***N*-(3,5-Dibromosalicylidene)-(*S*)-valine (4, Dbs-*S*-Val)** was prepared in a similar manner as described previously[9] (90% yield): mp 178–180 °C, $[\alpha]^{25}_D$ −32.5° (*c* 0.20, CH_3OH); ^1H NMR (270 MHz, CD_3OD) δ 8.40 (s, 1 H), 7.77 (d, *J* = 2.4 Hz, 1 H), 7.53 (d, *J* = 2.5 Hz, 1 H), 4.09 (d, *J* = 4.9 Hz, 1 H), 2.34–2.45 (m, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H); IR (KBr) 3450 (br), 2970, 2900 (br), 2460 (br), 2350, 1880 (br), 1710, 1650, 1590, 1480, 1340, 1260, 1230, 1220, 1200, 1030, 1000, 860, 680, 580, 540, 420 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3Br_2$: C, 38.02; H, 3.46; N, 3.70. Found: C, 37.97; H, 3.44; N, 3.67.

***N*-(3,5-Dibromosalicylidene)-(*S*)-valinol (5, Dbs-*S*-valinol).** To a solution of (*S*)-valinol (0.21 g, 2.0 mmol) in methanol (10 mL) was added 3,5-dibromosalicylaldehyde (0.62 g, 2.2 mmol) and anhydrous sodium sulfate (0.71 g, 10 mmol), and the mixture was stirred for 15 min at room temperature. After sodium sulfate was removed by filtration, the solvent was evaporated in vacuo to leave a yellow solid, which was washed with hexane and dried in vacuo (0.69 g, 95%). Recrystallization was carried out from methanol (10 g/L): mp 143–144 °C, $[\alpha]^{25}_D$ −6.57° (*c* 0.35, CH_3OH); ^1H NMR (270 MHz, $CDCl_3$) δ 14.71 (br, s, 1 H), 8.19 (s, 1 H), 7.66 (d, *J* = 2.6 Hz, 1 H), 7.31 (d, *J* = 2.1 Hz, 1 H), 3.89 ($^1/_2$ AB qd, *J* = 11.3, 3.2 Hz, 1 H), 3.74 ($^1/_2$ AB qd, *J* = 11.3, 8.8 Hz, 1 H), 3.17–3.23 (m, 1 H), 2.54 (br, s, 1 H), 1.92–2.04 (m, 1 H), 0.98 (d, *J* = 6.8 Hz, 6 H); IR (KBr) 3450 (br), 3270 (br), 2970, 2870, 2330, 1640, 1600, 1510, 1500, 1420, 1210, 1130, 1065, 1040, 1020, 900, 860, 750, 680, 650, 600, 530 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2Br_2$: C, 39.48; H, 4.14; N, 3.84. Found: C, 39.60; H, 4.19; N, 3.93.

***N*-(3,5-Dibromosalicylidene)-(*S*)-valylcyclohexylamide (6, Dbs-*S*-Val-NHCy)** was prepared in a similar manner as described previously[3b] (54% yield): mp 213.0–214.0 °C, $[\alpha]^{25}_D$ +45.0° (*c* 0.10, CH_3OH); ^1H NMR (270 MHz, $CDCl_3$) δ 16.32 (s, 1 H), 8.23 (s, 1 H), 7.77 (d, *J* = 2.6 Hz, 1 H), 7.44 (d, *J* = 2.1 Hz, 1 H), 5.69 (d, *J* = 8.6 Hz, 1 H), 3.75–3.89 (m, 1 H), 3.72 (d, *J* = 4.3 Hz, 1 H), 2.41–2.53 (m, 1 H), 1.05–1.98 (m, 10 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); IR (KBr) 3420 (br), 3280, 2920, 2840, 2340, 1630, 1540, 1440, 1360, 1340, 1210, 1160, 1080, 1040, 960, 880, 850, 670 cm^{-1}. Anal. Calcd for $C_{18}H_{24}N_2O_2Br_2$: C, 46.98; H, 5.26; N, 6.09. Found: C, 46.99; H, 5.06; N, 6.27.

General Procedure for Asymmetric Epoxidation of Allylic Alcohols. To 4 (19.0 mg, 0.05 mmol) and molecular sieves 4A (20 mg) in dry methylene chloride (2.0 mL) was added under nitrogen titanium(IV) isopropoxide (0.05 mmol) at room temperature, and the mixture was stirred for 30 min and then cooled to −40 °C. Nerol (1a, 77 mg, 0.5 mmol) and a hydroperoxide (1.0 mmol) were added successively, and the resulting mixture was stirred for the period stated in Tables I and II during which the consumption of starting allylic alcohol was monitored by TLC analysis (SiO_2, hexane/EtOAc (2:1)). The solution was poured over saturated aqueous ammonium chloride (20 mL), and the aqueous layer was extracted with ether (20 mL × 2). The combined organic layers were dried (Na_2SO_4) and concentrated to leave a crude oil. Purification of the crude product was performed by silica gel column chromatography (hexane/ethyl acetate (3:1)) to afford the corresponding epoxy alcohol which was identical with the authentic sample prepared as reported.[4] Optical purity of epoxynerol was determined by HPLC analysis (column, Sumitomo Chemical Co. Sumichiral OA-4700; eluent, 100:1 hexane/2-propanol, flow rate, 1.0 mL/min; detection, 215 nm; t_R, 18.6 min (2*R*,3*S*), 21.2 min (2*S*,3*R*)).

Enantiomeric excess values of other epoxy alcohols were determined by ^1H NMR analysis after transformation to the corresponding diastereomeric esters of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA). ^1H NMR signals due to the proton(s) on the epoxy ring (270 MHz, C_6D_6): for the epoxide of 1b, δ 2.72 (major), 2.82 (minor); for the epoxide of 1c, δ 2.59 (major), 2.71 (minor); for the epoxide of 1d, δ 2.73 (major), 2.81 (minor); for the epoxide of 1e, δ 2.45 (major), 2.52 (minor) and 2.33 (major), 2.41 (minor); for the epoxide of 1f, δ 2.64 (major), 2.52 (minor).

Kinetic Resolution of Racemic 2-Methyl-2-octen-4-ol (7). To the 1:1 complex of 4 and $Ti(O^iPr)_4$ (0.05 mmol) as prepared above in the presence of molecular sieves 4A (20 mg) in methylene chloride (2.0 mL) was added 7 (0.5 mmol) and CHP (0.3 mmol) at −20 °C under a nitrogen atmosphere. The resulting mixture was stirred for 3 h and poured over saturated aqueous ammonium chloride (20 mL) to quench the reaction. After workup as above, chromatographic separation of the crude oil (SiO_2, hexane/EtOAc (6:1)) afforded optically active 2-methyl-2-octen-4-ol along with the corresponding epoxy alcohol with the diastereomeric ratio of 93:7. Optical purity of the allylic alcohol was determined by HPLC analysis of the derived benzoate ester (column, Sumitomo Chemical Co. Sumichiral OA-2000; eluent, 200:1 hexane/1,1-dichloroethane; flow rate, 1.0 mL/min; detection, 230 nm; t_R, 19.2 min and 20.7 min).[10] The diastereomeric ratio of the epoxy alcohol was determined by ^1H NMR (270 MHz, C_6D_6) analysis: signals due to the proton on the epoxy ring, δ 2.58 (threo), 2.50 (erythro).[11]

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Registry No. 1a, 106-25-2; 1a (2*S*,3*R*)-epoxide, 76985-26-7; 1a (2*R*,3*S*)-epoxide, 62777-72-4; 1b, 106-24-1; 1b (2*S*,3*S*)-epoxide, 82188-73-6; 1c, 556-82-1; 1c epoxide, 18511-56-3; 1c aldehyde, 107-86-8; 1d, 928-94-9; 1d epoxide, 90528-63-5; 1e, 928-95-0; 1e epoxide, 90528-62-4; 1f, 38384-38-2; 1f epoxide, 143508-88-7; 1f aldehyde, 645-62-5; 2, 143614-93-1; 3, 143508-83-2; 4, 143508-84-3; *ent*-4, 143508-87-6; 5, 143508-85-4; 6, 143508-86-5; (±)-7, 119204-52-3; 7 *threo*-epoxide, 142952-65-6; 7 *erythro*-epoxide, 142940-78-1; TBHP, 75-91-2; CHP, 80-15-9; $Ph_2C(CH_3)OOH$, 2186-29-0; $(CH_3)_3CCH_2C(CH_3)_2OOH$, 5809-08-5; 4-$(CH_3)_2CHC_6H_4C(CH_3)_2OOH$, 98-49-7; Ph_3COOH, 4198-93-0; (*S*)-valinol, 2026-48-4; 3,5-dibromosalicaldehyde, 90-59-5.

(10) Absolute configuration of 7 was not identified.

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The Synthesis of Phosphonate Esters, an Extension of the Mitsunobu Reaction

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Introduction

In this paper a general and efficient synthesis of phosphonate esters utilizing the Mitsunobu reaction is described.[1] Phosphonate esters are recognized as effective transition-state analogue inhibitors for a variety of enzymes including a number of proteases and esterases.[2] They have been used as nonhydrolyzable analogues of phosphates to inhibit dinucleoside triphosphate hydrolase,[3] phosphatidyltransferase,[4] and squalene synthetase.[5] In addition, phosphonate esters have been used as haptens for the production of catalytic antibodies possessing esterase activity.[6] Our interests span a number of these fields, and

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Table I. Alkylphosphonic Acid Monoester Syntheses via Mitsunobu Condensations of Methyl Alkylphosphonates with Alcohols Followed by TMSBr Treatment

no.	phosphonate	alcohol	coupling time (h)	yield (%)
3a	methyl benzylphosphonate	EtOH	0.5	90
3b		*i*-PrOH	0.5	94
3c		methyl 3-L-phenyllactic acid	1	80
3d		methyl (*S*)-mandelate	2	81
3e	methyl *tert*-butylphosphonate	EtOH	0.5	81
3f		*i*-PrOH	0.5	88
3g		methyl 3-L-phenyllactic acid	2	82
3h	methyl [[*N*-CBZ-amino]methyl]phosphonate	methyl glycolate	0.5	86
3i		methyl 3-L-phenyllactic acid	1	78
3j		methyl 2-L-hydroxyisovalerate	3.5	76
3k	methyl (*R,S*)-[*N*-CBZ-valinyl]phosphonate	methyl glycolate	0.5	83
3l		methyl 3-L-phenyllactic acid	1	64
3m		methyl 2-L-hydroxyisovalerate	4	69

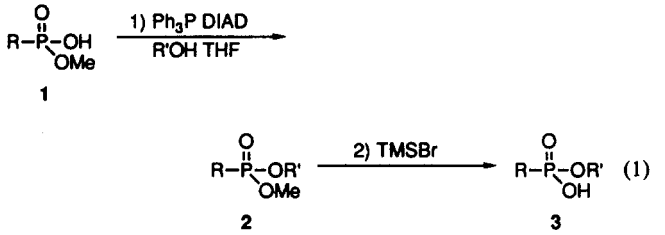
we required a synthetic methodology allowing the ready synthesis of a variety of phosphonate esters.

Phosphonic acid monoesters have typically been synthesized by one of two methods. In the first, a monomethyl alkylphosphoryl chloride (produced by the direct action of PCl_5 on a phosphonate diester[7] or by base hydrolysis of the phosphonate diester followed by reaction with thionyl chloride[2b]) is treated with an alcohol followed by selective deesterification of the methyl ester to yield the desired product. Alternatively, the direct monoesterification of a phosphonic acid can be accomplished with condensing reagents (DCC[8] or trichloroacetonitrile[9]) and the appropriate alcohol. A large excess of both the condensing agent and alcohol are required, and yields vary depending on the components being coupled. In addition, forcing conditions are required such as heating to reflux temperature in a solution of THF and triethylamine with DCC and 50–80 °C in pyridine with trichloroacetonitrile, conditions that can lead to decomposition of starting material. Product yields are extremely sensitive to steric encumbrance from the reacting components and in some cases no product formation is observed. This prompted the search for a mild coupling reaction that was compatible with a variety of functional groups and would consistently produce high yields.

The Mitsunobu reaction is a mild and effective method utilizing the redox chemistry of triphenylphosphine and a dialkyl azodicarboxylate to condense an acidic reagent with primary and secondary alcohols. It has been used with carboxylic acids, phenols, and phosphates as the acidic component. Only one example using a phosphonic acid has been described.[10] We have found that the Mitsunobu reaction provides a convenient and general route to mono and diesters of phosphonic acids, complimenting the phosphonous acid couplings of Karanewsky.[11]

Results and Discussion

The preparation of phosphonic acid monoesters is straightforward and begins with a methyl alkylphosphonate 1, readily obtained by a number of methods: saponification of dimethyl alkylphosphonates obtained either directly by the methodology of Arbuzov[12] or Seebach[13] or by the bisesterification of phosphonic acids. For base-sensitive compounds the alkylphosphonic acid could be monoesterified directly.[14] The Mitsunobu protocol (eq 1) consisted of adding diisopropyl azodicarboxylate (DIAD)



to a solution of 1, triphenylphosphine, and the appropriate alcohol dissolved in anhydrous THF. After esterification was complete, TMSBr was added directly to the reaction mixture to effect selective hydrolysis of the methyl ester and yield the desired product 3.

Initial reactions were performed in deuterated THF and monitored by ^{1}H-NMR. Typically, the condensation was quantitative by NMR. With sterically undemanding alcohols such as ethanol and 2-propanol the reaction occurred instantly regardless of the substituents on the alkylphosphonate. With more sterically hindered alcohols such as methyl mandelate, the reaction required up to 2 h to go to completion. In the slower reactions the protonated betaine 8 (Scheme I) was formed rapidly as evidenced by an upfield shift of the phosphonic acid monoester's methylene and methoxide ^{1}H-resonances and the appearance of a proton attributable to the carbamate NH in 8. The protonated betaine 8 then slowly reacted with alcohol to yield product and diisopropyl hydrazodiformate, similar to the reactions observed with carboxylic acids.[15]

Demethylation of the resulting unsymmetrical phosphonate diesters 2 with TMSBr yielded the desired phosphonic acid monoesters 3. Unlike the more reactive TMSI, TMSBr is able to selectively deesterify methyl phosphonate esters in the presence of substituted methyl phosphonate esters and carboxymethyl esters. Compounds 3a and 3e highlight the discrimination that can be achieved with TMSBr. Removal of the methyl group could be accomplished with only minimal displacement of the ethyl group (which reacts slowly with TMSBr at room temperature). With compounds 3a and 3e the reaction had to be monitored and quenched as soon as the methyl group

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Table II. Symmetrical Alkylphosphonate Diester Syntheses via Mitsunobu Condensations of Benzylphosphonic Acid and Alcohols

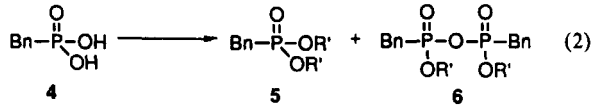
method	no.	alcohol	alcohol equiv	yield (%)
A	**5a**	MeOH	2.5	85
	5a	MeOH	25	91
	5b	*i*-PrOH	2.5	11
		i-PrOH	25	76
	5c	BnOH	2.5	87
B	**5a**	MeOH	5	81
	5b	*i*-PrOH	5	37
	5c	BnOH	5	90

was completely removed to ensure high yields. The other compounds were stable toward TMSBr and did not require such monitoring.

After successfully completing the initial studies with *tert*-butyl- and benzylphosphonic esters, extension of this method to the synthesis of phosphorus-containing peptide analogues was investigated (Table I). The phosphorus analogues of glycine and valine were used in order to observe the substituent effects of the phosphorus component on coupling rates and yields. Likewise, the hydroxy analogues of glycine, phenylalanine, and valine were used to examine the scope of this condensation method.

Based on the results of previous workers comparing coupling rates for N^{α}-(benzyloxycarbonyl)amino acid *p*-nitrophenyl ester derivatives with amino acid esters[16] it was anticipated that the rate of phosphonate ester formation in the Mitsunobu reaction would be sensitive to steric effects at both the alcohol and phosphorus centers. Upon comparing the reaction times required to achieve >99% coupling yields (estimated by ^{1}H-NMR for the phosphonic acid couplings), what is most striking is the insensitivity of the reaction rate to the steric bulk of the phosphoryl residue side chain. The phosphorus Gly and Val analogues had similar reaction times, unlike the active ester condensations which exhibited 16–22-fold differences. This tendency has been mentioned previously with regard to the coupling of amino carboxylic acids and azido compounds via trialkylphosphines.[17] The influence of steric effects from the hydroxy component on the reaction rate was comparable to that seen in the active ester condensations.

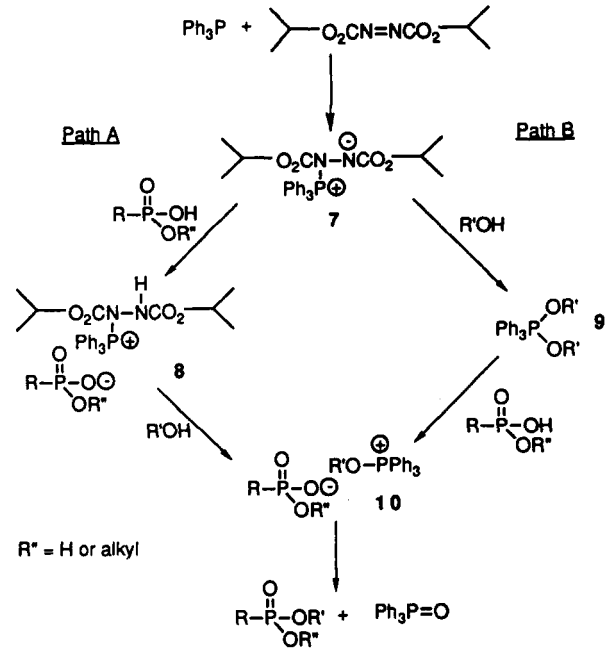
The synthesis of symmetrical phosphonate diesters **5** was also investigated. Bisesterification of commercially available benzylphosphonic acid **4** was initially attempted using standard Mitsunobu conditions, in which DIAD was added to a solution of **4**, an alcohol, and triphenylphosphine in THF (eq 2). When primary alcohols were



(2)

used the reaction was instantaneous and the symmetrical esters **5** were isolated in high yields (Table II). When 2-propanol was used diisopropyl benzylpyrophosphonate **6** was the major product. Similar products have been observed during the study of radical-based dephosphorylation in the production of monomeric metaphosphate.[18] Perturbations of the reaction conditions yielded mixed results: temperatures of −78 to 25 °C had no effect on the product ratios nor did changing the concentration of the

Scheme I



reactants. Predictably, increasing the stoichiometry of the alcohol relative to phosphonic acid resulted in higher yields of the bis-ester although some pyrophosphonate formation was still observed.

Significant progress has been made in determining the mechanism of the Mitsunobu reaction with carboxylic acids, and recent studies indicate that two pathways are operable.[15,19] Scheme I shows the analogous mechanism for phosphonic acids. In path A, the betaine **7** formed between triphenylphosphine and DIAD is protonated by an acidic component with $pK_a < 11$,[20] yielding the protonated betaine **8**, which in turn reacts with an alcohol to form the alkoxyphosphonium salt **10**. Subsequent S_N2 attack by the conjugate base of **10** yields the esterified product with inversion of configuration at the carbinol carbon. Path B only occurs when the acidic component is not present to protonate the betaine **7**. Two equiv of alcohol react with **7** to form a dialkoxyphosphorane **9**.[21] Upon addition of the acidic component, **9** is converted to the phosphonium salt **10** followed by product formation as in path A. Some investigators have suggested that **9** is in equilibrium with an (acyloxy)alkoxyphosphorane, but whether it has a significant role in product formation is unknown.[22]

Pyrophosphonate esters presumably arise from condensation of one molecule of an alkylphosphonic acid with some electrophilic phosphorus species formed via the protonated betaine **8**, followed by further esterification with excess alcohol. The electrophilic species derived from benzylphosphonic acid was trapped with 2-methyl-2-propanol yielding *tert*-butyl benzylphosphonate. Since Mitsunobu condensations are not normally observed with tertiary alcohols,[21a] and no reaction with 2-methyl-2-propanol was observed with benzylpyrophosphonate, or when methyl benzylphosphonate was substituted for benzylphosphonic acid, any *tert*-butyl ester that is formed

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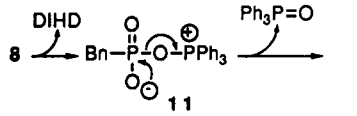
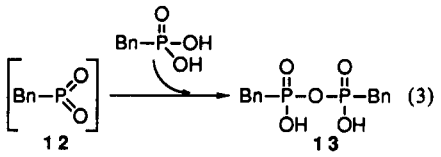
must result from nucleophilic attack by the alcohol on the electrophilic phosphorus species. It is anticipated that the availability of this additional pathway with phosphonic acids may result in a different stereochemical configuration of the alcohol component than the normally observed inverted carbinol carbon.

One explanation for the observed reactivity of benzylphosphonic acid is that intramolecular dehydration of 8 yields benzylmetaphosphonate 12, triphenylphosphine oxide, and diisopropyl hydrazodiformate (eq 3). Formation of phenylmetaphosphonate,[23] mesitylenemetaphosphonate,[24] and monomeric metaphosphate[25] have all been observed. The benzylmetaphosphonate 12 would be highly electrophilic and could readily undergo nucleophilic attack by 2-methyl-2-propanol to produce the *tert*-butyl ester or by another molecule of benzylphosphonic acid producing benzylpyrophosphonate 13. Normal Mitsunobu esterification of 13 with 2-propanol would then yield diisopropyl benzylpyrophosphonate (6). More work is required before an adequate description of the phosphorus intermediate can be given.





To circumvent formation of the electrophilic phosphorus species, path B in Scheme I was accessed using the method of Zbiral[26] in which the alcohol, triphenylphosphine, and DIAD are initially combined in order to produce the alkoxyphosphorane 9 before adding the acidic component. Formation of 9 prevents the acidic component from reacting with the betaine 7 to form the protonated betaine 8 and should eliminate pyrophosphonate formation. Formation of 9 was inferred by the significant upfield shifts in the ^{1}H-NMR spectrum of the alcohol protons upon addition of DIAD and triphenylphosphine. When methanol and benzyl alcohol were used, the alkoxyphosphorane formed reacted cleanly and rapidly with benzylphosphonic acid to form the phosphonate diesters. With 2-propanol the reaction was complicated by the ready decomposition of 9, presumably via an E2 elimination as has been observed by previous investigators.[21b,27]

In conclusion, a synthetic method based on the Mitsunobu reaction has been described for the high-yielding syntheses of a number of phosphonic acid monoesters. This reaction appears general and is relatively insensitive to the steric constraints of hindered phosphonic acids. This method can also be used for the synthesis of phosphonic diesters although this application suffers some limitations.

Experimental Section

^{1}H NMR spectra were recorded at 300 MHz. Mass spectral measurements were performed by the Mass Spectrometry Laboratory at the University of California, Berkeley.

Benzylphosphonic acid was purchased from Lancaster Syntheses and α-L-hydroxyisovaleric acid from Bachem Bioscience Inc., and all remaining chemicals were purchased from Aldrich Chemical Co. THF was refluxed over potassium and distilled prior to use.

The starting methyl benzylphosphonate (1a) and methyl *tert*-butylphosphonate (1b) were obtained by treatment of the respective alkylphosphonic acids with diazomethane, followed by saponification. The phosphorus glycine and valine analogues are known compounds synthesized from the CBZ-protected amino acids.[13,28]

General Procedure for the Preparation of Alkylphosphonic Acid Monoesters. To a solution of methyl alkylphosphonate (0.5 mmol), alcohol (0.75 mmol), and triphenylphosphine (0.75 mmol) dissolved in anhydrous THF (5 mL) was added diisopropyl azodicarboxylate (0.75 mmol). Upon completion of the condensation reaction TMSBr (1.5 mmol) was added and stirring continued an additional 1 h. The reaction mixture was diluted with ether (10 mL) and extracted with 5% $NaHCO_3$ (10 mL × 2). The aqueous phase was washed with ether (10 mL × 3), acidified to pH 2 with concentrated HCl, and then extracted with EtOAc (10 mL × 3). The EtOAc phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. This material was suitable for additional synthetic steps or could be isolated in pure form as the 1-adamantanamine salts from ether or hexane. The compounds obtained by this method are listed below.

Ethyl Benzylphosphonate (3a). Spectral characterization in agreement with ref 29. ^{1}H-NMR (CD_3OD) δ: 7.19 (m, 5 H), 3.87 (m, J = 7.5 Hz, 2 H), 3.03 (d, J = 22 Hz, 2 H), 1.20 (t, J = 7 Hz, 3 H). ^{13}C-NMR ($CDCl_3$) δ: 131.36 (d, J = 9 Hz), 129.58 (d, J = 7 Hz), 128.38 (s), 126.76 (d, J = 4 Hz), 61.60 (d, J = 7 Hz), 33.68 (d, J = 141 Hz), 16.11 (d, J = 6 Hz). ^{31}P-NMR δ: 29.06. FAB HRMS: calcd for $C_9H_{14}O_3P$ (MH^+) 201.0680, found 201.0681.

Isopropyl Benzylphosphonate (3b). ^{1}H-NMR (CD_3OD) δ: 7.19 (m, 5 H), 4.46 (m, J = 7 Hz, 1 H), 3.02 (d, J = 22 Hz, 2 H), 1.18 (d, J = 6 Hz, 6 H). ^{13}C-NMR ($CDCl_3$) δ: 131.50 (d, J = 9 Hz), 129.86 (d, J = 7 Hz), 128.32 (s), 126.69 (d, J = 4 Hz), 70.85 (d, J = 7.5 Hz), 34.08 (d, J = 142 Hz), 23.79 (d, J = 4.5 Hz). ^{31}P-NMR δ: 28.40. FAB HRMS: calcd for $C_{10}H_{16}O_3P$ (MH^+) 215.0836, found 215.0837.

Methyl D-2-[(Benzylhydroxyphosphoryl)oxy]-3-phenylpropionate (3c). ^{1}H-NMR (CD_3OD) δ: 7.17 (m, 10 H), 4.86 (m, 1 H), 3.58 (s, 3 H), 2.94 (m, 4 H). ^{13}C-NMR ($CDCl_3$) δ: 170.11, 135.18, 131.56 (d, J = 9 Hz), 129.92 (d, J = 7 Hz), 129.57, 128.36, 127.02, 126.83 (d, J = 4 Hz), 74.57 (d, J = 7.3 Hz), 52.01, 39.11 (d, J = 5 Hz), 33.74 (d, J = 140 Hz). ^{31}P-NMR δ: 29.42. FAB HRMS: calcd for $C_{17}H_{20}O_5P$ (MH^+) 335.1047, found 335.1048.

Methyl D-2-[(Benzylhydroxyphosphoryl)oxy]-2-phenylacetate (3d). ^{1}H-NMR (CD_3OD) δ: 7.27 (s, 5 H), 7.14 (m, 5 H), 5.51 (d, J = 8 Hz, 1 H), 3.58 (s, 3 H), 3.12 (d, J = 22 Hz, 2 H). ^{13}C-NMR ($CDCl_3$) δ: 169.51, 134.88 (d, J = 6 Hz), 130.71, 129.95 (d, J = 6 Hz), 129.04, 128.57, 128.39, 127.09, 126.89 (d, J = 3 Hz), 75.50 (d, J = 7 Hz), 52.65, 34.04 (d, J = 140 Hz). ^{31}P-NMR δ: 29.15. FAB HRMS calcd for $C_{16}H_{18}O_5P$ (MH^+) 321.0891, found 321.0892.

Ethyl *tert*-Butylphosphonate (3e). ^{1}H-NMR (CD_3OD) δ: 3.97 (m, J = 7 Hz, 2 H), 1.21 (t, J = 7 Hz, 3 H), 1.06 (d, J = 17 Hz, 9 H). ^{13}C-NMR ($CDCl_3$) δ: 61.00 (d, J = 7 Hz), 30.53 (d, J = 144 Hz), 24.34, 16.34 (d, J = 6 Hz). ^{31}P-NMR δ: 39.92. FAB HRMS: calcd for $C_6H_{16}O_3P$ (MH^+) 167.0836, found 167.0837.

Isopropyl *tert*-Butylphosphonate (3f). ^{1}H-NMR ($CDCl_3$) δ: 10.93 (s, 1 H), 4.70 (m, J = 6 Hz, 1 H), 1.36 (d, J = 6 Hz, 6 H), 1.19 (d, J = 16 Hz, 9 H). ^{13}C-NMR (CD_3OD) δ: 70.96 (d, J = 8 Hz), 31.98 (d, J = 144 Hz), 25.06, 24.37 (d, J = 4 Hz). ^{31}P-NMR δ: 38.96. FAB HRMS: calcd for $C_7H_{18}O_3P$ (MH^+) 181.0992, found 181.0994.

Methyl D-2-[(*tert*-Butylhydroxyphosphoryl)oxy]-3-phenylpropionate (3g). ^{1}H-NMR ($CDCl_3$) δ: 8.77 (s, 1 H), 7.26 (m, 5 H), 5.00 (m, J = 6 Hz, 1 H), 3.69 (s, 3 H), 3.17 (m, 2 H), 1.07 (d, J = 17 Hz, 9 H). ^{13}C-NMR ($CDCl_3$) δ: 170.48 (d, J = 3 Hz), 135.48, 129.74, 128.46, 127.14, 74.04 (d, J = 8 Hz), 39.52

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(d, J = 6 Hz), 30.97 (d, J = 143 Hz), 24.14. ^{31}P-NMR δ: 40.44. FAB HRMS: calcd for $C_{14}H_{22}O_5P$ (MH^+) 301.1203, found 301.1205.

Methyl 2-[[[1-[*N*-(Benzyloxycarbonyl)amino]methyl]-hydroxyphosphoryl]oxy]acetate (3h). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 8.68 (s, 1 H), 7.35 (m, 5 H), 5.95 (s, 1 H), 5.11 (s, 2 H), 4.61 (d, J = 10 Hz, 2 H), 3.75 (s, 3 H), 3.68 (m, 2 H). ^{13}C-NMR ($CDCl_3$) δ: 169.34 (d, J = 3 Hz), 156.32, 136.31, 128.22, 127.78, 127.70, 66.69, 61.79 (d, J = 4 Hz), 52.09, 37.38 (d, J = 156 Hz). ^{31}P-NMR δ: 22.64. FAB HRMS: calcd for $C_{12}H_{17}NO_7P$ (MH^+) 318.0741, found 318.0743.

Methyl D-2-[[[1-[*N*-(Benzyloxycarbonyl)amino]methyl]-hydroxyphosphoryl]oxy]-3-phenylpropionate (3i). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.64 (s, 1 H), 7.29 (m, 10 H), 5.57 (s, 1 H), 5.10 (m, 3 H), 3.71 (s, 3 H), 3.50 (m, 2 H), 3.16 (m, 2 H). ^{13}C-NMR (CD_3OD) δ: 172.10, 158.51 (d, J = 5 Hz), 138.12, 136.95, 130.78, 130.72, 129.49, 129.07, 128.95, 128.13, 76.20 (d, J = Hz), 67.92, 52.87, 40.29 (d, J = 5 Hz), 38.32 (d, J = 159 Hz). ^{31}P-NMR δ: 21.24. FAB HRMS: calcd for $C_{19}H_{23}NO_7P$ (MH^+) 408.1210, found 408.1212.

Methyl D-2-[[[1-[*N*-(Benzyloxycarbonyl)amino]methyl]-hydroxyphosphoryl]oxy]-3-methylbutyrate (3j). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 8.66 (s, 1 H), 7.33 (m, 5 H), 5.97 (s, 1 H), 5.11 (s, 2 H), 4.73 (m, 1 H), 3.74 (s, 3 H), 3.66 (m, 2 H), 2.12 (m, 1 H), 1.03 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H). ^{13}C-NMR (CD_3OD) δ: 172.43, 158.51, 138.13, 129.45, 129.04, 128.92, 79.90 (d, J = 7 Hz), 67.88, 52.79, 38.45 (d, J = 59 Hz), 32.76 (d, J = 6 Hz), 18.83, 16.96. ^{31}P-NMR δ: 22.01. FAB HRMS: calcd for $C_{15}H_{23}NO_7P$ (MH^+) 360.1210, found 360.1212.

Methyl 2-[[[(*R*,*S*)-1-[*N*-(Benzyloxycarbonyl)amino]-2-methylpropyl]hydroxyphosphoryl]oxy]acetate (3k). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.36 (m, 5 H), 5.82 (d, 1 H), 5.12 (s, 2 H), 4.58 (m, 2 H), 4.03 (m, 1 H), 3.74 (s, 3 H), 2.28 (m, 1 H), 1.03 (t, J = 6.5 Hz). ^{13}C-NMR (CD_3OD) δ: 170.67 (d, J = 6 Hz), 158.96 (d, J = 5 Hz), 138.26, 129.46, 129.01, 128.82, 67.86, 63.01 (d, J = 6 Hz), 55.04 (d, J = 154 Hz), 52.76, 30.26 (d, J = 4 Hz), 21.00 (d, J = 10 Hz), 18.71 (d, J = 6 Hz). ^{31}P-NMR δ: 23.95. FAB HRMS: calcd for $C_{15}H_{23}NO_7P$ (MH^+) 360.1210, found 360.1212.

Methyl D-2-[[[(*R*,*S*)-1-[*N*-(Benzyloxycarbonyl)amino]-2-methylpropyl]hydroxyphosphoryl]oxy]-3-phenylpropionate (3l). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.96 (s, 1 H), 7.33 (m, 5 H), 7.20 (m, 5 H), 5.76 (m, 0.5 H), 5.43 (m, 0.5 H), 5.10 (m, 3 H), 4.03 (m, 1 H), 3.65 (s, 3 H), 3.12 (m, 2 H), 2.14 (m, 1 H), 0.94 (m, 6 H). ^{13}C-NMR ($CDCl_3$) δ: 170.27 (d, J = 16 Hz), 156.32 (d, J = 6 Hz), 136.24 (d, J = 7 Hz), 135.12 (d, J = 5 Hz), 129.27 (d, J = 4 Hz), 128.02, 127.93, 127.86, 127.60, 127.53, 127.48, 127.37, 126.50, 73.97 (d, J = 6 Hz), 73.82 (d, J = 7 Hz), 66.45, 66.33, 53.34 (d, J = 152 Hz), 53.19 (d, J = 152 Hz), 51.76, 51.71, 39.03 (d, J = 8 Hz), 38.94 (d, J = 5 Hz), 28.61 (d, J = 4 Hz), 20.18 (d, J = 12 Hz), 17.43 (d, J = 5 Hz). ^{31}P-NMR δ: 23.64, 23.45. FAB HRMS: calcd for $C_{22}H_{29}NO_7P$ (MH^+) 450.1680, found 450.1682.

Methyl D-2-[[[(*R*,*S*)-1-[*N*-(Benzyloxycarbonyl)amino]-2-methylpropyl]hydroxyphosphoryl]oxy]-3-methylbutyrate (3m). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.34 (m, 5 H), 6.91 (s, 1 H), 5.91 (m, 0.5 H), 5.58 (m, 0.5 H), 5.11 (s, 2 H), 4.68 (m, 1 H), 4.04 (m, 1 H), 3.70 (s, 3 H), 2.28 (m, 1 H), 2.18 (m, 1 H), 0.96 (m, 12 H). ^{13}C-NMR (CD_3OD) δ: 172.19 (d, J = 6 Hz), 158.90 (d, J = 5 Hz), 138.25, 129.48, 129.02, 128.90, 79.83 (d, J = 7 Hz), 79.76 (d, J = 4 Hz), 67.88, 55.23 (d, J = 156 Hz), 55.07 (d, J = 156 Hz), 52.78, 52.66, 33.03 (d, J = 5 Hz), 32.86 (d, J = 6 Hz), 30.55 (d, J = 4 Hz), 30.48 (d, J = 7 Hz), 21.16 (d, J = 3 Hz), 21.00 (d, J = 3 Hz), 18.92, 18.79, 18.61, 18.53, 18.46, 17.24 (d, J = 11 Hz). ^{31}P-NMR δ: 24.23, 23.94. FAB HRMS: calcd for $C_{18}H_{29}NO_7P$ (MH^+) 402.1680, found 402.1682.

General Procedure for the Preparation of Benzylphosphonate Diesters. To a solution of benzylphosphonic acid (0.5 mmol), alcohol (1.25 mmol), and triphenylphosphine (1.25 mmol) dissolved in anhydrous THF (5 mL) was added diisopropyl azodicarboxylate (1.25 mmol). After 30 min the reaction mixture was concentrated under vacuum and then the triphenylphosphineoxide crystallized with acetone/pentane and removed by filtration. The filtrate was concentrated under vacuum and purified by chromatography (HOAc/EtOAc). The compounds obtained by this method are listed below.

Dimethyl Benzylphosphonate (5a). Spectral characterization in agreement with ref 30. ^{1}H-NMR ($CDCl_3$) δ: 7.30 (m, 5 H), 3.67 (d, J = 11 Hz, 6 H), 3.18 (d, J = 22 Hz). ^{13}C-NMR ($CDCl_3$) δ: 131.05 (d, J = 9 Hz), 129.61 (d, J = 6 Hz), 128.53, 126.91 (d, J = 3 Hz), 52.85 (d, J = 7 Hz), 32.73 (d, J = 138 Hz). ^{31}P-NMR δ: 28.92. FAB HRMS: calcd for $C_9H_{14}O_3P$ (MH^+) 201.0680, found 201.0681.

Diisopropyl Benzylphosphonate (5b). ^{1}H-NMR ($CDCl_3$) δ: 7.30 (m, 5 H), 4.61 (m, J = 7 Hz, 2 H), 3.12 (d, J = 22 Hz, 2 H), 1.28 (d, J = 6 Hz, 6 H), 1.16 (d, J = 6 Hz, 6 H). ^{13}C-NMR ($CDCl_3$) δ: 131.74 (d, J = 9 Hz), 129.75 (d, J = 6 Hz), 128.22 (d, J = 3 Hz), 126.58 (d, J = 4 Hz), 70.54 (d, J = 7 Hz), 34.60 (d, J = 140 Hz), 23.92 (d, J = 4 Hz), 23.63 (d, J = 5 Hz). ^{31}P-NMR δ: 27.46. FAB HRMS: calcd for $C_{13}H_{22}O_3P$ (MH^+) 257.1305, found 257.1307.

Dibenzyl Benzylphosphonate (5c). Spectral characterization in agreement with ref 31. ^{1}H-NMR ($CDCl_3$) δ: 7.26 (m, 15 H), 4.91 (d, J = 8 Hz, 4 H), 3.17 (d, J = 22 Hz, 2 H). ^{13}C-NMR ($CDCl_3$) δ: 136.23 (d, J = 6 Hz), 131.78 (d, J = 9 Hz), 129.77 (d, J = 7 Hz), 128.49, 128.42, 128.23, 127.81, 126.86 (d, J = 4 Hz), 67.52 (d, J = 7 Hz), 33.97 (d, J = 138 Hz). ^{31}P-NMR δ: 24.70. FAB HRMS: calcd for $C_{21}H_{22}O_3P$ (MH^+) 353.1305, found 353.1307.

Supplementary Material Available: ^{13}C-NMR spectra of compounds **3b–3m** as their 1-adamantanamine salts and **5b** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Synthesis of *N*-Thietan-3-yl-α-oxo Nitrogen Heterocycles from Imino Thioethers. A Novel Transformation

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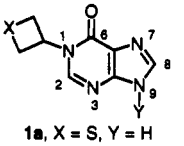
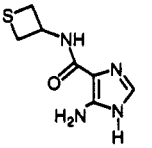
We recently reported the novel formation of thietane derivative **1a** during the course of synthetic studies on 6-mercaptopurine.[1] The structure of **1a** was deduced from analysis of NMR, IR, and HRMS data as well as chemical transformations to **1b**, **1c** and most notably the formation of imidazole derivative **2**. The structure of **2** was fully determined by X-ray crystallographic analysis.[1]



1a, X = S, Y = H
1b, X = SO_2, Y = H
1c, X = S, Y = $COCH_3$



2

Compound **1a** is prepared by alkylation of 6-mercaptopurine (**3**) with epichlorohydrin (**4**) to form **5** which subsequently rearranges in base to give **1a** (Scheme I). We reported that **1a** was isolated in modest (≈35%) yield as the sole product from **5** and proposed a mechanism wherein an intermediate bicyclic thiazoline forms by intramolecular alkylation at N-1.[1] Since this rearrangement seemed quite remarkable, we undertook a study to in-

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