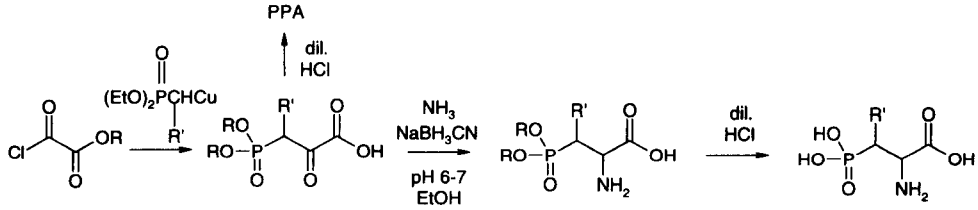
PAA (**79**, prepared by the method of Isbell, section 6.6) was converted to APPA (**64**) *via* Strecker synthesis and then transaminated with glyoxylate as the amino-group acceptor with Cu^{2+} and pyridine as catalysts to give PPA (**2**).[84]



79 **64** **2**

Non-enzymatic transamination of APPA (**64**) with pyridoxal phosphate gave PPA as the tetrahydrate of the disodium salt (4% yield). PPA has also been prepared from triethyl phosphonopyruvate (56% yield).[85]

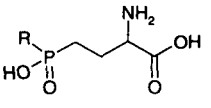
PPA has been synthesized by reaction of α-copper(I) alkanephosphonates with methyl and ethyl oxalyl chlorides **97** *via* alkyl dialkylphosphonopyruvates **98**. This intermediate was also reductively aminated to give phosphonic amino esters **99** which upon acid hydrolysis gave analogs of APPA (**100**).[86]



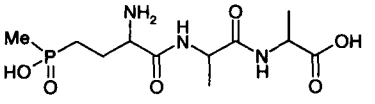
97 **98** **99** **100**

6.10. Bialaphos (Phosphinothricin)

L-Phosphinotricine (**101**, R = Me) is the name given to 2-amino-4-[hydroxy(methyl)phosphinoyl]-L-butyric acid by the founding German researchers. This material was isolated from acid hydrolysates of the tripeptide antibiotic bialaphos (phosphinothricyl-alanyl-alanine, hence the name "bi-ala-phos"), which was isolated from fermentation of *Streptomyces viridochromogenes*.[87] Bialaphos (**102**) was found independently by Ogawa as a structural component of antibiotic SF-1293, isolated from *Streptomyces hygroscopicus*.[88] Phosphinotricine, also known as phosphinothricin (PT) and glufosinate, is a structural analog of glutamine and glutamic acid, with a reduced phosphate (methylphosphinic acid) in place of a γ-carboxyl. It is unique among natural products in having a C-P-C bond array.



101
R = Me PT

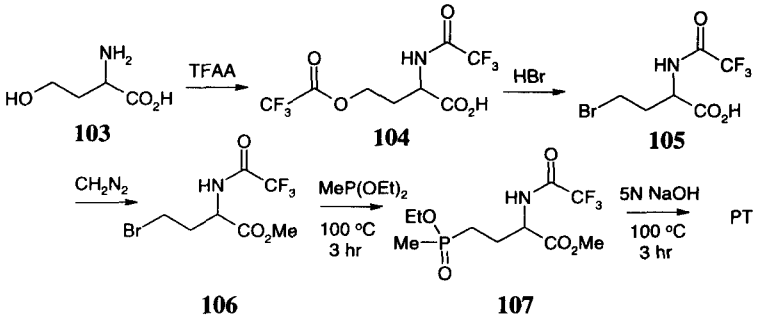


102
bialaphos

PT inhibits amination of glutamine by glutamine synthase.[89] While also possessing antibiotic activity, its major use has been as a non-selective herbicide sold under the trade name 'Basta'.[90] It is believed the two alanine residues allow for penetration of the tripeptide through the cell wall after which time the lethal PT is liberated. The bialaphos resistance gene has recently been expressed and transferred to crops.[91] PT is also contained in the herbicidal antibiotic phosalacine (phosphinothricylalanylleucine), isolated from *Kitasatosporia phosalacinea* KA-338 and trialaphos (phosphinothricylalanylalanylalanine), isolated from *Streptomyces hygroscopicus* sp. KSB-1285 by Kato *et al.*[92] The biosynthesis of bialaphos, thought to be derived from phosphonopyruvate, has recently been reviewed.[93] Owing to the extensive interest in this molecule as a commercial herbicide, numerous syntheses of PT and derivatives have been achieved and reviewed.[94] In fact, the synthesis and biological activity of several analogs of PT had been described prior to the isolation of bialaphos.[95] Therefore, only a few representative examples will be illustrated here.

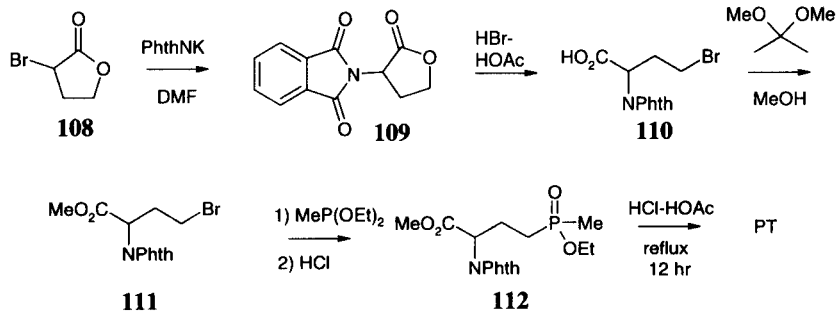
Most syntheses have employed glycine enolate equivalents either for alkylation with 2-haloethylphosphinates or for Michael addition to vinylphosphinates. Dialkyl methylphosphonites have also been utilized for conjugate addition or Michaelis-Arbusov reaction with unsaturated or halogenated glycine synthons, respectively, or carbonyl compounds which are subsequently converted to amino acids *via* Strecker reaction. A third, less utilized reaction, invokes successive carbonylation of methylvinylphosphinate *via* transition metal complexes. The carbonylation route appears to have advantages in that 1) highly toxic cyanide is not involved and 2) the amino acid is introduced inexpensively *via* CO and an amide.

6.10.1. Michaelis-Arbusov Reaction with β-Bromoethylglycine. The first synthesis by the authors who discovered PT was accomplished in milligram quantities from homoserine (**103**) using Arbusov phosphorylation.[88]



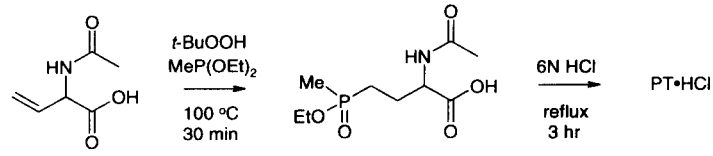
Readily available 4-bromo-2-pthalimidobutyrate (**110**) was used as a 2-amino-4-bromobutyrate equivalent.[96] Reaction of 2-bromo-4-butyrolactone (**108**) with potassium phthalimide in DMF at 100 °C quantitatively gave lactone **109** which was treated with HBr-acetic acid to give bromoacid **110** (95% yield). Esterification with 2,2-dimethyoxypropane gave 4-bromo-2-pthalimidobutyrate **111** (80% yield) which was reacted with an excess of diethyl methylphosphonite in toluene at 100 °C to give phosphinate **112** (90% yield). Cleavage of protecting groups in refluxing 6*N* HCl-HOAc and removal of the HCl *via* ethanolic propylene

oxide gave pure DL-PT (85% yield). Arbusov reaction with triethylphosphite gave the phosphonate analog which was only a weak inhibitor of glutamine synthetase.



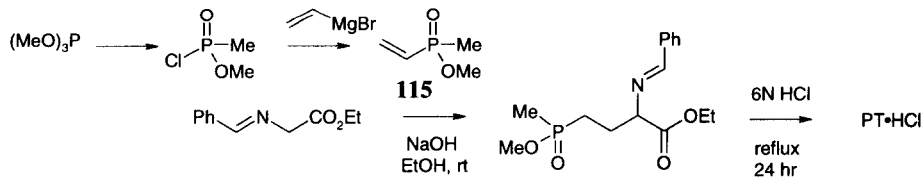
108 109 110 111 112

6.10.2. Michaelis-Arbusov Addition to Vinylglycines. In this method, introduction of the C-P bond differs from alternative syntheses by being performed last, thus minimizing consumption of expensive phosphonous reagents For example, radical addition of diethyl methylphosphinate to α-acetylaminovinylacetate **113** (prepared from vinylglycine) gave protected PT **114** which could be easily hydrolyzed to PT.[97]



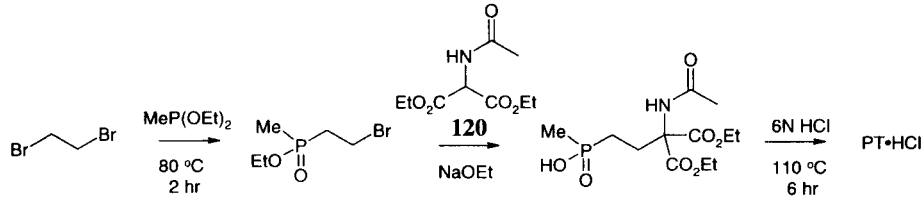
113 114

6.10.3. Glycine Enolate Addition to Vinylphosphonates. Addition of glycine Shiff's base anion **116** to the vinyl group of methyl vinylmethylphosphonite (**115**) gave protected PT **117**.[98] The key phosphorus reagent **115** could conveniently be prepared by direct vinylmagnesium bromide addition to the appropriate chlorophosphorus precursor, which could be generated in good yield from trimethylphosphite *via* either the phosphochlorodite or phosphoryl chloride. Deprotection to PT•HCL required 6*N* HCl reflux for 24 hr (65% yield).



116 117

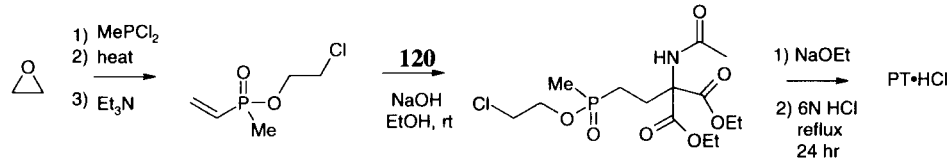
6.10.4. Malonate Reaction with β-Bromoethylphosphonate. The first synthesis of PT was accomplished by condensation of sodium diethyl acetaminomalonate **120** with the corresponding phosphinate **119**. Saponification, decarboxylation and subsequent deprotections of **121** gave PT•HCl.



118 119 121

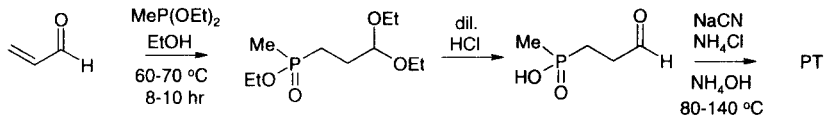
The synthesis of a number of analogs of PT with different substituents on the nitrogen or phosphorus, as well as homologs and isomers of PT, have been synthesized by conjugate additions to vinylphosphinate or methylenemalonate derivatives.[99]

6.10.5. Malonate Additions to Vinylphosphinates. Chloroethyl methylvinylphosphonite (**123**), which was generated from methyldichlorophosphine and ethylene oxide (**122**), was reacted with acetamidomalonate diester **120** to give the diester **124** (48% yield).[100] Saponification, decarboxylation and subsequent deprotections gave the PT•HCl (75% yield).



122 123 124

6.10.6. Michael Addition Followed by Strecker Synthesis. Dialkylmethylphosphonite was added to acrolein (**125**) (50-60% yield) followed by hydrolysis (91% yield) to the β-phosphinoaldehyde **127**.[101] The Strecker reaction was used to convert the aldehyde to the α-amino acid (31% overall yield).



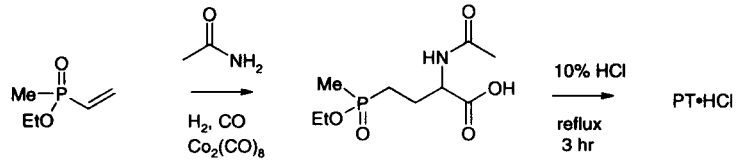
125 126 127

This method was also used to prepare *P*-ethyl, *P*-phenyl and the 2-oxa and 4-oxo analogs, which were essentially devoid of biological activity.

Bromopropionaldehyde acetals were reacted with triethylphosphite or suitable dialkyl alkylphosphonites to give the requisite phosphonopropanal acetals.[102] *In situ* conversion of the acetals to aldehydes followed by Strecker reaction gave the amino acids. Several analogs with other substituents in place of the methyl on phosphorus were prepared using this synthesis. The same authors also employed benzoyl peroxide initiated free radical addition of ethyl methylphosphonite to acrolein acetals followed by Strecker reaction.[103]

6.10.7. Amidocarbonylation. The olefin of methylvinylphosphinate (**115**) was converted *in situ* to an aldehyde and then Wakamatsu reaction (amidocarbonylation of the aldehyde)[104] gave the *N*-acylamino acid **114**.[105] The reaction proceeds by hydroformylation of the vinylphosphinate to give the unbranched isomer as the major product. Reaction with amide then forms the *N*-acylated hemiaminal which is carbonylated to give

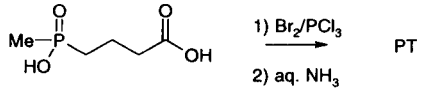
the *N*-acylamino acid. Hydrolysis with HCl gave PT•HCl (80% yield). Depending on the nature of the phosphinate ester and amide used, yields ranged from 41-85%.



115 114

The aforementioned method, which yields 2-chloroethyl methylvinylphosphonate *via* successive hydroformylation-amidocarbonylation, was generally superior to the two-step variation[106] in that it avoids isolation of aldehydes or acetals.

6.10.8. α-Amination. Bromination of 4-methylphosphinylbutanoic acid (**128**) followed by ammonolysis with aqueous ammonia solution also gives PT.[107]



128

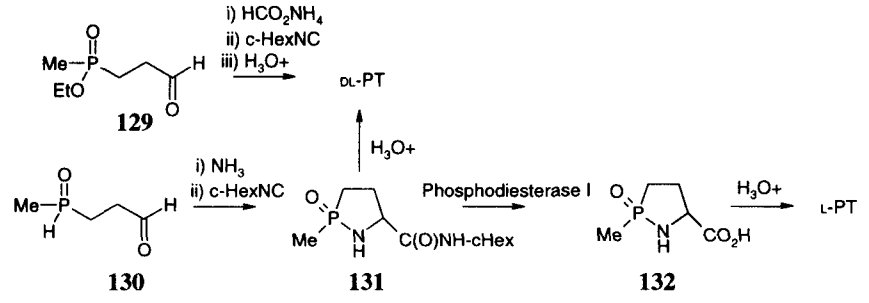
6.10.9. Enzymatic Syntheses. Owing to the commercial utility of this natural product, many companies have engaged in developing microbial and enzymatic syntheses of L-PT. A few of the more recent representative examples are listed below, but this listing is by no means comprehensive.

The most simple method for obtaining L-PT is by enzymatic degradation of the natural tripeptide. For example, hydrolysis of bialaphos with *E. coli* protease has been shown to give L-PT and L-alanine.

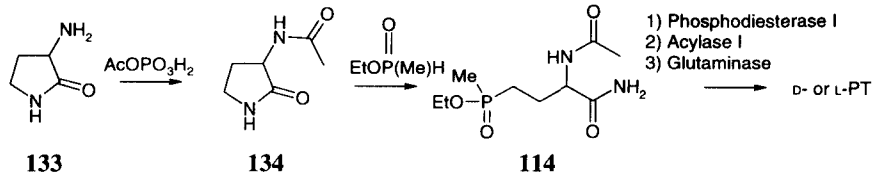
There are many examples of the preparative use of aminotransferases and transaminases in the preparation of L-PT. For example, transaminating 2-oxo-4-[(hydroxy)(methyl)phosphinoyl]butyric acid to L-PT with glutamic acid as the amino group donor was performed with a transaminase purified from *E. coli* K-12 .[108] Up to 50 g *per* L of column *per* hour were obtainable. A transaminase from cell-free lysate of *Alcaligenes faecalis* DSM 4115 produced 3.9 g/L (97.5% yield) in 20 hr at 30 °C. An aspartate transaminase from *Bacillus stearothermophilus* has also been used.[109]

Microbial hydrolases have been employed to stereoselectively resolve racemic phosphinoalkyl and aminoacylated PT amides to free L-PT.[110] A *Lactobacillus* glutamate dehydrogenase has also been employed.[111] *N*-acetyldemethyl-PT has been *P*-methylated using the microorganism *Streptomyces hygroscopicus* NP-8.[112] Acylases and proteases have also been used to stereospecifically degrade phosphinate esters and carboxylic esters.[113] Several members of the *Norcardia* species have also been used to hydrolyze acyl groups from pro-PT analogs.[114]

Optically active PT was obtained by enzymatic hydrolysis and separation of racemate with α-chymotrypsin.[115] Four-component isocyanide condensation of Ugi[116] -- the successive addition of the aldehyde and cyclohexyl isocyanide to a solution of aqueous methanolic ammonium formate -- was used to prepare protected PT from aldehydes **129** and **130**. Acid hydrolysis of the reaction products gave DL-PT (60-65% yield). Both D-PT and L-PT were synthesized using this method. The 1,2-azaphospholidine **131** (synthesized in 70% yield), which resulted from Ugi condensation of aldehyde **130**, gave superior enantioselectivity in the enzymatic hydrolyses. Optically pure PT was then carried on to bialaphos using the activated ester *t*-butyltrichlorophenyl carbonate as the coupling reagent.



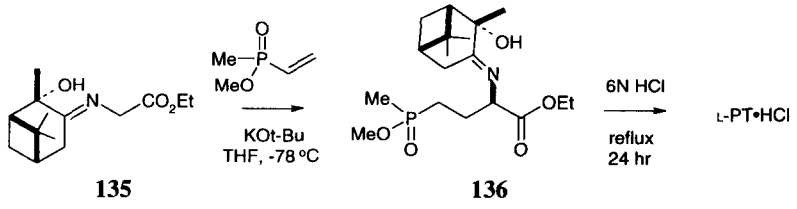
Acetylation of 3-amino-2-pyrrolidinone to the 3-acetamido derivative with the unusual acylating agent acetic phosphoric anhydride (95-98% yield) and treatment with ethyl methylphosphinate gave the butanamide addition product (50-55% yield).[117] Complete stereoselectivity was observed for the enzyme-catalyzed hydrolyses with phosphodiesterase I, acylase, and then glutaminase to give either D- or L-PT depending on the starting antipode. Boiling 20% HCl also liberated the protecting groups to give PT (90% yield), but with concomitant racemization.



The natural tripeptide bialaphos was synthesized by DCC-mediated condensation of L-PT with the dipeptide ala-ala ethyl ester (80% yield) followed by sequential hydrolysis with phosphodiesterase and α-chymotrypsin (90% yield).[118] The enzymatic methods were necessary to prevent hydrolysis of the sensitive peptide bonds, which has previously proven to be problematic.[119]

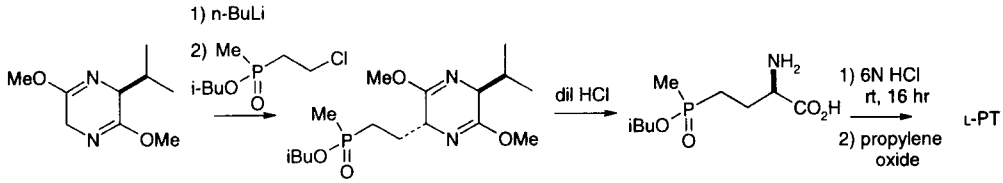
6.10.10. Other Enantioselective Syntheses. Enantioselective syntheses of L-PT have recently been reviewed.[120] A few representative examples are described here.

Via Chiral Glycine Enolate. An asymmetric variation of the Schiff's base sequence (section 6.10.3) was used to prepare both enantiomers of phosphinothricin using the chiral Schiff's base **135** derived from glycine and 2-hydroxypinan-3-one.[121] Optical purities ranged from 45-79% and yields from 42-68%. Most of the losses in optical purity were a result of the poor optical purity of the starting ketol.



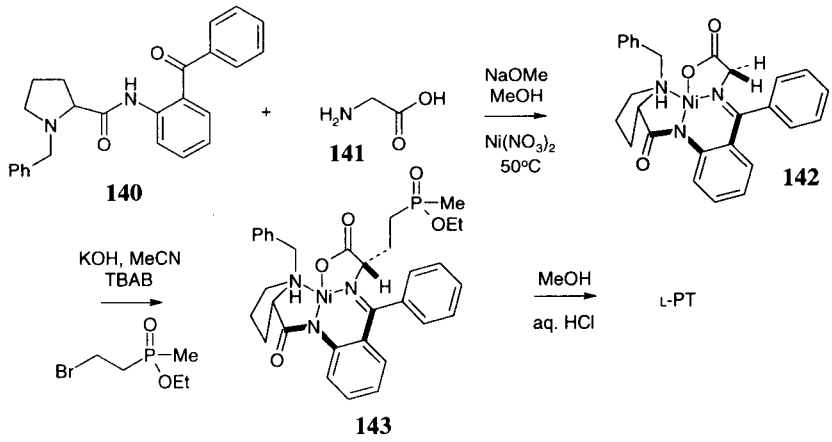
An efficient synthesis of both enantiomers of PT was accomplished by Zeiss by applying Schollkopf's synthesis of amino acids *via* metallated *bis*-lactim ethers.[122] Metallation of the *bis*-lactim ether **137** derived from D-valine followed by alkylation with isobutyl 2-chloroethyl-methylphosphinate gave the key alkylated *bis*-lactim ether **138** (85% yield). Cleavage of the protecting groups in two steps gave first the amino acid

phosphinate ester **139** and methyl-D-valinate (96% yield) which were separated by extraction at pH 9. Cleavage of the phosphinate ester gave L-PT in 94% ee (60% yield). The opposite enantiomer, D-PT, was synthesized starting with the *bis*-lactim ether derived from L-valine in the same optical purity.



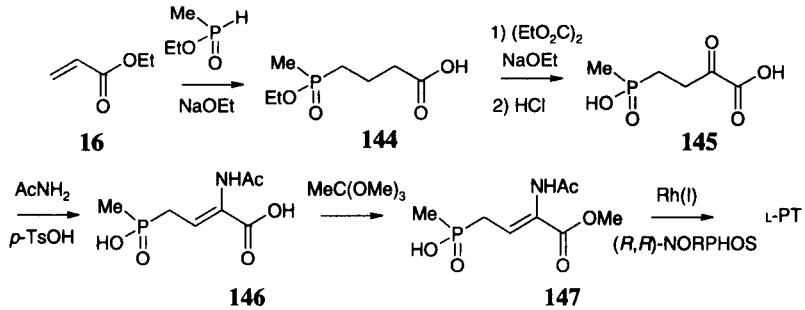
137 **138** **139**

Enantiomerically pure L-PT was synthesized by alkylation of Ni(II) complexes **142** of the Schiff's base of glycine **141** (derived from (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone **140**) with a β-bromoethylphosphonate (or by Michael addition to a vinylphosphonate) in acetonitrile at 25 °C with solid KOH as a catalyst.[123] Diastereoselectivities greater than 90% were achieved. Optically pure L-PT•HCl was obtained by diastereomer separation *via* column chromatography of **143** on silica gel followed by hydrolysis with aq. HCl. The chiral reagent **140** was recoverable (60-85%).

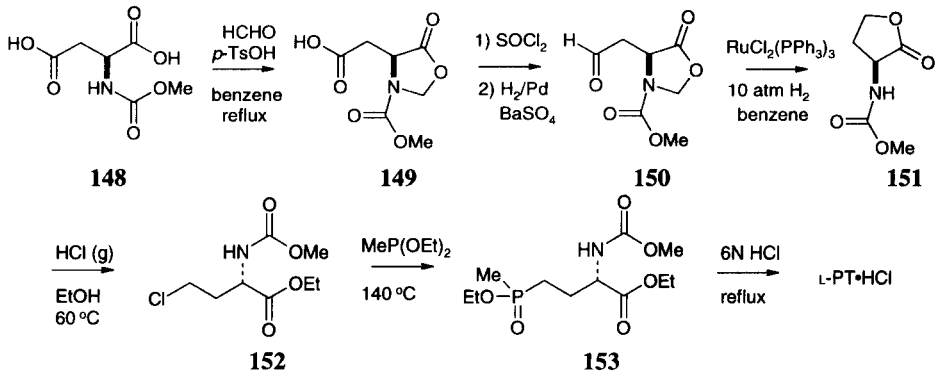


140 **141** **142** **143**

<u>*Via* Asymmetric Hydrogenation.</u> Enantioselective synthesis of both enantiomers of PT was achieved *via* asymmetric hydrogenation of α-acylamido acrylates.[124] Base-catalyzed addition of ethyl methylphosphinate to ethyl acrylate (**16**) gave the β-carboxyethylphosphinate **144** (80% yield) which after reaction with diethyl oxalate, saponification and decarboxylation furnished the α-keto acid **145**. The α-keto acid **145** was condensed with acetamide to give *N*-acylated dehydroamino acid **146** as a single stereoisomer, which was esterified using trimethoxyethane. Hydrogenation of **147** was achieved using rhodium (I) and the chiral *bis*(phosphine) ligands (*S,S*)-DIOP, (*S*)-PROPHOS, (*R,R*)-NORPHOS and (*S,S*)-CHIRAPHOS. Enantioselectivities up to 91% were achieved.

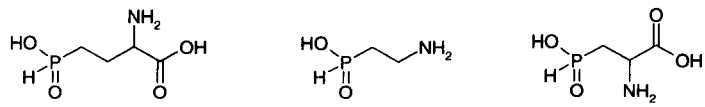


Via Pre-Built Chiral C4 Synthons. L-PT was synthesized from *N*-methoxycarbonyl-L-aspartic acid **148** *via* the L-homoserine lactone **151**.[125] The oxazolidinone **149** was converted to the acid chloride (90% yield), reduced to the aldehyde **150** *via* Rosenmund reduction (85% yield), and hydrogenated using a ruthenium catalyst to the corresponding alcohol which spontaneously cyclized to the homoserine lactone **151** (75% yield). The lactone ring was opened with HCl in ethanol to give the γ-chloro-α-amino butyrate **152** (72% yield). Arbusov reaction of the chloride with diethyl methylphosphonite gave protected L-PT **153** (85% yield). This was somewhat surprising as chlorides do not normally react well under Arbusov conditions. Hydrolysis gave L-PT•HCl in 94% ee (90% yield).



6.11. C-P-H Compounds

During the study of the biosynthesis of bialaphos, two new metabolites MP-101 (2-amino-4-phosphinobutyric acid, the P-H analogs of PT, **154**) and MP-102 (the tripeptide containing MP-101-alanyl-alanine) containing a C-P-H bond were isolated by Seto from the fermentation broth of a blocked mutant of *Streptomyces hygroscopicus* SF-1293 grown in the absence of Co^{2+}.[126] MP-103 (which is the P-H analog of AEP, **155**), MP-104 (which is the P-H analog of APPA, **156**), and MP-105 (which is AEP) were also found in this broth. These compounds can be synthesized by the methods described for the corresponding phosphinates.

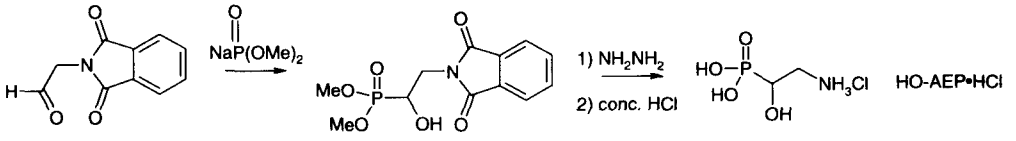


MP-101 **154** MP-103 **155** MP-104 **156**

6.12. 1-Hydroxy-2-aminoethylphosphonic acid (HO-AEP)

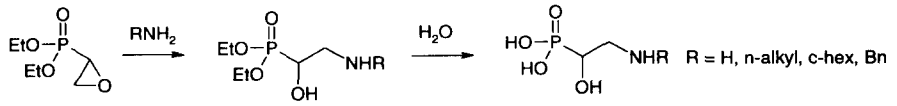
1-Hydroxy-2-aminoethylphosphonic acid (HO-AEP, **159**) was isolated from the plasma membrane of the soil amoeba *Acanthamoeba castellanii*.[127]

HO-AEP has been prepared by addition of sodium dimethylphosphite to *N*-(2-oxoethyl)phthalimide **157** (57-69%) followed by removal of the phthaloyl group of **158** with hydrazine and hydrolysis (21-36% yield).[128]



157 **158** **159**

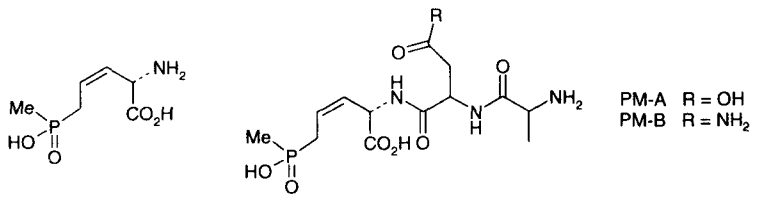
Oxirane ring opening of **160** with an amine followed by hydrolysis gave HO-AEP analogs **162** (30-65% yield).[129] The analog with the amine and hydroxyl groups interchanged was prepared by acid-catalyzed methanolysis of 2-phosphonylazidiridine (17%yield after hydrolysis and demethylation with refluxing 48% HBr).[130]



160 **161** **162**

6.13. 2-Amino-5-Phosphono-3-Pentenoic Acid

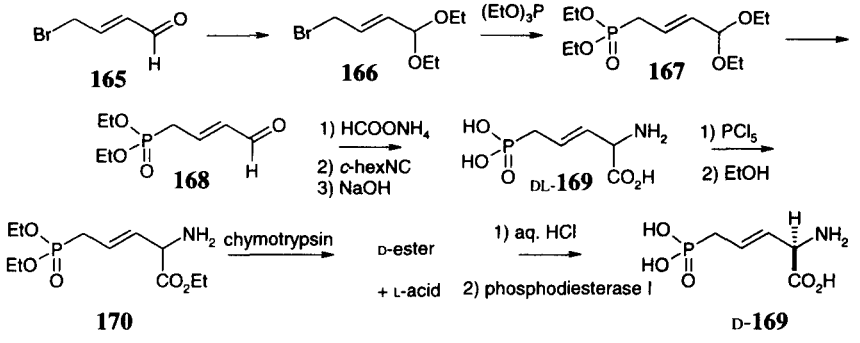
The unusual natural amino acid 3,4-didehydro-5-phosphono-D-norvaline (2-amino-5-phosphono-3-pentenoic acid) **163** was found by Park, Hirota and Sakai as a constituent of Plumbemycin B **164** (formerly called N-1409), a tripeptide antagonist of L-threonine produced by *Streptomyces plumbeus*.[131] A synthesis of the plumbemycins has been published,[132] although this work has been sharply criticized as having prepared the wrong olefin isomer because both rhizocticins and plumbemycins were subsequently shown by Fredenhagen *et. al* to contain L-(*Z*)-pentenoic acid as the unusual amino acid.[133] In addition, based on the latter work with rhizocticins, the absolute configurations of plumbemycins A and B have been found to require revision.



163 **164**

4-Bromocrotonaldehyde (**165**) was converted to its diethylacetal **166** followed by Michaelis-Arbusov reaction with triethylphosphite to give the diethylphosphonate **167** (48-52% yield).[132] Acidic hydrolysis gave the aldehyde **168**, which was subjected to Ugi's four-component isonitrile condensation to give the amino acid derivative **170** after esterification (80% yield). Enzymatic approaches were then used to separate optically active isomers from racemates. It appears based on the starting substrate, which is of the (*E*)-configuration

based on the reference given for its preparation, that the (*E*)-2-amino-5-phosphonopentenoic acid has been prepared rather than the desired (*Z*)-isomer as in **163**.

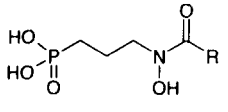


The tripeptide of **169** (PM-A?) was prepared using conventional peptide synthesis methods using **168** and a protected dipeptide followed by enzyme-catalyzed cleavage of the protecting groups. PM-B (or it's *trans* olefin isomer?) was prepared by analogy.

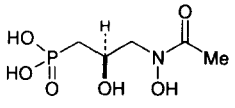
See section 6.20 for more on the (*E*)-2-amino-5-phosphonopentenoic acid and the rhizocticins.

6.14. 3-(*N*-Acyl-*N*-hydroxyamino)propylphosphonic Acids (AHAPPA and FHAPPA)

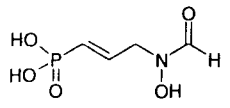
Four antibiotics were discovered by Fujisawa Pharmaceutical Co. during the search for new inhibitors of bacterial cell wall synthesis. 3-(*N*-Acetyl-*N*-hydroxyamino)propylphosphonic acid FR-90098 (AHAPPA, **171a**) and the hydroxypropyl analog FR-33289 (**172**) were first isolated by Okuhara in 1980 from *Streptomyces rubellomurinus* subsp. *indigoferus*.[134] The *N*-formyl analog FR-31564 (FHAPPA, **171b**) and the dehydro analog FR-32863 (**173**) were isolated from a fermentation broth of *Streptomyces lavendulae*.[135] Owing to the structural analogy of this class of antibiotics to the antibiotic hadacidin (**174**), these materials and a number of related analogs have been synthesized.



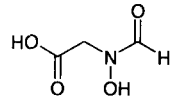
171
a R = Me FR-90098 AHAPPA
b R = H FR-31564 FHAPPA



172
FR-33289

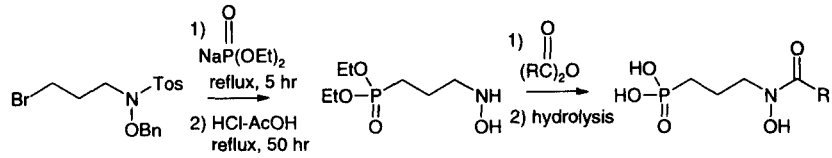


173
FR-32863



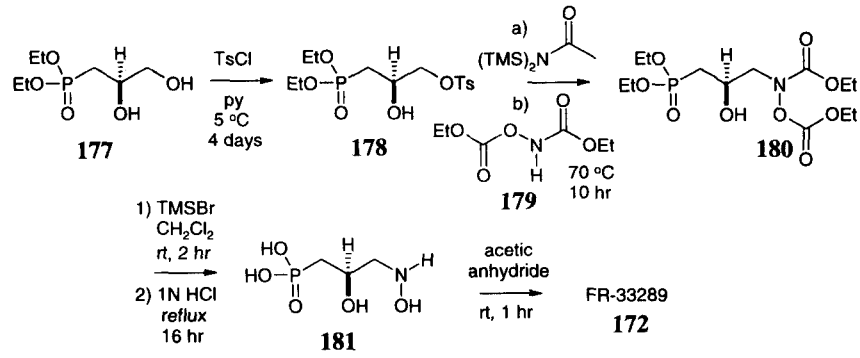
174
hadacidin

Michaelis-Becker reaction of sodium diethyl phosphonate with 3-(*N*-tosyl-*N*-benzyloxyamino)propyl bromide (**175**) followed by hydrolysis of the tosylate gave hydroxyaminopropylphosphonate **176** (63% yield).[136] Acetylation or formylation of **176** followed by hydrolysis gave AHAPPA **171a** (83%) and FHAPPA **171b** (70% yield) respectively.



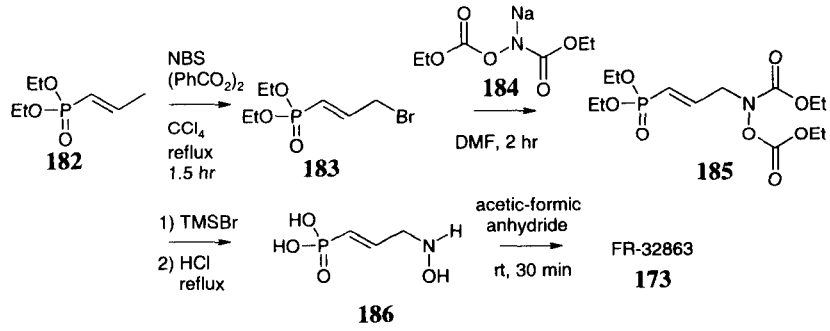
175 176 171

Diethyl (*R*)-3-dihydroxypropylphosphinate (**177**) was tosylated (83% yield) and condensed with *N,O*-dicarboethoxyhydroxamide **179** (41% yield) to give protected HOAPPA **180**.[137] Phosphonate deprotection with TMSBr followed by hydrolysis of the carboethoxy groups with 1*N* HCl gave the hydroxylamine **181** (47% yield), which was identical to sample derived from degrading the natural product with 1*N* HCl, establishing the C-2 configuration to be *R*. Acetylation as for AHAPPA gave FR-33289 **172**.



177 178 179 180 181 172

In the same paper, allylic bromination of diethyl 1-*trans*-propenylphosphonate **182** (64% yield) followed by reaction with sodium *N,O*-dicarboethoxyhydroxamide **184** (83% yield) gave the vinyl phosphonate **185**. Deprotection and formylation as for FHAPPA gave FR-32863 **173** (30% yield).



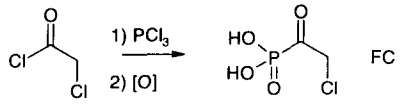
182 183 184 185 186 173

The same authors also developed syntheses to prepare a number of analogs.[138]

6.15. Fosfonochlorin (FC)

(Chloroacetyl)phosphonic acid (fosfonochlorin, FC, **188**) is an antibiotic found in the culture filtrate of four strains of fungi isolated from soil samples, *Talaromyces flavus, Fusarium oxysporum, F. avenaceum* and *F. tricinctum*.[139] It was named after the finding that it contained one phosphorus atom and one chlorine atom

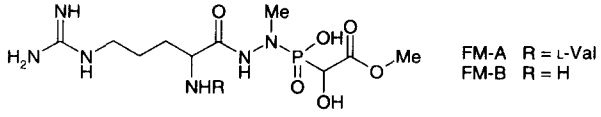
in its structure. FC exists as a ketal in water. It is a low MW antibiotic which inhibits bacterial cell wall biosynthesis. FC has been synthesized by addition of phosphorus trichloride to chloroacetic acid (**187**) followed by *in situ* oxidation.[140]



187 **188**

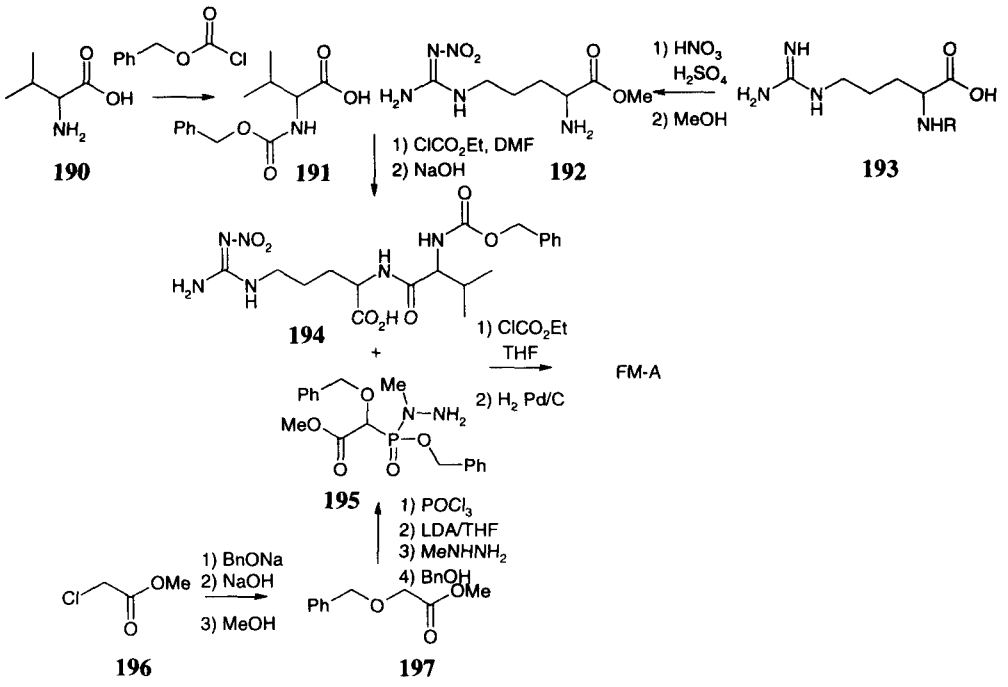
6.16. Fosfazinomycin (FM)

In an effort to detect new antifungal antibiotics with a selective mode of action, AC549 (a compound possibly related to gougeroxymycin), ATS1287 (leptomycin), and a molecule containing a C-P bond AM630 (fosfazinomycin, FM, **189**) were isolated from *Streptomyces lavendofoliae*.[141] AM630 was separated into two components A and B based on spectral characterization and degradation studies.[142] They share the tetrapeptide homology and a C-P-N linkage.



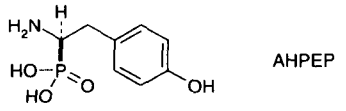
189

The total synthesis of FM-A has been achieved. *N*-carbobenzyloxyvaline was prepared by protecting DL-valine with carbobenzyloxychloride (85% yield).[143] L-Arginine was nitrated then esterified to give the nitroarginate (72% yield). These two fragments were then coupled using ethyl chloroformate to give a dipeptide (62% yield). Methyl methylhydrazinobenzyloxyphosphonobenzyloxyacetate was prepared in one pot from phosphorus oxychloride by reaction with methyl benzyloxyacetate followed by sequential displacement of chlorides first with methylhydrazine and then benzyl alcohol (12% yield). Coupling of this fragment with the previously synthesized protected dipeptide (71% yield) followed by hydrogenation in the presence of palladium on charcoal (65% yield) gave FM-A in 12 steps (0.7% overall yield). FM- B was prepared by analogy (4 steps, 24% yield for the coupling/reduction sequence).[144]



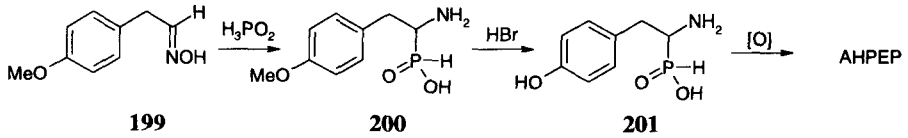
6.17. (*R*)-1-Amino-2-(4-hydroxyphenyl)ethylphosphonic acid (AHPEP)

During the course of screening for microbial angiotensin I converting enzyme (ACE) inhibitors, a new inhibitor named antibiotic I5B2 was isolated from the culture broth of *Actinomadura* sp. No. 937ZE-1.[145] This material was found to contain *N*-methylvaline, tyrosine, and a unique amino phosphinic acid analog of tyrosine (*R*)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid (AHPEP, **198**). Neither the structural homology nor synthesis of the tripeptide have been reported. Several years later, a different tripeptide containing AHPEP was isolated from actinomycete K-26 (FERM-P 5859, NRRL 12379).[146] This tripeptide was found to contain L-isoleucine, and L-tyrosine.

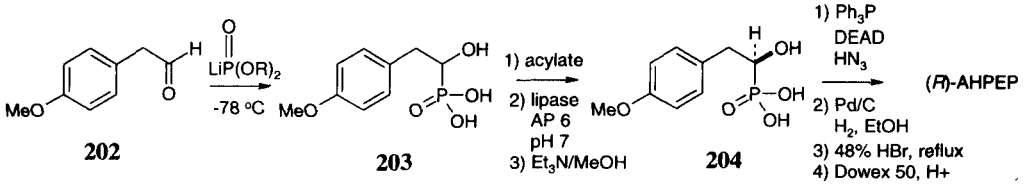


198

The synthesis and properties of AHPEP and its analogs have been reviewed.[147] Two representative syntheses are given here. Reaction of aralkyl aldoximes **199** with hypophosphorus acid resulted in aminophosphinic acids **200**, which were dealkylated to phenol **201** and oxidized to AHPEP.[148]



Phosphorylation of *p*-methoxyphenylacetaldehyde (**202**) with lithiodialkylphosphites gave racemic α-hydroxyphosphonates **203** which were acylated and resolved enzymatically with lipase AP 6 (from *Aspergillus niger*).[149] The optically active ester was hydrolyzed chemically (MeOH/Et_3N) to give optically pure **204**. The hydroxyl was converted to the amine via azide displacement under Mitsunobu conditions followed by reduction to the amine. The phenol was liberated with 48% HBr and the aminophosphonic acid was freed from HBr by ion exchange chromatography to give (*R*)-AHPEP (40% overall yield, 77% ee).

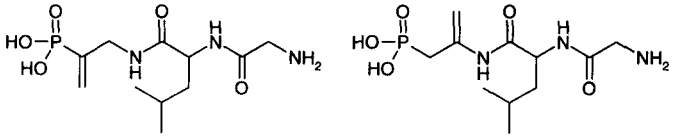


202 **203** **204**

The *des-p*-hydroxy analog, (*R*)-1-amino-2-phenylethylphosphonic acid (APEP), is an effective inhibitor (K_i = 1.5 μM) of phenylalanine ammonia lyase (PAL), the first enzyme in the pathway to produce lignins from L-Phe. This material was synthesized by analogy.

6.18. Antibiotic A53868A

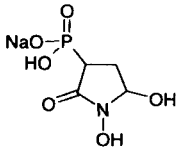
The leucylaminopropenylphosphonate immunomodulating agent A53868A (**205**) is a novel broad-spectrum anti-microbial and antibiotic produced by fermentation of *Streptomyces luridus* NRRL 15101.[150] Attempts to synthesize a series of analogs prompted re-examination of the structural elucidation and ultimate reassignment as the vinylphosphinate **205** rather than the originally postulated allylphosphinate **206** based on ^{13}C assignments.[151] The synthesis has never been successfully carried out; thus the structure assignment remains unconfirmed. The stereochemistry is also not known.



205 **206**

6.19. Antibiotic SF-2312

Phosphonic acid **207**, weakly active against Gram-positive and Gram-negative bacteria, was isolated from *Micromonospora* sp. SF-2312.[152] This molecule is unique in having a 1,5-dihydroxy-2-oxopyrrolidine ring. Only one other natural product, alahopcin (nourseimycin), a dipeptide, contains such a structure: SF-2312 has a phosphonic acid in place of the alanylaminoglycine moiety of alahopcin. This material has not been synthesized, and the stereochemistry has not been assigned.

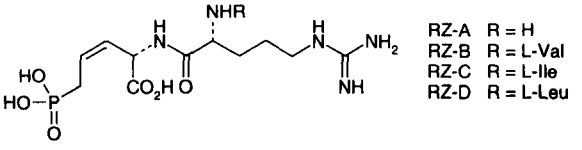


SF-2312

207

6.20. Rhizocticins (RZ)

The widely used and well-known bacterial strain *Bacillus subtilis* ATCC 6633 was found to produce two novel, antifungal hydrophilic peptide antibiotics, L-arginyl-L-2-amino-5-phosphono-3-*cis*-pentenoic acid (rhizocticin A, RZ-A) and L-valyl-L-arginyl-L-2-amino-5-phosphono-3-*cis*-pentenoic acid (rhizocticin B, RZ-B).[153] Two other rhizocticins, C and D, containing L-Ile and L-Leu respectively in place of L-Val, have also been isolated. Digestion of a mixture of rhizocticins A, B, and D afforded (*Z*)-L-2-amino-5-phosphono-3-pentenoic acid.[133] Both rhizocticins and plumbemycins were found to contain the (*Z*)-pentenoic acid as the unusual amino acid, and they are believed to act as L-threonine antagonists within the cell possibly by inhibiting threonine synthase. The amino acids bound on the *N*-terminus are necessary for efficient uptake into the target cell. None of the four natural products have been synthesized.



208

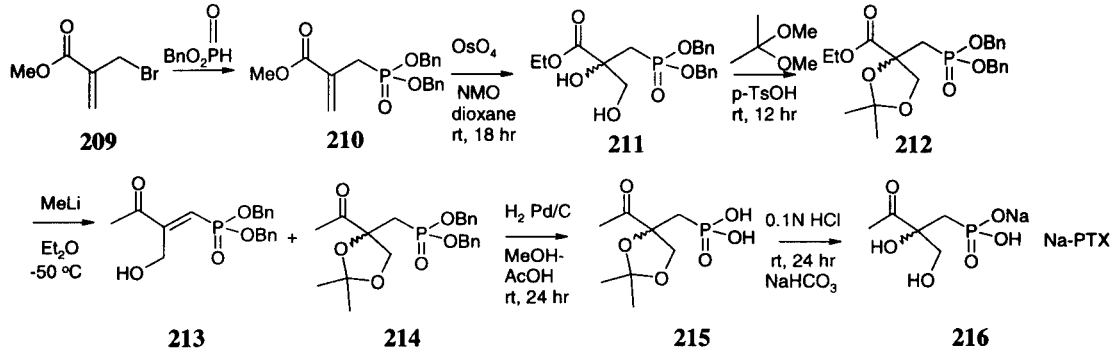
See section 6.13 for more on (*E*)-2-amino-5-phosphonopentenoic acid and the plumbemycins.

6.21. Phosphonothrixin (PTX)

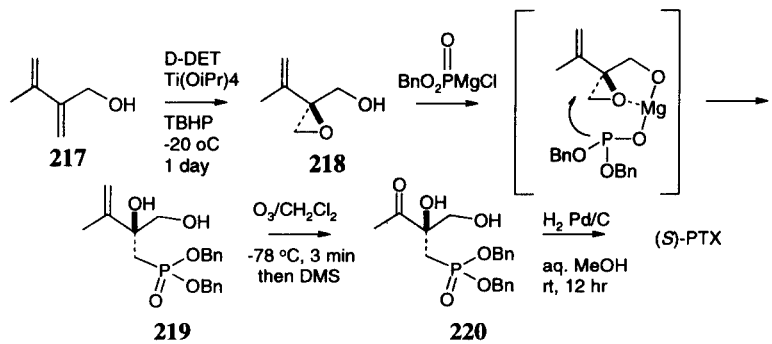
In the course of screening for new herbicidal antibiotics, a soil isolate *Saccharothrix* sp. ST-888 was found to produce an active compound phosphonothrixin (**216**, PTX).[154] This compound was found to significantly inhibit germination of grass and broadleaf weeds as well as to produce chlorosis upon foliar application on all weeds tested.

The structure and total synthesis have been described by the original authors.[155] The synthetic challenge of this molecule is forming the C-P bond while differentiating three oxygen functionalities. The first reported synthesis of PTX employed a carboxylic ester as a latent ketone.[156] This was necessary because attempted Michaelis-Becker reaction with bromomethyl allyl ketone resulted in Perkow reaction which gave the enolphosphinate rather than the desired allylphosphonate.

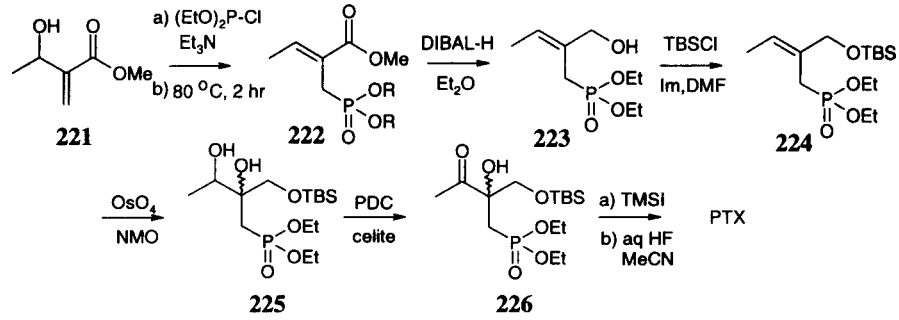
The C-P bond was formed by Michaelis-Becker reaction with methyl β-(bromomethyl)acrylate **209** (61% yield). *Vic*-dihydroxylation with osmium tetroxide/NMO gave the diol **211** (92% yield) which was protected as the ketal with 2,2-dimethoxypropane (86% yield). Attempted conversion of the methyl ester to a methyl ketone gave two major products, the desired product **214** (18% yield) and the elimination product **213** (12% yield). Deprotection of the ketal and benzyl groups (91% yield) gave PTX as the monosodium salt **216**.



An asymmetric synthesis by the same authors employed an olefin as the latent ketone.[157] Catalytic asymmetric epoxidation of the dienyl alcohol **217** using D-DET gave chiral (*R*)-epoxy alcohol **218** (92% ee, 57% yield). The C-P bond was formed by adding the chloromagnesium salt of dibenzyl phosphite (40% yield), using the magnesium as a Lewis acid to aid epoxide opening. Ozonolysis (79% yield) and debenzylation of **219** (quantitative) gave (*S*)-PTX in 92% ee. The (*R*)-enantiomer was also prepared using this methodology.



A third synthesis was accomplished in 6 steps (24% overall yield) from the commercially available methyl 3-hydroxy-2-methylene butyrate, the Baylis-Hillman adduct derived from acetaldehyde and methyl acrylate.[158] Thus, **221** was phosphorylated with diethyl chlorophosphite in the presence of triethylamine to give the *E*-allylphosphonate **222** (60% yield), forming the key C-P bond via an intramolecular Arbusov rearrangement.[159] Reduction of the carboxylic ester with DIBAL-H gave primary alcohol **223** (79% yield) which was silylated with TBSCl/imidazole in DMF to give silyl ether **224** (94% yield). Vicinal dihydroxylation to diol **225** followed by oxidation of the resultant secondary alcohol with PDC/celite gave protected phosphonothrixin **226** (80% yield). Deprotection to salt-free protonated PTX was achieved first using an excess of TMSI in CH_2Cl_2 to cleave the phosphonate ester, followed by aqueous HF in MeCN to cleave the TBS group and any silylated hydroxyls created by use of excess TMSI (83% yield).



7. Summary

Since the original discovery in 1959 of AEP by Horiguchi and Kandatsu, over 20 distinct classes of natural products have been isolated which contain a C-P bond. The diverse biological activities associated with these molecules has driven aggressive synthetic programs. Syntheses have been devised for the vast majority of these which have not only validated the structure assignments but also enabled examination of the structure-activity relationships.

8. References

† This paper is dedicated to the memory of my father, Donald L. Fields, who passed away Oct. 31, 1998.

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Biographical sketch

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Stephen Fields was born in1963 in Rochester, New York and obtained his B. S. degree with Honors in Chemistry from Bucknell University in 1985. His graduate studies as a McElvain Scholar at the University of Wisconsin-Madison were carried out under the guidance of Ed Vedejs. His most significant achievement was in the discovery and development of homochiral oxazaborolidinones as substrates for asymmetric memory applications and the synthesis of novel amino acids, which led to seven publications. He also wrote the chemistry database management system RXN Index (© 1989, Trinity Software) while in graduate school.

After completing his Ph.D. studies in 1990, Stephen joined DowElanco, an agrochemical joint venture between Dow Chemical and Eli Lilly based in Indianapolis Indiana, as a Research Chemist in Weed Management's Discovery Research. He became a Senior Research Chemist in 1992 and a Senior Scientist for Dow AgroSciences after Eli Lilly sold their interest to Dow in 1996. He led Weed Management's Natural Products Group in Discovery Research for two years before becoming a Project and Technical Leader in Weed Management in 1999.

Research interests and publication topics in his tenure at Dow have included synthesis and study of the natural products cornexistin, pyridazocidin, phosphonothrixin, phaseolotoxin (octicidin), and abscisic acid as well as the use of boron for amino acid protection during sidechain manipulation.