Catalytic Antibodies in Synthesis: Design and Synthesis of a Hapten for Application to the Preparation of a Scalemic Pyrrolidine Ring Synthon for Ptilomycalin A

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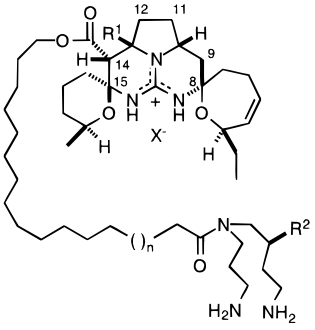
A catalytic antibody-based approach toward the synthesis of an optically active pyrrolidine ring synthon potentially useful for ptilomycalin A is described. Enantiomerically pure hapten **37** was designed and constructed with the eventual goal of generating antibodies for the enantioselective partial hydrolysis of a *meso* diester such as **44** into a monoacid **45**. This transition state analog possesses a phosphonate group containing the requisite oxyanionic character of the tetrahedral intermediate for ester hydrolysis. A newly developed carbamate-based linker, which was found to be much more hydrolytically stable than the commonly used glutarate ester, was developed for coupling of the hapten to a carrier protein.

Introduction

Recently the groups of Kashman and Kakisawa reported the isolation of the novel polycyclic guanidine alkaloid ptilomycalin A (**1**) from the Caribbean sponge *Ptilocaulis spiculifer* and from a red *Hemimycale* sp. found in the Red Sea.[1] Shortly afterward, a related series of alkaloids, exemplified by the crambescidins 800 (**2**), 816 (**3**), and 844 (**4**), was obtained from the Mediterranean sponge *Crambe crambe*.[2] This alkaloid group is characterized by a structurally unique pentacyclic guanidinium core that has a spermidine or hydroxyspermidine residue tethered by a long-chain ω-hydroxy carboxylic acid spacer.

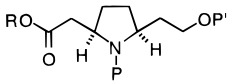
Ptilomycalin A shows cytotoxicity against P388, L1210, and KB cells with an IC_{50} = 0.1, 0.4, and 1.3 μg/mL, respectively, and antifungal and antimicrobial activity against *Candida albicans* (MIC = 0.8 μg/mL) as well as antiviral activity (HSV) at 0.2 μg/mL.[1] Overman and coworkers have recently reported an elegant enantioselective total synthesis of (−)-ptilomycalin A,[3] and notable progress toward assembling the guanidinium core of this alkaloid group by a biomimetic strategy has been reported by Snider and co-workers.[4]

We envisioned a synthetic approach to ptilomycalin A (**1**) starting from an N-protected pyrrolidine derivative **5**, which corresponds to the C(8)−C(15) portion of the guanidinium core. It was initially hoped that **5** could be



ptilomycalin A (**1**, $R^1 = R^2 = H$; n = 1)
crambescidin 800 (**2**, $R^1 = H$, $R^2 = OH$; n =1)
crambescidin 816 (**3**, $R^1 = R^2 = OH$; n = 1)
crambescidin 844 (**4**, $R^1 = R^2 = OH$; n = 3)

obtained in optically pure form by first effecting an enzymatic enantiospecific conversion of *meso* diester **6**



5

into the monoacid **7** (eq 1). A closely related transformation has been reported by Norin and co-workers,[5] who used pig liver esterase (PLE) to convert *meso* diester **8** into monoacid **9** in 100% ee (eq 2). However, we were disappointed to find that treatment of diester **6** with PLE under a variety of conditions gave only poor yields and low ee's of the desired monoacid **7**.[6]

This failure to prepare acid **7** by partial enzymatic hydrolysis prompted us to investigate the use of catalytic antibodies for the preparation of the desired intermediate.[7] A wide range of chemical transformations have been shown to be catalyzed by antibodies, including

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(1) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925. (b) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472. (c) Ohtani, I.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2525.

(2) (a) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712. (b) Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805. (c) Taveras, R.; Daloze, D.; Braekman, J. C.; Hajdue, E. *Biochem. Syst. Ecol.* **1994**, *22*, 645.

(3) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657.

(4) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549. See also: Grillot, A.-L.; Hart, D. J. *Heterocycles* **1994**, *39*, 435. Rama Rao, A. V.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369.

(5) Boutelje, J.; Hjalmarsson, M.; Hult, K.; Lindback, M.; Norin, T. *Bioorg. Chem.* **1988**, *16*, 364.

(6) Alexander, M. D. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 1991.

(7) For reviews of catalytic antibodies, see: (a) Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659. (b) Schultz, P. G.; Lerner, R. A.; Benkovic, S. J. *Chem. Eng. News* **1990**, *68*, 26. (c) Schultz, P. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1283.

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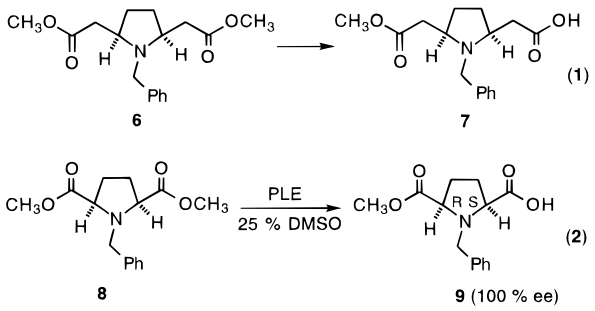
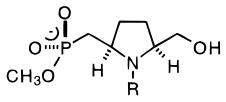


hydrolysis of esters and carbonates.[8] In addition, Lerner, Danishefsky, *et al.* have produced antibodies which hydrolyze *meso*-1,4-diacetoxycyclopent-2-ene to give a monoester alcohol with >98% ee.[9] Therefore, it seemed reasonable that the conversion of *meso* diester **6** into scalemic acid ester **7** might be effected in high ee (eq 1). In order to generate the required catalytic antibodies for such a transformation, it is necessary to first prepare an appropriate transition state analog which would mimic the tetrahedral intermediate of the ester hydrolysis. We envisioned that a scalemic phosphonate derivative such as **10** might function in this role. This substrate possesses the required oxyanionic character of the tetrahedral intermediate, as well as a hydroxyl group which could be attached to a linker to couple the hapten to a carrier protein.[10] We hope that the antibodies produced

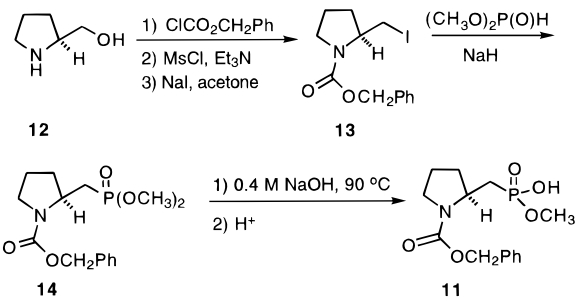


will ultimately lead to an efficient enantioselective synthesis of the desired scalemic pyrrolidine **5**. In addition, these studies should provide a good opportunity to evaluate the potential of catalytic antibodies in complex natural product synthesis.[11]

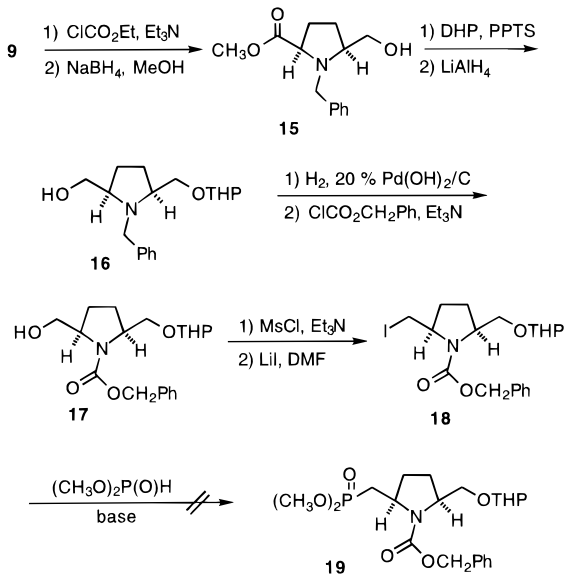
Results and Discussion

Before the synthesis of the desired transition state analog was attempted, it was decided that it would be beneficial to work out the requisite chemistry on a simple model system such as the (*S*)-proline-derived phosphonate **11**. The approach used for the synthesis of **11** is outlined in Scheme 1. Treatment of (*S*)-prolinol[12] with benzyl chloroformate, followed by *O*-mesylation and reaction with NaI, afforded iodide **13** (80%). A Michaelis−Becker[13] reaction of **13** with the sodium salt of dimethyl phosphite gave phosphonate **14** (56%), and this intermediate was then hydrolyzed with 0.4 M NaOH[14] at 90 °C to afford, after acidification, the desired phosphonic acid monomethyl ester **11** (60%).

Scheme 1



Scheme 2



With suitable reaction conditions available for preparing this model phosphonate, we set out to construct the desired hapten **10**. Scalemic monoester **9**, prepared as described by Norin,[5] was reduced to alcohol **15** via a mixed anhydride (73%) (Scheme 2). Alcohol **15** was then protected as the tetrahydropyranyl ether, and the ester group was reduced with $LiAlH_4$ to give primary alcohol **16** (96%). Hydrogenation of **16** with Pearlman's catalyst,[15] followed by protection of the amine as its benzyl carbamate, provided **17** (69%), which upon reaction with mesyl chloride, followed by LiI[16] in DMF, afforded the requisite iodide **18** (51%).

Many attempts were then made to prepare the dimethyl phosphonate derivative **19** by displacement of iodide **18** with the anion of dimethyl phosphite, analogous to the preparation of phosphonate **14** (*cf.* Scheme 1). However, a variety of bases, solvents, and reaction temperatures were tried in this process with no success. In all cases, either starting iodide **18** or decomposition products were obtained with no trace of the desired phosphonate **19**.

It is not immediately evident why this reaction works for the model iodide **13** but not for iodide **18**. One conceivable explanation is that the bulky (tetrahydropyranyloxy)methyl group at C(5) sterically hinders the approach of the dimethyl phosphite anion in the S_N2 displacement reaction. With this possibility in mind, we decided to prepare the cyclic carbamate derivative (*cf.* **22**, Scheme 3) in hope that displacement of the iodide

(8) For example, see: Janda, K. D.; Benkovic, S. J.; Lerner, R. A. *Science* **1989**, *244*, 437.
(9) Ikeda, S.; Weinhouse, M. I.; Janda, K. D.; Lerner, R. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 7763.
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(11) The first use of catalytic antibodies in a natural product total synthesis has recently been reported: Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 3653.
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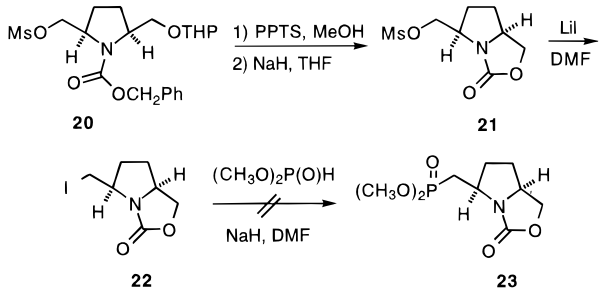
(13) Myers, T. C.; Preis, S.; Jensen, E. V. *J. Am. Chem. Soc.* **1954**, *76*, 4172.
(14) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2528.
(15) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209.
(16) Dean, P. D. *J. Am. Chem. Soc.* **1965**, *87*, 6655.

Scheme 3



would be less sterically hindered. Deprotection of mesylate **20** with PPTS, followed by cyclization with NaH in THF, afforded bicyclic mesylate **21** (69%) (Scheme 3). This compound was then converted to the desired iodide **22** with LiI in DMF (47%).

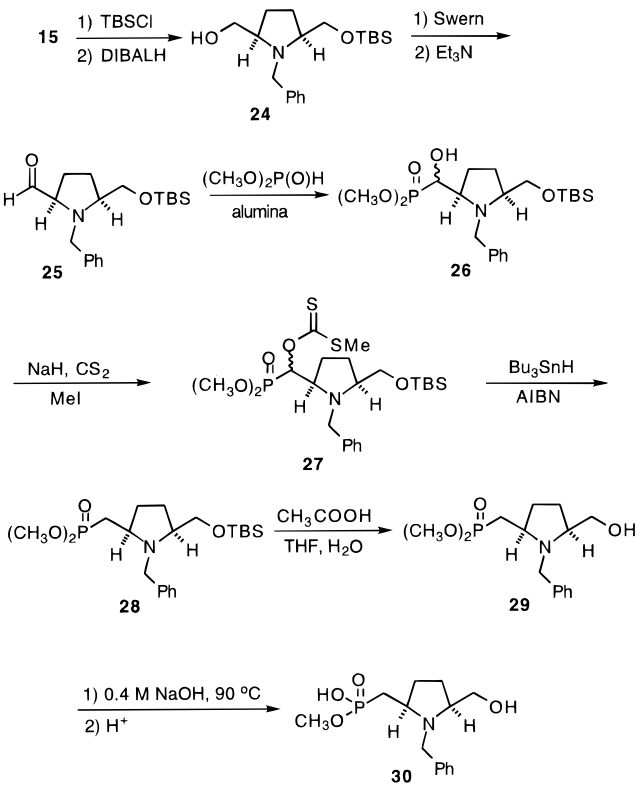
Unfortunately, all attempts at displacing the iodide with the Na, K, or Li anion of dimethyl phosphite led only to decomposition products or recovered starting material, with none of the desired phosphonate **23** detected. It therefore seems likely that the failures in these displacements may be due to a long-range electronic effect rather than a steric one.[17]

It was then decided to investigate an alternative route for the synthesis of phosphonates using the Pudovik reaction,[18a] which involves preparation of α-(hydroxymethyl) phosphonates through addition of phosphite to carbonyl compounds under base catalysis.[18b] We expected that the resultant secondary alcohol functionality could then be removed by a two-step radical deoxygenation process[19] to afford the dialkyl phosphonate derivative.

Protection of scalemic alcohol **15** as its (*tert*-butyldimethyl)silyl ether (95%), followed by reduction of the ester with DIBALH, provided alcohol **24** (78%) (Scheme 4). Swern oxidation[20] of **24** gave aldehyde **25** (96%), which was treated with dimethyl phosphite in the presence of basic alumina to afford α-hydroxy phosphonate **26** as an inseparable mixture of alcohol diastereomers in 69% yield. Reaction of **26** with NaH in the presence of carbon disulfide and methyl iodide gave a mixture of diastereomeric xanthates **27** (81%), which was reduced with tributyltin hydride to afford the desired dimethyl phosphonate **28** (85%). Removal of the silyl ether was then effected under acidic conditions[21] to provide the desired alcohol phosphonate **29** (87%).

We next attempted to hydrolyze phosphonate **29** with 0.4 M NaOH, as was done in the simpler proline model system (*cf*. Scheme 1). Reaction of **29** under these conditions met with only partial success. Although it appeared that product **30** had formed, the compound proved too polar to be easily separated from the inorganic byproducts. Numerous attempts to purify phosphonic acid **30** via ion exchange, reverse phase, or alumina chromatography all failed. In addition, there was concern that protonation of the pyrrolidine nitrogen was occurring upon acidification, forming the amino acid salt, thus making purification even more difficult.

Scheme 4



Since a benzyl carbamate protecting group had been used on the pyrrolidine nitrogen in the model study in Scheme 1, the same was done in this system, hoping to simplify the purification process by eliminating the basic nitrogen. Thus, hydrogenation of silyl ether **24** with Pearlman's catalyst, followed by protection of the secondary amine as its benzyl carbamate, provided compound **31** (93%) (Scheme 5). Swern oxidation of alcohol **31** gave aldehyde **32** (96%). However, on reaction with dimethyl phosphite in the presence of basic alumina, this aldehyde epimerized to give after addition a complex mixture of the *cis* and *trans* α-hydroxy phosphonates. It was discovered that this epimerization could be prevented by using a preformed solution of sodium dimethyl phosphite in DMF at 0 °C, which afforded α-hydroxy phosphonate **33** as an inseparable mixture of alcohol diastereomers (91%). Conversion of alcohols **33** to xanthates **34** (92%), followed by reduction with tributyltin hydride (94%), successfully provided the key phosphonate **35**. Deprotection of the silyl ether was again done under acidic conditions to afford phosphonate alcohol **36** (95%).

The next step was to prepare the desired phosphonic acid monoester **37**. However, hydrolysis of intermediate **36** with 0.4 M NaOH at 90 °C led only to decomposition products, and running the reaction at lower temperatures resulted in only recovered starting material. It is not evident why this hydrolysis, which worked well in previous examples, affords none of the desired monoester **37**. Some of the other known methods for monodemethylation of dimethyl phosphonates were then tried, and we were pleased to discover that refluxing **36** in *tert*-butylamine[22] for 7 days, followed by acidification by passage through a Dowex H^+ ion exchange column, afforded monoester **37** (46%).

(17) For lead references to retardation of S_N2 reactions by remote electronegative substituents, see: Behrens, C. H.; Sharpless, K. B. *Aldrichchimica Acta* **1983**, *16*, 67.

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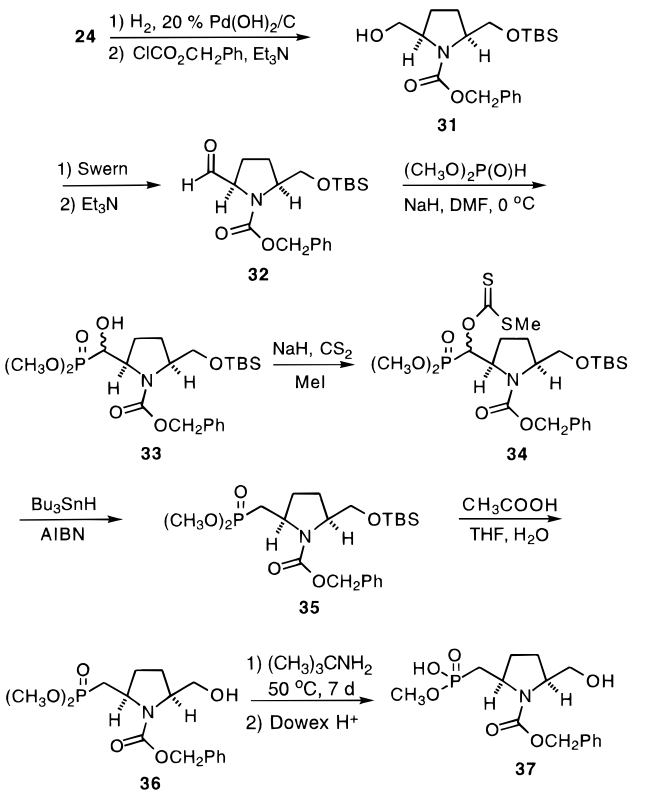
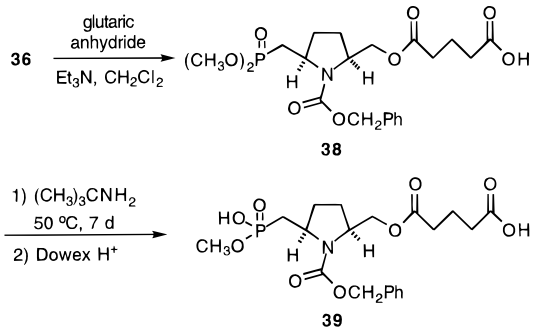
(20) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(21) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Scheme 5



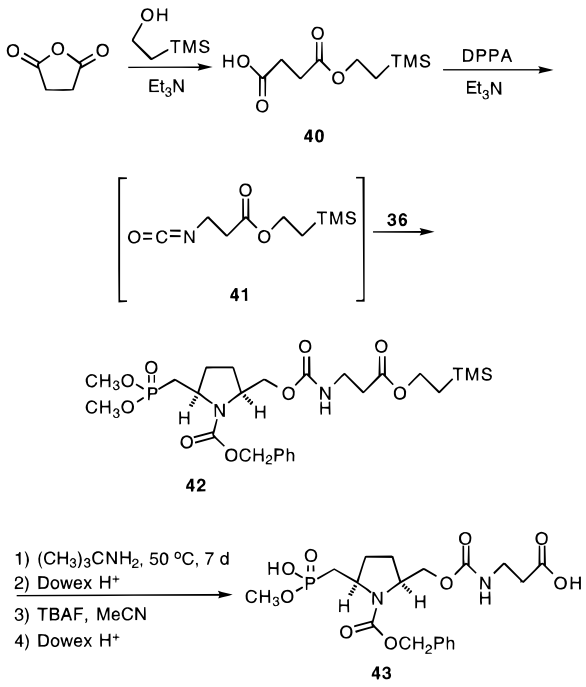
Scheme 6



Although phosphonate ester cleavage worked successfully, for simplicity of operation and purification it seemed preferable to attach the requisite linker to the alcohol functionality prior to the demethylation step. Typically, a five-carbon spacer such as a glutarate ester has been used as the linker in hapten syntheses.[7] Reaction of alcohol **36** with glutaric anhydride in the presence of triethylamine in fact afforded glutarate **38** (82%) (Scheme 6). This compound was then refluxed in *tert*-butylamine for 7 days and acidified on a Dowex H^+ ion exchange column, and the crude product was purified by reverse phase HPLC to give the desired acid **39** in 47% yield.

It was discovered, however, that monoester **39** was surprisingly unstable, and after storage in the freezer at 0 °C for 1 week, a major decomposition product was detected in the sample of **39** which was determined to be monoester alcohol **37**. Since this decomposition happened simply on storage in the freezer, presumably via hydrolysis by adventitious water, there were concerns that this same hydrolysis might also occur under physiological conditions. What was needed, therefore, was an alternative linker system which would be more stable, and we focused our efforts on developing a new type of carbamate-based linker.

Scheme 7



Thus, succinic anhydride was combined with 2-(trimethylsilyl)ethanol to afford acid **40** (72%), which was converted to an intermediate acyl azide with diphenyl phosphorazidate (DPPA) (Scheme 7).[23] After Curtius rearrangement of the azide to the isocyanate **41,** formed *in situ*, addition of alcohol **36** produced the stable carbamate ester **42** (38%).[24]

With carbamate **42** in hand, all that was needed to complete the synthesis of the hapten was to demethylate the phosphonate to the monoacid and remove the silylethyl ester protecting group. Refluxing **42** in *tert*-butylamine for 7 days, followed by acidification with a Dowex H^+ ion exchange column, achieved the required transformation and afforded a crude phosphonate monoester. Cleavage of the β-(trimethylsilyl)ethyl ester group was then effected with TBAF,[25] which after acidification with Dowex H^+ and purification by reverse phase HPLC afforded the desired phosphonate monoester **43** in 57% yield. This carbamate-linked hapten was indeed much more stable than glutarate ester **39**, with no decomposition being detected after storage at 0 °C for several months. We anticipate that isocyanate **41** should be generally useful as a linker in the field of catalytic antibodies.

Work is beginning on using hapten **43** to generate catalytic antibodies, which will then be screened for activity in the partial hydrolysis of *meso* diester **44** to produce scalemic monoester **45** (eq 3). These studies will be reported in due course.

Experimental Section

Chemical ionization mass spectra (CIMS) were obtained using isobutane as a carrier gas. Analytical and preparative

(22) Patel, D.; Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591.

(23) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

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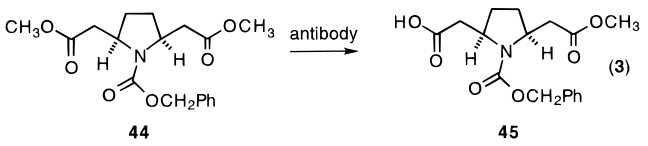
(25) Capson, T. L.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 3515.



44 45

TLC were performed on E. M. Science silica gel 60 PF_{254}. Flash column chromatography was performed using Baker silica gel (25−40 mm). THF was dried over and distilled from sodium/benzophenone ketyl. Methylene chloride, triethylamine, pyridine, DMF, and DMSO were distilled from CaH_2 and methanol was distilled from magnesium turnings.

Preparation of Iodide 13. To a solution of amine **12** (2.93 g, 0.029 mol) in CH_2Cl_2 (60 mL) at 0 °C under argon was added triethylamine (5.24 mL, 0.038 mol), followed by dropwise addition of benzyl chloroformate (4.95 mL, 0.035 mol). The reaction mixture was slowly warmed to rt and stirred for 18 h. Water was added to the mixture, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate/hexanes (1/2), to afford 6.07 g of the intermediate benzyl carbamate as a colorless oil.

To the above benzyl carbamate (5.5 g, 0.023 mol) in CH_2Cl_2 (80 mL) at 0 °C under argon was added triethylamine (4.24 mL, 0.030 mol), followed by dropwise addition of methanesulfonyl chloride (2.17 mL, 0.028 mol). The mixture was slowly warmed to rt and was stirred for 18 h. Water was added to the mixture, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to afford 7.3 g of the intermediate mesylate as a colorless oil.

To a solution of the above mesylate (5.35 g, 0.017 mol) in acetone (200 mL) at rt under argon was added NaI (25.6 g, 0.17 mol). The reaction mixture was heated at 55 °C and stirred for 24 h. The sodium salts were removed by filtration, and the solvent was concentrated *in vacuo*. The residue was extracted three times with ether, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to afford 5.25 g (80% overall) of iodide **13** as a dark yellow oil: IR (film) 3020, 2950, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.34 (m, 5 H), 5.12 (bs, 2 H), 3.95 (m, 1 H), 3.38 (m, 4 H), 1.98 (m, 4 H); CIMS ($M^+ + 1/z$) 346, 204, 149, 128, 91; HRMS exact mass calcd for $C_{13}H_{16}NO_2I$ 345.0228, found 345.0225. Anal. Calcd for $C_{13}H_{16}NO_2I$: C, 45.24; H, 4.67; N, 4.06. Found: C, 45.25; H, 4.71; N, 4.09.

Preparation of Phosphonate 14. To NaH (80% dispersion in mineral oil, 0.308 g, 0.010 mol) in DMF (8.0 mL) at rt under argon was added dropwise dimethyl phosphite (0.94 mL, 0.010 mol). The reaction mixture was stirred at rt for 1 h, and then iodide **13** (0.354 g, 0.001 mol) in DMF (4 mL) was added dropwise over 5 min. The reaction mixture was heated at 55 °C for 18 h, and saturated NH_4Cl (10 mL) was added. The solvents were removed *in vacuo*, and the residue was extracted three times with ether. The organic layer was washed twice with water and then brine and was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate/methanol (9/1), to afford 0.190 g (56%) of phosphonate **14** as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.26 (m, 5 H), 5.05 (s, 2 H), 4.01 (m, 1 H), 3.57 (m, 6 H), 3.28 (m, 2 H), 2.30 (m, 1 H), 1.88 (m, 2 H), 1.68 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 154.3, 154.2, 136.6, 136.3, 128.2, 127.9, 127.7, 127.5, 66.8, 66.3, 53.0, 52.9, 52.4, 52.3, 52.0, 46.4, 46.0, 31.2, 30.6, 30.3, 29.0, 28.9, 27.5, 23.5, 22.6; ^{31}P NMR ($CDCl_3$, 146 MHz) δ 30.3, 29.9; amide rotamer ratio 1.2/1.0; HRMS exact mass calcd for $C_{15}H_{22}NO_5P$ 327.1236, found 327.1216.

Preparation of Phosphonate Monoacid 11. To phosphonate **14** (0.21 g, 0.064 mmol) at rt was added 0.4 M NaOH (1.6 mL, 0.64 mmol). The reaction mixture was heated at 90 °C for 18 h, and the solvents were removed *in vacuo*. The residue was dissolved in water, and the aqueous layer was extracted three times with ethyl acetate. The aqueous layer was then acidified with 5% HCl and extracted five times with ethyl acetate. The organic layers from this latter extraction were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to afford 0.012 g (60%) of monoacid **11** as a colorless oil: IR (film) 3350, 3020, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.24 (m, 5 H), 5.11 (s, 2 H), 4.73 (bs, 1 H), 4.15 (m, 1 H), 3.62 (m, 3 H), 3.40 (m, 2 H), 2.41 (m, 2 H), 1.90 (m, 4 H); MS (FAB$^+$, glycerol) m/z 314 ($M + H^+$, 100).

Preparation of Ester Alcohol 15. To a solution of monoacid **9** (2.9 g, 0.011 mol) in THF (120 mL) at 0 °C under argon was added triethylamine (1.7 mL, 0.012 mol), followed by dropwise addition of ethyl chloroformate (1.19 mL, 0.012 mol). The reaction mixture was stirred for 3 h, the triethylamine hydrochloride was filtered off, and the filter cake was washed three times with THF. The filtrate was then added dropwise to a suspension of $NaBH_4$ (1.67 g, 0.044 mol) in water (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, water was added, and the mixture was extracted three times with ether. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with hexanes/ethyl acetate (1/1), to afford 2.01 g (73%) of ester alcohol **15**: $[\alpha]^{21}_D$ +16.4° (*c* 0.01, CH_2Cl_2); IR (film) 3430, 3020, 2940, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25 (m, 5 H), 3.79 (AB q, J = 13.5 Hz, 2 H), 3.50 (s, 3 H), 3.50 (m, 2 H), 3.34 (m, 2 H), 3.07 (bs, 1 H), 1.90 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.6, 138.3, 128.9, 128.2, 127.2, 66.0, 65.4, 61.9, 57.9, 51.7, 29.8, 27.3; CIMS ($M^+ + 1/z$) 250, 232, 218, 91, 65; HRMS exact mass calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1372. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.05; H, 7.71; N, 5.54.

Preparation of Tetrahydropyranyl Ether 16. To ester alcohol **15** (0.42 g, 1.70 mmol) in toluene (5 mL)/CH_2Cl_2 (5 mL) under argon was added a catalytic amount of PPTS followed by dihydropyran (0.76 mL, 8.30 mmol). The reaction mixture was heated at 90 °C for 3 h and cooled to rt, and toluene (20 mL) was added. The organic solution was washed sequentially with saturated $NaHCO_3$, water, and brine and was dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (7/3), to afford a colorless oil, which was dissolved in THF (50 mL) and added dropwise to $LiAlH_4$ (0.52 g, 13.0 mmol) in dry THF (50 mL) at 0 °C under argon. The reaction mixture was warmed to rt and stirred for 24 h. Excess hydride was destroyed by the sequential addition of ethyl acetate (0.8 mL), 15% NaOH (0.6 mL), water (0.6 mL), and saturated NH_4Cl (1.7 mL). The aluminum salts were filtered off, and the filter cake was washed with THF. The filtrate was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford 1.28 g (96%) of THP ether **16**, which was used directly in the next step without further purification: IR (film) 3400, 3040, 2900 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25 (m, 5 H), 4.45 (m, 1 H), 3.80 (m, 3 H), 3.56−2.94 (m, 8 H), 1.89−1.47 (m, 10 H); CIMS ($M^+ + 1/z$) 306, 204, 190, 85.

Preparation of Benzyl Carbamate 17. To THP ether alcohol **16** (0.18 g, 0.57 mmol) and 20% $Pd(OH)_2/C$ (0.035 g) at rt under argon was added ethanol (5 mL). The reaction flask was evacuated and filled with hydrogen gas (1 atm), and the mixture was stirred for 18 h. The catalyst was removed by filtration through Celite, and the pad was washed with ethyl acetate (5 × 10 mL). The solvents were removed *in vacuo* to afford the intermediate amine as a pale yellow oil.

The above amine was dissolved in CH_2Cl_2 (5 mL), and triethylamine (0.098 mL, 0.70 mmol) was added at 0 °C under argon, followed by dropwise addition of benzyl chloroformate (0.085 mL, 0.59 mmol). The reaction mixture was stirred at 0 °C for 18 h, water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (1/1), to afford 0.096 g (73%) of benzyl carbamate **17** as a colorless oil: IR (film) 3400, 2920, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.33 (m, 5 H), 5.14 (m, 2 H), 4.55 (m, 1 H), 4.31

(bs, 1 H), 4.05 (m, 2 H), 3.80 (m, 3 H), 3.43 (m, 3 H), 1.73 (m, 10 H); CIMS ($M^+ + 1/z$) 350, 318, 266, 222, 190, 91, 85.

Preparation of Iodide 18. To a solution of benzyl carbamate **17** (1.53 g, 4.40 mmol) in CH_2Cl_2 (50 mL) at 0 °C under argon was added triethylamine (0.79 mL, 5.70 mmol), followed by dropwise addition of methanesulfonyl chloride (0.41 mL, 5.30 mmol). The reaction mixture was slowly warmed to 25 °C and was stirred for 18 h. Water was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (1/1), to afford the intermediate mesylate as a colorless oil.

To a solution of the above mesylate (0.053 g, 0.12 mmol) in DMF (2.0 mL) at rt under argon was added LiI (0.33 g, 2.48 mmol). The reaction mixture was stirred at 80 °C for 18 h, water was added, and the mixture was extracted three times with ether. The organic layer was washed with water and brine and was dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate/hexanes (1/1), to afford 0.026 g (51% overall) of iodide **18** as a light yellow oil: IR (film) 3010, 2920, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.33 (m, 5 H), 5.13 (s, 2 H), 4.56 (m, 1 H), 4.12 (m, 2 H), 3.57 (m, 5 H), 3.20 (m, 1 H), 2.00 (m, 4 H), 1.57 (m, 6 H); CIMS ($M^+ + 1/z$) 460, 419, 414, 376, 332, 149, 91.

Preparation of Mesylate 20. To a solution of benzyl carbamate **17** (1.53 g, 4.40 mmol) in CH_2Cl_2 (50 mL) at 0 °C under argon was added triethylamine (0.79 mL, 5.70 mmol), followed by dropwise addition of methanesulfonyl chloride (0.41 mL, 5.30 mmol). The reaction mixture was slowly warmed to 25 °C and was stirred for 18 h. Water was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (1/1), to afford 1.80 g (96%) of mesylate **20** as a colorless oil: IR (film) 2920, 1680, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25 (m, 5 H), 5.04 (bs, 2 H), 4.47 (m, 1 H), 4.23 (m, 1 H), 4.03 (m, 3 H), 3.63 (m, 2 H), 3.35 (m, 2 H), 2.84 (m, 3 H), 1.93 (m, 4 H), 1.42 (m, 6 H); CIMS ($M^+ + 1/z$) 428, 390, 386, 384, 344, 300, 268, 158, 91.

Preparation of Cyclic Carbamate Mesylate 21. To a solution of mesylate **20** (0.389 g, 0.91 mmol) in methanol (20 mL) at 25 °C under argon was added a catalytic amount of PPTS. The reaction mixture was heated to 40 °C and stirred for 18 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate/hexanes (4/1), to afford 0.287 g of the intermediate alcohol as a colorless oil.

To a solution of NaH (60% dispersion in mineral oil, 0.030 g, 0.75 mmol) in dry THF (20 mL) at rt under argon was added the above alcohol (0.180 g, 0.52 mmol) in THF (5 mL). The reaction mixture was stirred for 48 h, poured into water, and extracted with ethyl acetate. The organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with ethyl acetate, to afford 0.090 g (69% overall) of cyclic carbamate mesylate **21** as a pale yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 5.02 (dd, J = 3.7, 10.6 Hz, 1 H), 4.52 (t, J = 7.8 Hz, 1 H), 4.37 (dd, J = 3.3, 10.6 Hz, 1 H), 4.18 (m, 1 H), 3.86 (m, 1 H), 3.02 (s, 3 H), 2.29 (m, 2 H), 1.97 (m, 1 H), 1.72 (m, 2 H).

Preparation of Iodide 22. To a solution of mesylate **21** (0.084 g, 0.36 mmol) in dry DMF (10 mL) under argon was added LiI (0.86 g, 6.43 mmol). The reaction mixture was heated at 80 °C for 24 h, poured into water, and extracted with ether. The organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with ethyl acetate, to afford 0.045 g (47%) of iodide **22** as a pale yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 4.49 (t, J = 8.2 Hz, 1 H), 4.20 (m, 2 H), 3.70 (m, 3 H), 2.30 (m, 2 H), 1.89 (m, 2 H); CIMS ($M^+ + 1/z$) 268, 176, 140, 126.

Preparation of Alcohol 24. To ester alcohol **15** (1.73 g, 6.94 mmol) in DMF (35 mL) at rt under argon was added imidazole (1.04 g, 15.3 mmol) followed by (*tert*-butyldimethyl)-silyl chloride (1.19 g, 7.89 mmol). The reaction mixture was stirred at 25 °C for 24 h, poured into water, and extracted with CH_2Cl_2. The organic layer was washed sequentially with saturated $NaHCO_3$, water, and brine and was dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (3/1), to afford 2.40 g of the intermediate silyl ether as a pale yellow oil.

To the above silyl ether (3.43 g, 9.43 mmol) in toluene (85 mL) at 0 °C under argon was added DIBALH (18.0 mL, 1.0 M solution in hexanes). The reaction mixture was stirred at 25 °C for 50 min, poured into a saturated solution of Rochelle's salts, and stirred with ethyl acetate for 1 h. The solution was extracted with ethyl acetate, washed with Rochelle's salts and brine, and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (1/1), to afford 3.17 g (78%) of alcohol **24** as a pale yellow oil: $[\alpha]^{23}_D$ −10.6° (*c* 0.01, CH_2Cl_2); IR (neat) 3429 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.28 (m, 5 H), 3.79 (s, 2 H), 3.30 (m, 4 H), 2.96 (m, 3 H), 1.74 (m, 4 H), 0.81 (s, 9 H), −0.04 (d, J = 4.5 Hz, 6 H); CIMS ($M^+ + 1/z$) 336, 320, 318, 304, 278, 258, 204, 190, 156, 91.

Preparation of α-Hydroxy Phosphonates 26. To oxalyl chloride (1.8 mL, 20.6 mmol) in CH_2Cl_2 (18 mL) at −78 °C under argon was added DMSO (2.5 mL, 35.2 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred for 2 min, and then alcohol **24** (2.48 g, 7.39 mmol) in CH_2Cl_2 (11 mL) was added over 5 min. The reaction mixture was stirred at −78 °C for 15 min, and triethylamine (8.2 mL, 58.8 mmol) was added. The mixture was stirred for 5 min, warmed to rt, poured into water, and extracted with CH_2Cl_2. The organic layer was washed sequentially with 1% HCl, water, 5% Na_2CO_3, water, and brine and was dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to afford 2.35 g (96%) of aldehyde **25** as a pale yellow oil, which was used directly in the next step without purification.

To the above aldehyde (1.15 g, 3.45 mmol) in dimethyl phosphite (0.4 mL, 4.36 mL) at rt under argon was added basic aluminum oxide (Brockmann Activity I, 1.0 g, 9.8 mmol). The reaction mixture was stirred at 25 °C for 48 h, the alumina was filtered off and washed with CH_2Cl_2 (100 mL). The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate, to afford 1.05 g (69%) of a diastereomeric mixture of α-hydroxy phosphonates **26** as a pale yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.27 (m, 5 H), 3.90 (AB q, J = 15.8 Hz, 2 H), 3.78 (m, 1 H), 3.72 (d, J = 10.9 Hz, 3 H), 3.67 (d, J = 10.9 Hz, 3 H), 3.48 (m, 2 H), 3.20 (m, 2 H), 3.02 (m, 1 H), 1.76 (m, 4 H), 0.78 (s, 9 H), −0.07 (d, J = 4.5 Hz, 6 H); CIMS ($M^+ + 1/z$) 444, 376, 334, 304, 188, 111, 91.

Preparation of Xanthates 27. To phosphonates **26** (0.88 g, 1.87 mmol) in DMF (10 mL) at rt under argon were added carbon disulfide (1.2 mL, 19.95 mmol) and NaH (60% dispersion in mineral oil, 0.083 g, 2.08 mmol). The reaction mixture was stirred for 30 min, and iodomethane (1.2 mL, 19.28 mmol) was added. This mixture was stirred for 30 min, concentrated *in vacuo*, poured into water, and extracted with ethyl acetate. The organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate, to afford 0.81 g (81%) of a diastereomeric mixture of xanthates **27** as a brown oil: CIMS ($M^+ + 1/z$) 534, 518, 474, 426, 388, 304, 218, 111, 91.

Preparation of Phosphonate 28. To xanthates **27** (1.14 g, 2.14 mmol) in toluene (28 mL) at rt under argon were added tributyltin hydride (0.85 mL, 3.16 mmol) and AIBN (0.007 g, 0.04 mmol). The reaction mixture was stirred at 115 °C for 3 h. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate, to afford 0.77 g (85%) of phosphonate **28** as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (m, 5 H), 3.78 (AB q, J = 13.9 Hz, 2 H), 3.57 (d, J = 10.9 Hz, 3 H), 3.56 (d, J = 10.9 Hz,

3 H), 3.22 (m, 2 H), 3.03 (m, 1 H), 2.83 (m, 1 H), 2.1−1.6 (m, 6 H), 0.79 (s, 9 H), −0.11 (d, J = 2.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.7, 128.9, 128.0, 126.8, 67.0, 65.7, 60.5, 58.3, 51.9, 31.3 (d, J = 133.1 Hz), 30.9, 26.9, 25.8, −5.5; CIMS ($M^+ + 1/z$) 428, 412, 380, 304, 282, 192, 125, 91.

Preparation of Hydroxy Phosphonate 29. To TBDMS phosphonate **28** (0.11 g, 0.26 mmol) in THF (1 mL) were added acetic acid (3 mL) and water (1 mL). The reaction mixture was stirred at 60 °C for 24 h. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate/methanol (20/1), to afford 0.071 g (87%) of phosphonate **29** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 5 H), 5.05 (bs, 1 H), 3.78 (AB q, J = 14.0 Hz, 2 H), 3.58 (d, J = 10.9 Hz, 3 H), 3.57 (d, J = 10.9 Hz, 3 H), 3.20 (m, 3 H), 2.97 (m, 1 H), 2.10−1.60 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 129.1, 128.4, 127.4, 65.3, 62.6, 60.0, 57.6, 52.2, 31.2, 30.7 (d, J = 135.7 Hz), 26.7; CIMS ($M^+ + 1/z$) 314, 282, 264, 224, 190, 125, 91; HRMS exact mass calcd for $C_{15}H_{24}NO_4P$ 313.1443, found 313.1433.

Preparation of Benzyl Carbamate 31. To alcohol **24** (2.13 g, 6.35 mmol) and 20% $Pd(OH)_2$/C (0.35 g) at 25 °C under argon was added ethanol (25 mL). The reaction flask was evacuated and filled with hydrogen gas (1 atm), and the mixture was stirred for 18 h. The catalyst was removed by filtration through a Celite pad, and the pad was washed with ethyl acetate (5 × 25 mL). The solvents were removed *in vacuo* to afford 1.56 g (100%) of the intermediate amino alcohol as a pale yellow oil, which was used directly in the next step without further purification.

To a solution of the above amino alcohol (2.45 g, 9.98 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C under argon was added triethylamine (1.45 mL, 10.4 mmol), followed by dropwise addition of benzyl chloroformate (1.80 mL, 12.6 mmol). The reaction mixture was stirred at 0 °C for 18 h, water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with hexanes/ethyl acetate (1/3), to afford 3.50 g (93%) of benzyl carbamate **31** as a pale yellow oil: $[\alpha]^{23}_D$ −16.9 (*c* 0.01, MeOH); IR (neat) 3445, 3025, 2940, 1675 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz, 345 K) δ 7.34 (m, 5 H), 5.08 (s, 2 H), 4.37 (t, J = 5.5 Hz, 1 H), 3.84 (m, 2 H), 3.69 (dd, J = 3.5, 9.8 Hz, 1 H), 3.57 (m, 2 H), 3.38 (m, 1 H), 1.89 (m, 4 H), 0.86 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (DMSO, 75 MHz, 383 K) δ 154.1, 136.5, 127.5, 127.1, 126.7, 65.4, 63.2, 59.7, 59.1, 25.5, 25.1, 25.0, 17.2, −6.1; CIMS ($M^+ + 1/z$) 380, 362, 322, 304, 233, 214, 190, 156, 108, 91; HRMS exact mass calcd for $C_{20}H_{33}NO_4Si$ 379.2179, found 379.2163. Anal. Calcd for $C_{20}H_{33}NO_4Si$: C, 63.29; H, 8.76; N, 3.69. Found: C, 63.06; H, 8.66; N, 3.78.

Preparation of Phosphonate 33. To oxalyl chloride (0.80 mL, 9.17 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C under argon was added DMSO (0.70 mL, 9.86 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 2 min, and then alcohol **31** (1.25 g, 3.29 mmol) in CH_2Cl_2 (5 mL) was added over 5 min. The reaction mixture was stirred at −78 °C for 15 min, and triethylamine (3.40 mL, 24.3 mmol) was added. The mixture was stirred for 5 min, warmed to rt, poured into water, and extracted with CH_2Cl_2. The organic layer was washed sequentially with 1% HCl, water, 5% Na_2CO_3, water, and brine and was dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to afford 1.24 g (100%) of aldehyde **32** as a pale yellow oil, which was used directly in the next step without purification.

To dimethyl phosphite (0.35 mL, 3.82 mmol) in dry DMF (100 mL) under argon was added NaH (60% dispersion in mineral oil, 0.131 g, 3.28 mmol). The reaction mixture was stirred for 1 h and cooled to 0 °C, and the above aldehyde (1.24 g, 3.28 mmol) in DMF (5 mL) was added. The mixture was stirred at 0 °C for 48 h, poured into saturated NH_4Cl, and extracted with ethyl acetate. The organic layer was washed twice with water and then brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate, to afford 1.46 g (91%) of a diastereomeric mixture of phosphonates **33** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32 (m, 5 H), 5.11 (s, 2 H), 4.25 (m, 3 H), 3.73 (d, J = 10.7 Hz, 6 H), 3.59 (m, 4 H), 1.90 (m, 3 H), 0.82 (s, 9 H), −0.07 (d, J = 4.5 Hz, 6 H); CIMS ($M^+ + 1/z$) 488, 430, 378, 348, 304, 156, 111, 91.

Preparation of Phosphonate 35. To a mixture of diastereomeric phosphonates **33** (1.47 g, 3.01 mmol) in dry DMF (40 mL) at rt under argon were added carbon disulfide (2.0 mL, 33.3 mmol) and NaH (60% dispersion in mineral oil, 0.145 g, 3.63 mmol). The reaction mixture was stirred for 30 min, and iodomethane (2.0 mL, 32.1 mmol) was added. The mixture was stirred for 30 min, poured into water, and extracted with ethyl acetate. The organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate, to afford 1.60 g (92%) of a diastereomeric mixture of xanthates **34** as a brown oil which was used without further purification: CIMS ($M^+ + 1/z$) 578, 506, 464, 356, 111, 91.

To the above xanthates **34** (1.60 g, 2.77 mmol) in dry toluene (40 mL) at rt under argon were added tributyltin hydride (0.95 mL, 3.53 mmol) and AIBN (0.020 g, 0.12 mmol). The reaction mixture was stirred at 115 °C for 3 h. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate, to afford 1.22 g (94%) of phosphonate **35** as a pale yellow oil: $[\alpha]^{23}_D$ −10.4° (*c* 0.01, CH_2Cl_2); IR (neat) 3470, 2940, 1755, 1682 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz, 345 K) δ 7.32 (m, 5 H), 5.09 (s, 2 H), 4.03 (bs, 1 H), 3.83 (bs, 1 H), 3.62 (m, 2 H), 3.58 (d, J = 11.0 Hz, 3 H), 3.57 (d, J = 11.0 Hz, 3 H), 1.93 (m, 6 H), 0.87 (s, 9 H), −0.07 (d, J = 2.6 Hz, 6 H); ^{13}C NMR (DMSO, 75 MHz, 383 K) δ 153.5, 136.3, 127.5, 127.0, 126.8, 65.5, 62.9, 59.0, 53.4, 50.9, 29.5 (d, J = 132.5 Hz), 28.9, 25.3, 25.0, 17.2, −6.2; CIMS ($M^+ + 1/z$) 472, 414, 364, 282, 91.

Preparation of Phosphonate 36. To TBDMS phosphonate **35** (0.59 g, 1.25 mmol) in THF (2 mL) were added acetic acid (6 mL) and water (2 mL). The reaction mixture was stirred at 60 °C for 24 h. The solvents were removed *in vacuo*, and the residue was purified by column chromatography, eluting with ethyl acetate/methanol (20/1), to afford 0.43 g (95%) of phosphonate **36** as a pale yellow oil: $[\alpha]^{23}_D$ −1.1° (*c* 0.01, CH_3OH); IR (neat) 3240, 2850, 1660 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz, 345 K) δ 7.33 (m, 5 H), 5.09 (s, 2 H), 4.57 (bs, 1 H), 4.04 (m, 1 H), 3.81 (m, 1 H), 3.60 (d, J = 10.9 Hz, 6 H), 3.44 (m, 2 H), 1.89 (m, 6 H); ^{13}C NMR (DMSO, 75 MHz, 383 K) δ 153.6, 136.9, 127.6, 127.0, 126.8, 65.2, 61.9, 59.9, 53.0, 50.9, 29.5 (d, J = 138.0 Hz), 29.0, 25.2; CIMS ($M^+ + 1/z$) 358, 326, 250, 115, 91; HRMS exact mass calcd for $C_{16}H_{24}NO_6P$ 357.1341, found 357.1341. Anal. Calcd for $C_{16}H_{24}NO_6P$: C, 53.78; H, 6.77; N, 3.92. Found: C, 53.43; H, 6.84; N, 3.86.

Preparation of Glutarate 38. To a solution of phosphonate **36** (0.120 g, 0.34 mmol) in dry CH_2Cl_2 (4 mL) at rt under argon were added triethylamine (0.10 mL, 10.4 mmol) and glutaric anhydride (0.165 g, 1.35 mmol). The reaction mixture was stirred for 3 d, the solvents were removed *in vacuo*, and the residue was acidified with 1% HCl. The product was purified by column chromatography, eluting with CH_2Cl_2/methanol (20/1), to afford 0.130 g (82%) of glutarate **38** as a yellow oil: $[\alpha]^{23}_D$ −2.5° (*c* 0.01, MeOH); ^{31}P NMR (acetone, 360 MHz) δ 32.1; ^{1}H NMR (DMSO, 300 MHz, 345 K) δ 7.35 (m, 5 H), 5.10 (s, 2 H), 4.10 (m, 4 H), 3.60 (d, J = 10.9 Hz, 6 H), 2.33 (t, J = 7.4 Hz, 2 H), 2.24 (t, J = 7.4 Hz, 2 H), 1.80 (m, 8 H); ^{13}C NMR (DMSO, 75 MHz, 383 K) δ 172.7, 171.5, 153.7, 136.2, 127.5, 126.9, 126.7, 65.7, 64.0, 56.5, 56.4, 53.7, 53.3, 51.0, 32.3, 28.4 (d, J = 149.0 Hz), 25.8, 19.4; MS (FAB$^-$, glycerol) m/z 471, 456, 379, 358, 342, 336, 293, 265, 190, 145, 131.

Preparation of Phosphonic Acid 39. To glutarate **38** (0.098 g, 0.208 mmol) under argon was added dry *tert*-butylamine (5 mL). The reaction mixture was stirred at 50 °C for 7 d. The solvents were removed *in vacuo*, and the residue was acidified by ion exchange chromatography (Dowex 50X-8), eluting with H_2O, to give 0.075 g of crude product. This material was purified by reverse phase HPLC (Partisil 10 ODS, 10 μm × 50 cm) with a linear gradient of 0.1% TFA in H_2O/CH_3CN (80−50% over 30 min) to give 0.045 g (47%) of phosphonic acid **39** as a pale yellow oil: $[\alpha]^{23}_D$ −2.3° (*c* 0.01, MeOH); ^{31}P NMR (DMSO, 360 MHz) δ 23.2, 26.9; ^{1}H NMR

(DMSO, 300 MHz, 345 K) δ 7.35 (m, 5 H), 5.10 (s, 2 H), 4.08 (m, 4 H), 3.53 (d, J = 10.9 Hz, 3 H), 2.32 (t, J = 7.2 Hz, 2 H), 2.24 (t, J = 7.3 Hz, 2 H), 1.80 (m, 8 H); ^{13}C NMR (DMSO, 75 MHz, 385 K) δ 171.9, 171.4, 153.7, 136.3, 127.5, 126.9, 126.8, 65.6, 64.0, 61.9, 56.4, 54.1, 50.4, 48.0, 31.3 (d, J = 136.2 Hz), 29.0, 25.8, 19.3; MS (FAB$^-$, glycerol) m/z 456, 442, 362, 342, 324, 310, 234, 208, 190, 176, 145, 131.

Preparation of Acid Ester 40. To succinic anhydride (0.50 g, 5.0 mmol) in dry CH_2Cl_2 (10 mL) at rt under argon were added triethylamine (0.70 mL, 5.0 mmol) and (trimethylsilyl)ethanol (0.75 mL, 5.2 mmol). The reaction mixture was stirred at rt for 24 h, the solvents were removed *in vacuo*, and the residue was purified by flash chromatography, eluting with ethyl acetate, to afford 0.78 g (72%) of acid ester **40** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.92 (bs, 1 H), 4.12 (t, J = 8.5 Hz, 2 H), 2.54 (m, 4 H), 0.90 (t, J = 8.5 Hz, 2 H), −0.05 (s, 9 H).

Preparation of Phosphonate 42. To acid ester **40** (0.15 g, 0.69 mmol) in dry toluene (5 mL) under argon were added triethylamine (0.10 mL, 0.72 mmol), DPPA (0.15 mL, 0.70 mmol), and alcohol **36** (0.083 g, 0.23 mmol) in toluene (2 mL). The reaction mixture was stirred at 80 °C for 24 h. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. This solution was washed with dilute NaOH, dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography, eluting with ethyl acetate, to give 0.103 g of crude product as a yellow oil. This material was further purified by HPLC using ethyl acetate as an eluant to give 0.051 g (38%) of phosphonate **42** as a yellow oil: $[\alpha]^{23}_D$ −3.4 (*c* 0.01, MeOH); IR (neat) 3270, 2945, 1726, 1696 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz, 345 K) δ 7.35 (m, 5 H), 6.84 (bs, 1 H), 5.10 (s, 2 H), 4.13 (t, J = 8.2 Hz, 2 H), 4.05 (m, 4 H), 3.59 (d, J = 10.8 Hz, 6 H), 3.24 (t, J = 7.0 Hz, 2 H), 2.42 (t, J = 7.0 Hz, 2 H), 1.91 (m, 6 H), 0.95 (t, J = 8.2 Hz, 2 H), 0.03 (s, 9 H); ^{13}C NMR (DMSO, 75 MHz, 385 K) δ 170.3, 155.2, 153.7, 136.3, 127.7, 126.9, 126.7, 65.6, 63.9, 61.1, 56.9, 53.7, 53.1, 50.9, 36.1, 33.9, 29.2, 26.6 (d, J = 130.8 Hz), 16.4, −2.2; MS (FAB$^-$, glycerol) m/z 571, 557, 463, 437, 423, 364, 342, 291, 248, 232, 208, 176, 131.

Preparation of Phosphonic Acid 43. To phosphonate **42** (0.051 g, 0.089 mmol) under argon was added dry *tert*-butylamine (5 mL). The reaction mixture was stirred at 50 °C for 7 d. The solvents were removed *in vacuo*, and the residue was purified by ion exchange chromatography (Dowex 50X-8), eluting with H_2O, to give 0.043 g of a brown oil. This material was dissolved in dry THF (5 mL) under argon, and TBAF (0.1 mL, 0.10 mmol) was added. The reaction mixture was stirred at rt for 2 h. The solvents were removed *in vacuo*, and the residue was acidified by ion exchange chromatography (Dowex 50X-8), eluting with H_2O, to give 0.035 g of crude product. This compound was purified by reverse phase HPLC (Partisil 10 ODS, 10 μm × 50 cm) with a linear gradient of 0.1% TFA in H_2O/CH_3CN (80−50% over 30 min) to give 0.020 g (57%) of phosphonic acid **43** as a pale yellow oil: $[\alpha]^{23}_D$ −13.4° (*c* 0.005, MeOH); ^{31}P NMR (DMSO, 360 MHz) δ 27.3, 27.0; ^{1}H NMR (DMSO, 300 MHz, 345 K) δ 7.35 (m, 5 H), 6.80 (bs, 1 H), 5.10 (s, 2 H), 4.02 (m, 4 H), 3.52 (d, J = 10.9 Hz, 3 H), 3.19 (m, 2 H), 2.38 (t, J = 7.0 Hz, 2 H), 1.87 (m, 6 H); ^{13}C NMR (DMSO, 75 MHz, 385 K) δ 171.6, 155.3, 153.7, 136.5, 127.6, 126.4, 65.5, 64.0, 56.7, 56.5, 53.9, 48.0, 36.2, 33.8, 29.0, 26.8 (d, J = 136.4 Hz); MS (FAB$^-$, glycerol) m/z 457, 443, 342, 323, 310, 234, 220, 208, 190, 176, 162, 135.

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Supporting Information Available: NMR spectra of new compounds (23 pages). This material is contained in 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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