# Ready Access to Fluorinated Phosphonate Mimics of Secondary Phosphates. Synthesis of the (α,α-Difluoroalkyl)phosphonate Analogues of L-Phosphoserine, L-Phosphoallothreonine, and L-Phosphothreonine

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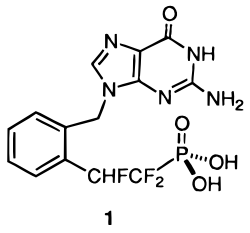
In addition to the previously recorded reactions of diethyl lithio(difluoromethyl)phosphonate (**8**) with primary triflates and aldehydes, we report here that **8** reacts with functionalized, but unactivated, methyl esters to give efficient acyl substitution. Thus, **8** reacts cleanly (−78 °C, THF) with the following methyl esters (product, yield): methyl (*S*)-isopropylideneglycerate (**14**, 99%), methyl (*S*)-3-*O*-(*tert*-butyldimethylsilyl)-2 -*O*-tetrahydropyranylglycerate (**16**, 85%), and the Garner ester derived from D-serine (**15**, 77%). Expeditious treatment of the resultant α,α-difluoro-*β*-keto phosphonates with hydride or Grignard reagents followed by alcohol deoxygenation provides a general method for the synthesis of (α,α-difluoroalkyl)phosphonate analogues of secondary phosphates. For tertiary alcohols, Dolan−MacMillan deoxygenation conditions are employed. The requisite methyl oxalate esters are obtained by an improved procedure wherein the lithium alkoxide of the hindered tertiary alcohol is irreversibly generated at low temperature and then condensed with methyl oxalyl chloride. Relative stereochemistry is assigned via conversion of the Garner ester derived Boc-amino alcohols to the corresponding cyclic, six-membered phosphonate esters and examination of their $^1$H NMR spectra. The relevant vicinal coupling constants are extracted from these spectra by performing double quantum-filtered phase-sensitive COSY experiments. This new (difluoromethylene)phosphonate anion−methyl ester condensation, Grignard (hydride) addition, deoxygenation sequence has been applied to the synthesis of (α,α-difluoroalkyl)phosphonate analogues of L-phosphoserine (≥96% ee) and L-phosphoallothreonine (93% ee) from D-serine and of L-phosphothreonine (91% ee) from L-glycerate, respectively.

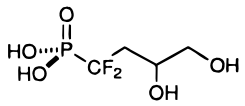
## Introduction

The postulate that (α,α-difluoroalkyl)phosphonates are especially effective, hydrolytically stable mimics of the corresponding phosphate esters, put forward largely by Blackburn,[1] has gained notable experimental support in recent years. For example, Danzin and co-workers noted the superiority of an α,α-difluorinated phosphonate bisubstrate analogue inhibitor of purine nucleoside phosphorylase (PNP) over the corresponding nonfluorinated phosphonate.[2] Recently, these workers have reported several related, second-generation PNP inhibitors, among which **1** is particularly effective, displaying $K_i \approx 1$ nM, ranking this compound among the best PNP inhibitors known.[3]

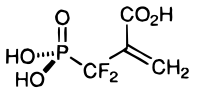
The (α,α-difluoroalkyl)phosphonate analogues of glycerol 3-phosphate, **2**, and of phosphoenolpyruvate, **3**, bind to glycerol 3-phosphate dehydrogenase (alternative substrate)[4] and EPSP synthase (irreversible inhibitor),[5] respectively. Syntheses of the (α,α-difluoroalkyl)phosphonate analogues of ribonucleoside monophosphates,[6a,b] AZT-triphosphate,[6c] phosphatidylinositol,[7] and phosphatidylcholine[8] have also appeared. Perhaps, most impressively, Burke and co-workers have shown that a hexapeptide containing difluorinated phosphotyrosine analog **4b**[9] inhibits protein phosphotyrosine phosphatase 1B with $K_i$ = 100 nM.[10] The otherwise identical peptide containing the nonfluorinated phosphotyrosine analogue **4a** in place of **4b** exhibits a 1000-fold higher $K_i$, attesting to the remarkable potential of (α,α-difluoroalkyl)phosphonates for such applications.




**1**




**2**




**3**

The protein phosphoserine/threonine phosphatases (PP1−PP2C) constitute another important class of phos-

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1996.

(1) (a) Blackburn, G. M.; Brown, D.; Martin, S. J.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 181−186. (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913−917. (c) Blackburn, G. M.; Brown, D.; Martin, S. J. *J. Chem. Res., Synop.* **1985**, 92−93.

(2) Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991**, *113*, 315−317.

(3) Halazy, S.; Ehrhard, A.; Eggenspiller, A.; Berges-Gross, V.; Danzin, C. *Tetrahedron* **1996**, *51*, 177−184.

(4) Chambers, R. D.; Jaouhari, R.; O'Hagan, D. *J. Chem. Soc., Chem. Commun.* **1988**, 1169−1170.

(5) Phillion, D. P.; Cleary, D. G. *J. Org. Chem.* **1992**, *57*, 2763−2764.

(6) (a) Matulic-Adamic, J.; Haeberli, P.; Usman, N. *J. Org. Chem.* **1995**, *60*, 2563−2569. (b) Matulic-Adamic, J.; Usman, N. *Tetrahedron Lett.* **1994**, *35*, 3227−3230. (c) Hebel, D.; Kirk, K. L.; Kinjo, J.; Kovacs, T.; Lesiak, K.; Balzarini, J.; DeClercq, E.; Torrence, P. F. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 357−360.

(7) Vinod, T. K.; Griffith, O. H.; Keana, J. F. W. *Tetrahedron Lett.* **1994**, *35*, 7193−7196.

(8) Martin, S.-F.; Wong, Y.-L.; Wagman, A. S. *J. Org. Chem.* **1994**, *59*, 4821−4831.

(9) For syntheses of **4b**, see: (a) Solas, D.; Hale, R. L.; Patel, D. V. *J. Org. Chem.* **1996**, *61*, 1537−1539. (b) Smyth, M. S.; Burke, T. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 551−554. (c) Burke, T. R., Jr.; Smyth, M. S.; Otaka, A.; Roller, P. P. *Tetrahedron Lett.* **1993**, *34*, 4125−4128. (d) Wrobel, J.; Dietrich, A. *Tetrahedron Lett.* **1993**, *34*, 3543−3546.

(10) Burke, T. R., Jr.; Kole, H. K.; Roller, P. P. *Biochem. Biophys. Res. Commun.* **1994**, *204*, 129−134.

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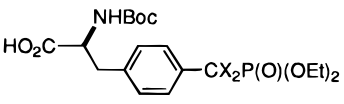
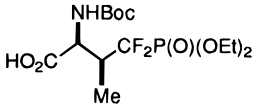
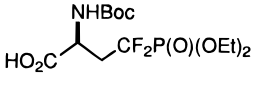
phoprotein phosphatases with a significant, albeit incompletely understood, role in cellular signal transduction.[11] These enzymes will accept relatively short phosphopeptides as surrogate substrates in addition to their usual phosphoprotein substrates. Interestingly, these phosphatases typically display a pronounced preference for L-phosphothreonine-containing peptides relative to L-phosphoserine-containing peptides.[12] Indeed, this property has been used to distinguish PP activity from alkaline or acid phosphatase activity, for which an L-phosphoserine cleavage site preference is observed.[12a] The propensity for PP's to cleave at phosphothreonine is somewhat surprising, considering that the structural perturbation involved in going from phosphoserine to phosphothreonine—introduction of a $C_3$-methyl group in place of a $C_3$-hydrogen—is potentially sterically encumbering, at least insofar as phosphate hydrolysis is concerned. This raises the issue as to how the stereochemistry of the introduced $C_3$-methyl group influences binding to PP-active sites.[13] We, therefore, chose to target suitably protected (α,α-difluoromethyl)phosphonate analogues of L-phosphoserine (**5**),[14] L-phosphoallothreonine (**6**), and L-phosphothreonine (**7**).[15] These unnatural amino acids would, in principle, provide a set of building blocks, with which one could study the effects of sterics and stereochemistry, in addition to peptide sequence, upon binding to the targeted phosphoamino acid binding site for a given PP.



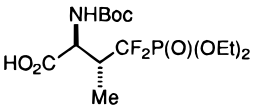

**4a**: X = H; **4b**: X = F




**6**



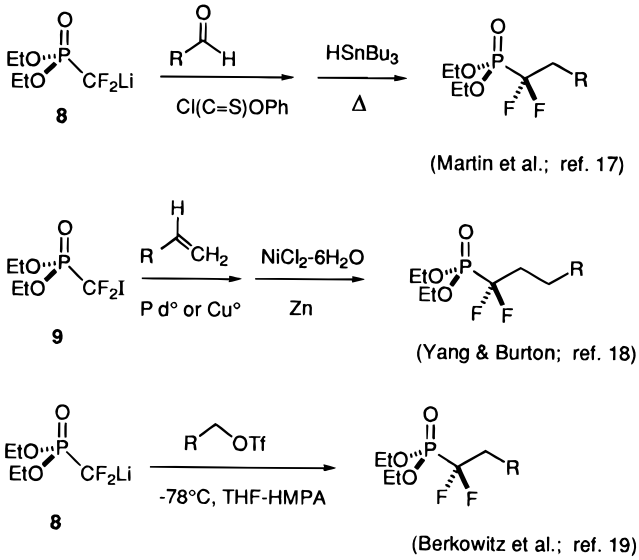

**5**




**7**

Most convergent synthetic approaches to (α,α-difluoroalkyl)phosphonates involve construction of the $PCF_2$–C bond (Scheme 1) as the requisite dialkyl difluoromethylphosphonates (i.e., the intact P–$CF_2$ bond) are readily available via the reaction of a sodium dialkyl phosphite upon chlorodifluoromethane.[16] Thus, Martin and coworkers reported a convenient procedure whereby diethyl lithio(difluoromethyl)phosphonate is condensed with an aldehyde and the resultant lithium alkoxide is trapped with phenyl thionochloroformate.[17] Subsequent Barton deoxygenation delivers the desired (α,α-difluoromethylene)phosphonates. Burton described an elegant $Pd^0$- or $Cu^0$-mediated addition of **9** to alkenes, wherein the alkene serves as solvent.[18] Reductive deiodination then provides the fluorinated phosphonates. We described an efficient direct displacement approach to this class of compounds, in which primary triflates are subjected to nucleophilic attack by anion **8** at −78 °C in THF–HMPA.[19] This method obviates the need for dehalogenation or deoxygenation.

**Scheme 1. $PCF_2$–C Bond Formation: Access to Analogues of Primary Phosphates**




## Results and Discussion

The triflate displacement methodology was recently applied to the synthesis of (α,α-difluoroalkyl)phosphonate analogues of ribonucleoside monophosphates,[6a] phosphatidylinositol,[7] and L-phosphoserine (**5**). For **5**, two such routes were developed, emanating from D-serine and (*R*)-isopropylideneglycerol, respectively.[14a] The latter sequence (Scheme 2) proved to be the more efficient, and we provide complete details of that synthetic procedure herein. Conveniently, (*R*)-isopropylideneglycerol is available commercially or may be obtained in bulk quantities from ascorbic acid[20] or glycerol itself.[21]

As previously noted, the principal limitation of the triflate displacement procedure is that it applies only to primary triflates.[19] Secondary triflates are apparently

(11) (a) Hunter, T. *Cell* **1995**, *80*, 225–236. (b) Cohen, P. *BioEssays* **1994**, *16* (8), 583–588. (c) Krebs, E. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1122–1129. (d) Fischer, E. H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1130–1137. (e) Cohen, P. *TIBS* **1992**, *17*, 408–413. (f) Cohen, P. *Annu. Rev. Biochem.* **1989**, *58*, 453–508. (g) Cohen, P.; Cohen, P. T. W. *J. Biol. Chem.* **1989**, *264*, 21435–21438.

(12) (a) Donella-Deana, A.; Meyer, H. E.; Pinna, L. A. *Biochim. Biophys. Acta* **1991**, *1094*, 130–133. (b) Donella-Deana, A.; MacGowan, C. H.; Cohen, P.; Marchiori, F.; Meyer, H. E.; Pinna, L. A. *Biochim. Biophys. Acta* **1990**, *1051*, 199–202. (c) Agostinis, P.; Goris, J.; Pinna, L. A.; Marchiori, F.; Perich, J. W.; Meyer, H. E.; Merlevede, W. *Eur. J. Biochem.* **1990**, *189*, 235–241.

(13) To our knowledge, no data are available on the effectiveness of L-phosphoallothreonine-containing peptides as substrates. However, the technology now appears to be in place to probe this question more readily: Fischer, P. M.; Sandosham, J. *Tetrahedron Lett.* **1995**, *36*, 5409–5412.

(14) For previously reported syntheses of **5**, see: (a) Berkowitz, D. B.; Shen, Q.; Maeng, J.-H. *Tetrahedron Lett.* **1994**, *35*, 6445–6448. (b) Otaka, A.; Miyoshi K.; Burke, T. R., Jr.; Roller, P. P.; Kubota, H.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **1995**, *36*, 927–930.

(15) For syntheses of the nonhalogenated phosphonate analogues of L-phosphothreonine and L-phosphoallothreonine, see: (a) Ojea, V.; Ruiz, M.; Shapiro, G.; Pombo-Villar, E. *Tetrahedron Lett.* **1994**, *35*, 3273–3276. (b) Ruiz, M.; Ojea, V.; Shapiro, G.; Weber, H.-P.; Pombo-Villar, E. *Tetrahedron Lett.* **1994**, *35*, 4551–4554.

(16) Soborovskii, L. Z.; Baina, N. F. *J. Gen. Chem. U.S.S.R. (Engl.)* **1959** *29*, 1115–1117.

(17) (a) Martin, S. F.; Dean, D. W.; Wagman, A. S. *Tetrahedron Lett.* **1992**, *33*, 1839–1842. (b) Obayashi, M.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2327–2328.

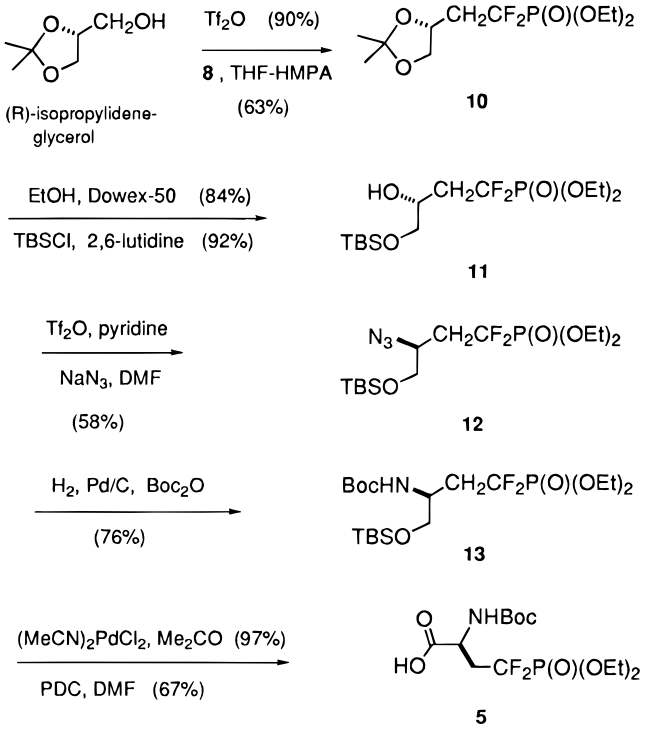
(18) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1992**, *57*, 4676–4683. These workers do report one example of an analogue of a secondary phosphate derived from the addition of diethyl iodo(difluoromethyl)-phosphonate to cyclohexene (69%).

(19) Berkowitz, D. B.; Eggen, M.; Shen, Q.; Sloss, D. G. *J. Org. Chem.* **1993**, *58*, 6174–6176.

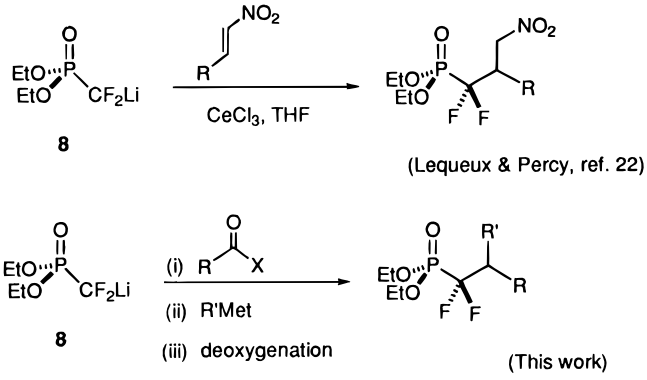
(20) Hubschwerlen, C. *Synthesis* **1986**, 962–964.

(21) (a) Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1994**, *5*, 5–8. (b) Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127–3129.

**Scheme 2. Triflate Displacement Approach to 5**




**Scheme 3. $PCF_2$–C Bond Formation: Access to Analogues of Secondary Phosphates**

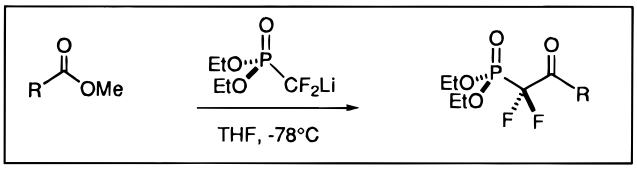


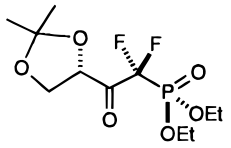
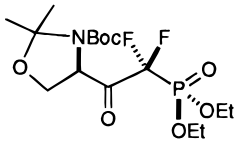
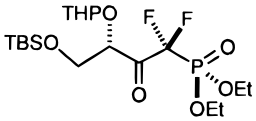

too hindered to undergo backside displacement with **8**. Indeed, in general, there is a dearth of methodology available for the synthesis of (α,α-difluoroalkyl)phosphonate analogues of secondary phosphates. The only somewhat general such method of which we are aware is due to Lequeux and Percy, who recently reported that anion **8** undergoes conjugate addition to (*E*)-nitroalkenes in fair to good yields, in the presence of $Ce^{III}$ (Scheme 3).[22]

We envisioned an alternative procedure, potentially more structurally flexible, in which anion **8** would add to a carbonyl group at the carboxylic acid oxidation state to produce a β-keto(α,α-difluoromethylene)phosphonate. Interception of this electrophilic intermediate with an alkylmetal species carrying the appropriate R′ group, followed by deoxygenation, would then provide the desired secondary phosphate analogue (Scheme 3). The reduction of this scheme to practice requires: (i) a readily available carboxyl equivalent that can be condensed with **8**; (ii) an alkylmetal which chemoselectively adds to the keto functionality over the phosphonate functionality in

(22) Lequeux, T. P.; Percy, J. M. *Synlett* **1995**, 361–362.

**Scheme 4**




| | Product | Yield |
|---|---|---|
| **14** |  | 99% |
| **15** |  | 77% |
| **16** |  | 85% |

β-keto(α,α-difluoromethylene)phosphonates; and (iii) a method for the deoxygenation of hindered tertiary alcohol intermediates, which is compatible with the presence of electrophilic phosphonate functionality.

It has been established that dialkyl lithio(difluoromethylene)phosphonates such as **8** are thermally unstable[23] and that at low temperatures they rather inefficiently displace alkyl halides.[2,8,24] On the other hand, at −78 °C, **8** readily adds to *aldehydic* carbonyls and displaces primary triflates. Encouraged by the report of Phillion and Cleary that **8** does add to an α-keto ester carbonyl,[5] we set out to examine the reactivity of **8** toward less electrophilic ester carbonyls.

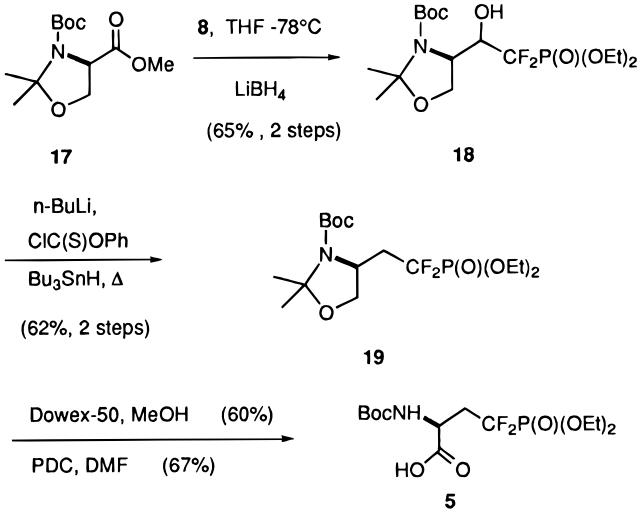
*We are pleased to report that **8** reacts cleanly (−78 °C, THF) with functionalized, but unactivated, methyl esters to give the corresponding β-keto(α,α-difluoromethylene)-phosphonates (Scheme 4) in very good yield.* Condensations were performed upon protected methyl esters derived from D-serine and L-glycerate as potential chiral pool precursors to the analogues of L-phosphoallothreonine (**6**) and L-phosphothreonine (**7**). To our knowledge, these are the only reported condensations of **8** with simple carboxylate esters.[5] From the yields obtained, it appears that anion **8** is, in general, quite reactive toward even modest carbonyl electrophiles (i.e., methyl esters, in addition to the aldehyde electrophiles studied by others). This observation is likely to prove useful for the synthesis of other densely functionalized (α,α-difluoromethylene)phosphonates in the future. For our purposes here, condensation of **8** with the D-serine-derived Garner ester[25] provided **15**, a potential precursor to all three targeted phosphoamino acid analogues **5**–**7**.

Low-temperature reduction of β-keto(α,α-difluoromethylene)phosphonate **15** with $LiBH_4$ proceeded chemoselectively to deliver the corresponding diastereomeric alcohols **18** (Scheme 5) previously reported by

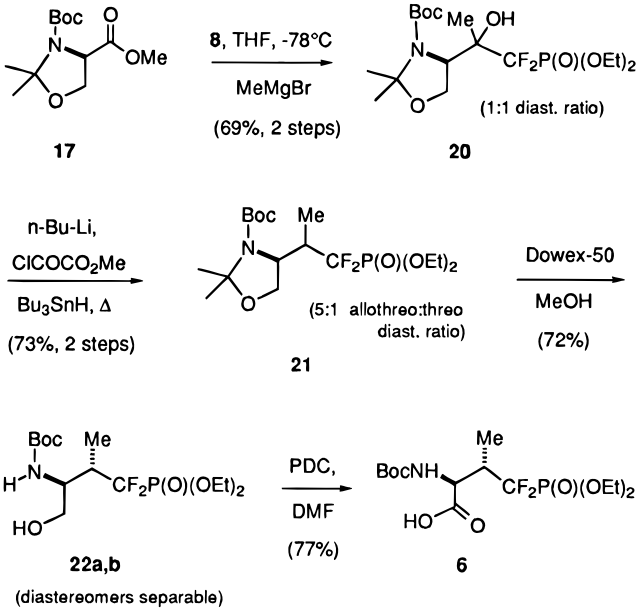
(23) Burton, D. J.; Sprague, *J. Org. Chem.* **1989**, *54*, 613–617 and references therein.

(24) Kim, C.-U.; Luh, B. Y.; Misco, P. F.; Bronson, J. J.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem.* **1990**, *33*, 1207–1213.

**Scheme 5**




**Scheme 6**



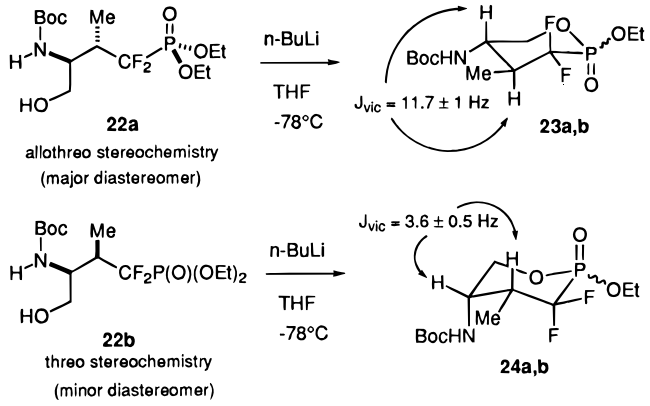

Burke and co-workers.[14b] The remainder of the sequence leading to L-phosphoserine analogue **5** proceeds smoothly and is similar to that reported by the Burke group.

Alternatively, ketone **15** may be converted to the L-phosphoallothreonine analogue **6** by condensation with methylmagnesium bromide in place of hydride reduction (Scheme 6). The diastereomeric tertiary alcohols (**20**) thereby obtained are deoxygenated by a modification of the Dolan−MacMillan procedure.[26] Initial attempts to synthesize the requisite methyl oxalate esters from **20** under the reported conditions, using methyl oxalyl chloride and DMAP in pyridine, showed essentially no reaction at rt to 50 °C and extensive decomposition at higher temperatures. On the other hand, when **20** is deprotonated irreversibly with 1 equiv of *n*-BuLi at −78 °C and then condensed with methyl oxalyl chloride, the corresponding methyl oxalate esters are cleanly obtained. The subsequent deoxygenation step with $Bu_3SnH$ proceeds with considerable diastereoselectivity to provide

(25) Garner, P.; Park, J. M. *Org. Syn.* **1991**, *70*, 18−28. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364.

(26) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588−1589.

**Scheme 7. Determination of the Relative Stereochemistry**



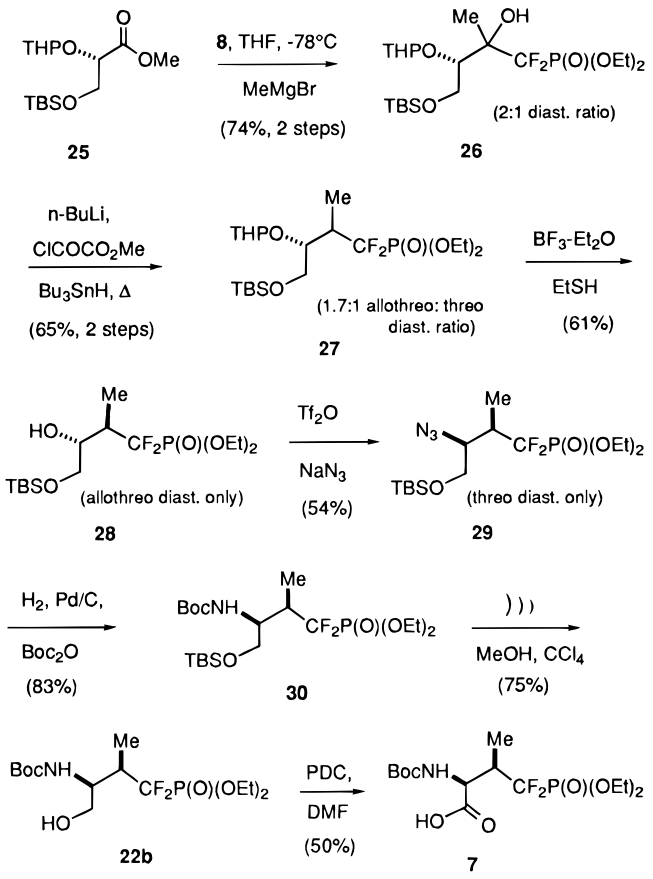

predominantly (allothreo:threo = 5:1) the protected L-allothreoninol−phosphate analogue **21**. Dowex 50-mediated *N*,*O*-acetal cleavage, followed by four-electron Corey−Schmidt oxidation[27] yields the desired Boc-protected analogue of L-phosphoallothreonine, **6**. Separation of the allothreo and threo diastereomers is readily achieved via standard silica gel chromatography at the stage of the Boc-protected alcohols **22a**,**b**. Thus, quite conveniently, both **5** (≥96% ee) and **6** (93% ee) are available from Garner ester **17** via six-step routes that diverge following the initial ester condensation with difluorinated phosphonate anion **8**.

To establish the relative stereochemistry in **22a** and **22b**, these δ-hydroxy phosphonates may be transformed into the corresponding cyclic, six-membered phosphonate esters **23a**,**b** and **24a**,**b**, respectively, through the agency of *n*-BuLi in THF. The hydroxy phosphonates **22a** and **22b** each yield a pair of diastereomeric cyclic phosphonates, **23a**,**b** and **24a**,**b**, respectively, as the cyclization produces a new stereogenic center at phosphorus. The relevant vicinal coupling constants, buried in the one-dimensional $^1H$ NMR, are extracted from the appropriate cross-peaks in the spectra obtained from double quantum-filtered phase sensitive COSY experiments. For **23**, the relevant vicinal coupling constant is approximately 12 Hz, indicating a trans, diaxial relationship between the relevant vicinal protons (Scheme 7). This corresponds to allothreo stereochemistry. For **24**, the analogous vicinal coupling constant is about 4 Hz, corresponding to a cis, axial−equatorial relationship and, hence, to threo stereochemistry.

Given the 5:1 allothreo diastereoselection observed starting from Garner's ester, it was also of interest to pursue a threo-selective synthesis. One strategy that does provide exclusively the L-phosphothreonine analogue, though in perceptibly reduced overall efficiency, is outlined in Scheme 8. Emanating from the differentially protected L-glycerate derivative **25**, the usual (difluoromethylene)phosphonate condensation, methyl-Grignard addition sequence yields tertiary alcohol **26** as a mixture of diastereomers. Deoxygenation under the modified Dolan−MacMillan conditions employed for **20** produces **27** as a 1.7:1 mixture, favoring the allothreo diastereomer. Thus, the tertiary radicals derived from **20** and **27** exhibit the same (allothreo) sense of diastereoselection upon hydrogen atom abstraction from $Bu_3SnH$; however, the cyclic system (derived from **20**) displays markedly greater diastereoselection.

(27) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399−402.

**Scheme 8**




Perhaps, most interestingly in this sequence, a very modest diastereoselectivity is greatly enhanced upon THP-ether deprotection. Thus, subjection of diastereomers **27** (four total diastereomers, owing to the stereogenic center in the THP group) to the THP deprotection conditions of Nambiar and Mitra[28] provides only allothreo alcohol **28**.[29] The subsequent end-game then parallels that employed in our original synthesis of the L-phosphoserine analogue **5**.[14a] The secondary alcohol **28** is inverted via triflation and displacement with azide ion to introduce the amino group with the desired L-threo stereochemistry. Catalytic hydrogenation in the presence of $Boc_2O$ then proceeds smoothly to give **30**. Deprotection of the TBS-ether is achieved under the mild sonication conditions recently described by Lee and co-workers.[30] Corey−Schmidt oxidation then yields the Boc-protected L-phosphothreonine analogue **7**.

In summary, we describe a new reaction of the (α,α-difluoromethylene)phosphonate anion, **8**, namely its condensation with methyl esters. This bond construction is efficient and, when followed by Grignard addition and modified Dolan−MacMillan deoxygenation, constitutes a flexible route to α,α-difluorinated phosphonate analogues of secondary phosphates. It is important to note that the intermediate *β*-keto(α,α-difluoromethylene)phosphonates (e.g., **14**−**16**) are prone to racemization. Thus, prolonged storage or exposure of these ketones to silica gel chromatography may lead to marked erosion of optical purity (e.g., 85% ee was observed in one multigram-scale synthesis of **6**). However, racemization can be minimized (91−98% ee's are achievable) by subjecting the crude ketones to hydride reduction or Grignard addition (Schemes 5, 6, and 8) immediately following workup of the (difluoromethylene)phosphonate anion−methyl ester condensation reaction. In this way, the (α,α-difluoroalkyl)phosphonate analogues of L-phosphoallothreonine and of L-phosphothreonine have been synthesized for the first time, and in forms appropriate for solid phase peptide synthesis, from D-serine and L-glycerate, respectively.

## Experimental Section

**General Procedures.** All general experimental procedures were as described previously.[31] *n*-Butyllithium in hexanes was purchased from Aldrich and titrated before use.[32] 2D-DQF-COSY data were acquired on the GE-Omega 500 NMR instrument operating at 500.1 MHz for proton observation. The data were acquired as 2K × 2K hypercomplex points and zero-filled to 4K × 4K points, yielding a digital resolution of 0.5 Hz/point in both dimensions.

**Synthesis of L-Phosphoserine Analogue 5 via Triflate Displacement. (*S*)-2,3-*O*-Isopropylidene-1-*O*-(trifluoromethanesulfonyl)glycerol (31).** To a solution of (*R*)-isopropylideneglycerol (1.25 g, 9.46 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.94 g, 9.46 mmol) in $CH_2C1_2$ (30 mL) at −40 °C was added $Tf_2O$ (1.75 mL, 10.4 mmol), dropwise via syringe. After 30 min at −40 °C $NaHCO_3$ (aqueous, 50 mL) was added. Following extractive workup with $CH_2C1_2$ (3 × 30 mL), the organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5−30% $Et_2O$−hexanes) provided primary triflate **31** (2.25 g, 90%) as a colorless oil, displaying a $^1H$ NMR spectrum corresponding to that reported in the literature.[33]

**Diethyl [(*R*)-1,1-Difluoro-3,4-(*O*-isopropylidene)-3,4-dihydroxybutyl]phosphonate (10).** To a deoxygenated solution of diisopropylamine (2.38 mL, 17.0 mmol) and HMPA (2.96 mL, 17.0 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (10.6 mL, 1.6 M solution in hexanes). After 25 min at 0 °C, the LDA solution thereby obtained was cooled to −78 °C. To this solution was added **8** (2.67 mL, 17.0 mmol) in THF (8 mL) at −78 °C dropwise via cannula. After 30 min, **33** (2.24 g, 8.48 mmol) in deoxygenated THF (7 mL) was added at −78 °C via cannula. After 15 min, the reaction was quenched with $NH_4Cl$ (aqueous, 30 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Silica gel chromatography (25% EtOAc−hexanes) yielded **10** as a colorless oil (1.61 g, 63%) and with spectral characteristics identical to those already described.[8]

**Diethyl [(*R*)-1,1-Difluoro-3,4-dihydroxybutyl]phosphonate (32).** To a solution of **10** (1.61 g, 5.33 mmol) in EtOH (30 mL) was added Dowex 50 × 8 (6 g, washed with EtOH before use) and the resulting suspension stirred for 24 h at rt. The Dowex resin was filtered and washed with EtOH (2 × 15 mL). The combined filtrates were evaporated and subjected to flash chromatography (50% hexanes−EtOAc → 5% MeOH−EtOAc) to provide **32** (1.18 g, 84%) as a colorless oil with the reported spectral characteristics.[8]

(28) Nambiar, K. P.; Mitra, A. *Tetrahedron. Lett.* **1994**, *35*, 3033−3036.

(29) The threo THP-ethers apparently decompose to, as yet unidentified, polar byproducts. That only the allothreo alcohol **28** was obtained could be confirmed by reprotection of this alcohol (DHP, PPTS, see Experimental Section) to give only two (**27a** and **27d**) of the original four THP ethers.

(30) Lee, A. S.-Y.; Yeh, H.-C.; Tsai, M.-H. *Tetrahedron Lett.* **1995**, *36*, 6891−6894.

(31) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966−6975.

(32) Winkle, M. R.; Lansinger, J. H.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, *26*, 87−88.

(33) Schmidt, R, R.; Reichrath, M.; Moering, U. *J. Carbohydr. Chem.* **1984**, *3*, 67−84.

**Diethyl [(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,1-difluoro-3-hydroxybutyl]phosphonate (11).** To a solution of diol **32** (773 mg, 2.90 mmol) and 2,6-lutidine (676 μL, 5.80 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (497 mg, 3.30 mmol) and stirring continued for 17 h at rt. Following evaporation of the volatiles, $Et_2O$ (25 mL) was added. The resulting off-white precipitate was removed by filtration. The $Et_2O$ was then evaporated on a rotary evaporator and the remaining volatiles were removed by Kugerohr distillation to provide **11** (1.02 g, 92%) as a colorless oil of sufficient purity (as judged by $^1$H NMR) to be used directly for the triflation: $^1$H NMR (360 MHz, $CDC1_3$) $\delta$ 4.32−4.24 (app dquint, $J$ = 3, 7.2 Hz, 4 H), 4.11−4.05 (m, 1 H), 3.59−3.58 (d, $J$ = 5.6 Hz, 2 H), 2.43−2.11 (m, 2 H), 1.40−1.36 (t, $J$ = 7.2 Hz, 6 H), 0.89 (s, 9 H), 0.06 (s, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 66.5, 66.1, 64.8−64.6 (m), 38.9−38.5 (m), 25.8, 18.2, 16.33, 16.29, −5.5.

**Diethyl [(*S*)-3-Azido-4-[(*tert*-butyldimethylsilyl)oxy]-1,1-difluorobutyl]phosphonate (12).** To a solution of alcohol **11** (352 mg, 945 μmol) and pyridine (115 μL, 1.42 mmol) in $CH_2C1_2$ (15 mL) at −40 °C was added $Tf_2O$ (190 μL, 1.12 mmol) dropwise via syringe. After 45 min, $NaHCO_3$ (aqueous, 15 mL) was added, followed by extraction with $CH_2C1_2$ (2 × 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated. To a solution of the crude triflate in DMF (5 mL) at −40 °C was added sodium azide (307 mg, 4.73 mmol) and the cooling bath removed. After 4 h at rt, water (20 mL) was added, followed by extraction with $Et_2O$ (3 × 30 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by $SiO_2$ chromatography (30% EtOAc−hexanes) yielded **12** (220 mg, 58% over two steps) as an oil: IR (atr) 2104 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.32−4.23 (app dquint, $J$ = l.6, 7.2 Hz, 4 H), 3.803.76 (m, 1 H), 3.76−3.72 (dd, $J$ = 10, 4.4 Hz, 1 H), 3.69−3.64 (dd, $J$ = 6, 10 Hz, 1 H), 2.41−2.12 (m, 2 H), 1.40−1.36 (app t, $J$ = 7.2 Hz, 4 H), 0.90 (s, 9 H), 0.08 (s, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 66.1, 64.7−64.6, 56.8, 35.0−34.5, 25.7, 18.2, 16.4, 16.3, −5.6; HRMS (CI) calcd for $C_{14}H_{30}NO_4F_2SiP$ (M + H)$^+$ 402.1790, obsd 402.1789.

**(*S*)-*O*-(*tert*-Butyldimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)-3-[1′,1′-difluoro(diethylphosphono)methyl]-alaninol (13).** To **12** (789 mg, 1.96 mmol) and $Boc_2O$ (598 mg, 2.73 mmol) in EtOAc (20 mL) was added 10% palladium on carbon (180 mg). Hydrogenation was carried out for 4 h at 40 psi in a Parr hydrogenator. Filtration through Celite, evaporation, and flash chromatography (30% EtOAc−hexanes) provided **13** (710 mg, 76%) as an oil: $^1$H NMR (360 MHz, $CDC1_3$) $\delta$ 4.85−4.83 (br d, $J$ = 7 Hz, 1 H), 4.30−4.22 (app quint, $J$ = 7.2 Hz, 4 H), 4.10−4.02 (br s, 1 H), 3.71−3.67 (dd, $J$ = 3, 10 Hz, 1 H), 3.65−3.61 (dd, $J$ = 4.5, 10 Hz, 1 H), 2.45−2.15 (m, 2 H), 1.43 (s, 9 H), 1.38−1.34 (app t, $J$ = 7.2 Hz, 6 H), 0.88 (s, 9 H), 0.04 (s, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155, 64.8, 64.5, 64.4, 46.8−46.7, 35.1−34.7, 28.4, 25.8, 25.7, 16.4, 16.3, −5.5; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{19}H_{40}NO_6PF_2Li$ (M + Li)$^+$ 482.2491, obsd 482.2484.

**(*S*)-*N*-(*tert*-butyloxycarbonyl)-3-[1′,1′-difluoro(diethylphosphono)methyl]alaninol (33).** A solution of **13** (710 mg, 1.49 mmol) and $PdCl_2(CH_3CN)_2$ (194 mg, 746 μmol) in acetone (150 mL) was stirred overnight at rt.[34] Evaporation of the volatiles and column chromatography (50 → 100% EtOAc−hexanes) yielded **33** (521 mg, 97%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.10−5.04 (br s), 4.32−4.23 (app dquint, $J$ = 3, 7.2 Hz, 4 H), 4.12-3.96 (m, 1 H), 3.73−3.72 (m, 2 H), 2.45−2.33 (m, 2 H), 1.43 (s, 9 H), 1.40−1.36 (app t, $J$ = 7.2 Hz, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.7, 123.2−117.3 (dt, $J$ = 216, 260 Hz), 79.7, 65.0, 64.8, 64.70, 64.66, 47.4, 35.1−34.7 (m), 28.3, 16.31, 16.27; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{13}H_{26}NO_6F_2PLi$ (M + Li)$^+$ 368.1626, obsd 368.1625.

**(*S*)-*N*-(*tert*-Butyloxycarbonyl)-3-[1′,1′-difluoro(diethylphosphono)methyl]alanine (5).** A solution of **33** (521 mg, 1.44 mmol) and PDC (3.23 g, 8.65 mmol) in DMF (4 mL) was stirred overnight at rt. After partitioning between $H_2O$ (60 mL) and EtOAc (60 mL), the organic layer was further extracted with EtOAc (4 × 50 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated, and subjected to $SiO_2$ chromatography (0 → 5% MeOH−EtOAc) to give **5** (362 mg, 67%): $[\alpha]_D$ −10.8° (*c* 2.2, MeOH); $^1$H NMR (360 MHz, $CDC1_3$) $\delta$ 5.45−5.43 (br s, 1 H), 4.58−4.56 (br s, 1 H) 4.33−4.25 (app quint, $J$ = 7.2 Hz, 4 H), 2.75−2.61 (m, 2 H), 1.44 (s, 9 H), 1.40−1.36 (app t, $J$ = 7.2 Hz, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.0, 155.5, 80.5, 65.1, 65.0, 35.4−35.3 (m), 28.3, 16.29, 16.27; HRMS (FAB, 3-NOBA/$Na_2CO_3$) calcd for $C_{13}H_{24}NO_7F_2PNa$ (M + Na)$^+$ 398.1155, obsd 398.1163. Optical Purity. **5** was judged to have ≥98% ee as only one diastereomer was seen in the $^1$H NMR spectrum (500 MHz, $CDCl_3$) of its Mosher amide, obtained via the following sequence: (a) $CH_2N_2$; (b) HCl, EtOAc;[35] (c) (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride,[36] $NEt_3$, DMAP, $CH_2Cl_2$ [see the supporting information for copies of this $^1$H NMR spectrum and of the corresponding reference spectrum obtained using (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.]

**General Procedure A: The (Difluoromethylene)phosphonate Anion−Methyl Ester Condensation Reaction. Diethyl [(3*S*)-1,1-Difluoro-3,4-dihydroxy-3,4-(*O*-isopropylidene)-2-ketobutyl]phosphonate (14).** To diisopropylamine (12.3 mL, 87.4 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (67.2 mL, 1.3 M in hexanes) dropwise via syringe. The resulting solution was allowed to warm to 0 °C for 25 min and then cooled to −78 °C before **8** (13.7 mL, 87.4 mmol) was added in THF (20 mL). After 30 min at −78 °C, methyl (*S*)-2,3-*O*-isopropylideneglycerate (10.0 g, 67.5 mmol) in THF (20 mL) was added, dropwise, via cannula. After 60 min, the reaction was quenched by the addition of HOAc (8.9 mL, 156 mmol), followed by $NH_4Cl$ (saturated aqueous, 200 mL). Following extraction with EtOAc (3 × 200 mL), the combined organics were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (85% hexanes−EtOAc) yielded **14** as a partially hydrated ketone (ketone:hydrate = 2:1). The pure ketone (19.7 g, 99%) was obtained as a colorless oil by azeotroping with dry benzene (3 × 200 mL): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.10−5.05 (dd, $J$ = 5.5, 7.6 Hz, 1 H), 4.32−4.25 (q, $J$ = 7 Hz, 4 H), 4.27−4.22 (dd, $J$ = 7.5, 9 Hz, 1 H), 4.13−4.08 (dd, $J$ = 5, 9 Hz, 1 H), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.38−1.34 (t, $J$ = 7 Hz, 3 H), 1.37−1.33 (t, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 196.0−195.2 (dt, $J$ = 13, 24 Hz), 119.0−109.0 (dt, $J$ = 196, 274 Hz), 111.3, 76.8, 65.4, 65.3, 25.2, 24.9, 15.9; HRMS (FAB, 3-NOBA, NaI) calcd for $C_{11}H_{19}O_6F_2PNa$ (M + Na)$^+$ 339.0785, obsd 339.0798.

**Synthesis of L-Phosphoserine Analogue 5 via Methyl Ester Condensation with 8. Diethyl [(3*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-1,1-difluoro-4-hydroxy-3,4-(*N*,*O*-isopropylidene)-2-ketobutylphosphonate (15).** From Garner ester **17**[25] (9.09 g, 35.1 mmol), following general procedure A, was obtained **15** (11.2 g, 77%) after purification by flash chromatography (10% EtOAc−hexanes) (note that for optimum optical activity material was taken on directly to the next step, following workup, without performing chromatography): $^1$H NMR (360 MHz, $CDCl_3$; *listed NMR peaks are common to both Boc-rotamers unless otherwise stated; rotamers are denoted by major and minor and are present in a 3:2 ratio at rt*) $\delta$ 5.09−5.06 (dd, $J$ = 3, 7.5 Hz, 1 H; *minor*), 5.01−4.98 (d, $J$ = 7 Hz, 1 H; *major*), 4.35−4.30 (app sextet, $J$ = 7 Hz, 4 H), 4.25−4.14 (m, 2 H), 1.67 (s, 3 H; *major*), 1.63 (s, 3 H; *minor*), 1.54 (s, 3 H; *major*), 1.50 (s, 3 H; *minor*), 1.46 (s, 9 H; *minor*), 1.39 (s, 9 H; *major*), 1.45−1.36 (buried, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 164.3, 151.4 (*minor*), 150.6 (*major*), 116.2−110.3 (m), 95.0 (*major*), 94.3 (*minor*), 80.8, 65.5, 64.7 (*major*), 64.3 (*minor*), 61.4 (*minor*), 61.2 (*major*), 28.0 (*minor*), 27.9 (*major*), 25.5 (*minor*), 25.0 (*minor*), 24.7 (*major*), 24.0 (*major*), 16.0. Anal. Calcd for $C_{16}H_{28}NO_7F_2P$: C, 46.25; H, 6.80; N, 3.37. Found: C, 46.06; H, 6.71; N, 3.35.

**Diethyl [(3*R*,2*R*/*S*)-3-[(*tert*-Butyloxycarbonyl)amino]-1,1-difluoro-2,4-dihydroxy-3,4-(*N*,*O*-isopropylidene)butyl]-phosphonate (18).** To a solution of the crude ketone **15**

(34) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708.

(35) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216−3218.

(36) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

obtained from Garner ester **17**[25] (3.79 g, 14.6 mmol) in $Et_2O$ (75 mL) at −78 °C was added $LiBH_4$ (1.75 mL, 3.51 mmol, 2 M in THF) dropwise via syringe. After 3 h at −78 °C, $NH_4Cl$ (aqueous, 50 mL) was added and the ether layer separated in a separatory funnel. Following further extraction of the aqueous layer with $Et_2O$ (4 × 50 mL), the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (30% EtOAc−hexanes) yielded alcohol(s) **18** as a colorless oil (3.97 g, 65% over two steps): $^1$H NMR (500 MHz, $CDC1_3$) $\delta$ 4.95 (br s, 1 H), 4.45 (br s, 1 H), 4.33−4.24 (m, 4 H), 4.28 (br s, 1 H), 4.03−4.01 (app br d, $J$ = 9 Hz, 1 H), 3.97−3.94 (dd, $J$ = 6, 9.7 Hz, 1 H), 1.58 (s, 3 H), 1.50 (s, 3 H), 1.48 (s, 9 H), 1.38−1.34 (app q, $J$ = 7 Hz, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.6, 93.7, 82.0, 73.9 (br), 65.1 (br), 64.6, 64.5, 56.8, 28.3, 27.1, 24.1, 16.34, 16.30. Anal. Calcd for $C_{16}H_{30}O_7NF_2P$: C, 46.02; H, 7.25; N, 3.36. Found: C, 45.90; H, 7.23; N, 3.31.

**Diethyl [(3*R*,2*R*/*S*)-3-[(*tert*-Butyloxycarbonyl)amino]-1,1-difluoro-2,4-dihydroxy-3,4-(*N*,*O*-isopropylidene)-2-(*O*-phenoxythionocarbonyl)butyl]phosphonate (34).** To alcohol(s) **18** (3.96 g, 9.51 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (6.79 mL, 9.51 mmol, 1.4 M in hexanes), followed immediately by phenyl thionochloroformate (1.97 mL, 14.3 mmol). After 15 min, the reaction was quenched with $NaHCO_3$ (aqueous, 25 mL) and extracted with $Et_2O$ (4 × 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10 → 30% EtOAc−hexanes) afforded **34** (4.05 g, 79%): $^1$H NMR (360 MHz, $CDC1_3$) $\delta$ 7.42−7.38 (app t, 2 H, $J$ = 8 Hz), 7.30−7.26 (t, $J$ = 7.5 Hz, 1 H), 7.08−7.06 (d, $J$ = 8 Hz, 1 H), 6.08−6.00 (br m, 1 H), 4.85−4.80 (m, 1 H, *minor*), 4.70−4.66 (m, 1 H, *major*), 4.36−4.28 (app quint, 4 H, $J$ = 7 Hz), 4.20−4.18 (d, $J$ = 9 Hz, 1 H, *minor*), 4.11−4.09 (m, 2 H *major*, 1 H *minor*), 1.65 (s, 3 H), 1.51 (s, 3 H), 1.50 (s, 9 H), 1.43−1.39 (m, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 194.8, 154, 129.6 (2 C), 126.7, 121.8 (2 C), 80.7, 79.3, 66.0, 65.1, 65.0, 54.3, 28.2, 26.5, 22.7, 16.4, 16.3. Anal. Calcd for $C_{23}H_{34}O_8NF_2PS$: C, 49.89; H, 6.19; N, 2.53. Found: C, 49.79; H, 5.98; N, 2.52.

**(*S*)-*N*-(*tert*-Butyloxycarbonyl)-1,2-(*O*,*N*-isopropylidene)-3-[1′,1′-difluoro(diethylphosphono)methyl]alaninol (19).** A solution of thionocarbonate **34** (899 mg, 1.52 mmol), $Bu_3SnH$ (610 $\mu$L, 2.27 mmol), and AIBN (50 mg, 0.30 mmol) in toluene (7.6 mL) was purged with argon. The reaction flask was placed in a preheated oil bath at 60 °C and then heated from 60 to 90 °C over 15 min. After evaporation of the volatiles in vacuo, flash chromatography (10 → 30% $Et_2O$−toluene) yielded **19** as a colorless oil (479 mg, 79%): $^1$H NMR (500 MHz, $CDC1_3$; *listed NMR peaks are common to both Boc-rotamers unless otherwise stated; individual rotamers are denoted as major and minor)* $\delta$ 4.29−4.23 (app quint, $J$ = 7.2 Hz, 4 H), 4.23 (m, buried, 1H), 4.00−3.97 (dd, $J$ = 5, 9 Hz, 1 H), 3.94−3.92 (br m), 2.70−2.58 (m, *minor*), 2.49−2.23 (m, *major*), 1.57 (s, 3 H, *major*), 1.52 (s, 3 H, *minor*), 1.47 (s, 3 H, *major*), 1.46 (s, 12 H), 1.39−1.36 (app t, $J$ = 7 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 151.1, 120 (m), 93.2 *major*, 92.8 *minor*, 80.4 *minor*, 79.9 *major*, 67.6 *major*, 67.2 *minor*, 64.42 *major*, 64.38 *major*, 64.3 (2 C) *minor*, 51.7 *minor*, 51.3 *major*, 37.3−36.9 (m) *major*, 36.1−35.9 (m) *minor*, 28.2, 27.4 *minor*, 26.6 *major*, 24.3, *minor*, 23.0 *major*, 16.2, 16.1. Anal. Calcd for $C_{16}H_{30}O_6NF_2P$: C, 47.86; H, 7.54; N, 3.49. Found: C, 47.97; H, 7.54; N, 3.39.

**(*S*)-*N*-(*tert*-Butyloxycarbonyl)-3-[1′,1′-difluoro(diethylphosphono)methyl]alaninol (33).** A solution of *N*,*O*-acetal **19** (400 mg, 1.00 mmol) and Dowex-50 × 8 (2.00 g) in MeOH (4 mL) was stirred for 14 h at rt. The resin was removed by filtration and washed with MeOH (40 mL). The combined filtrates were evaporated and subjected to silica gel chromatography (50 → 100% EtOAc−hexanes) to provide **33** (215 mg, 60%), with the same spectral characteristics as the compound obtained via the triflate displacement route (vide supra). Optical Purity. **5** obtained via this route was judged to be ≥96% ee from the $^1$H NMR spectrum (500 MHz, $CDCl_3$) of its Mosher amide, obtained via the following sequence: (a) $CH_2N_2$; (b) HCl, EtOAc;[35] (c) (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride,[36] $NEt_3$, DMAP, $CH_2Cl_2$ [see the supporting information for copies of this $^1$H NMR spectrum and of the corresponding reference spectrum obtained using (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride].

**Synthesis of L-Phosphoallothreonine Analogue 6. Diethyl [(2*R*/*S*,3*R*)-3-[(*tert*-butyloxycarbonyl)amino]-1,1-difluoro-2,4-dihydroxy-3,4-(*N*,*O*-isopropylidene)-2-methylbutyl]phosphonate (20).** To a solution of ketone **15** (6.04 g, 14.5 mmol) in $Et_2O$ (150 mL) at −78 °C was added MeMgBr (7.27 mL, 3 M in $Et_2O$, 21.8 mmol). After 3 h at −78 °C and 1 h at 0 °C the reaction was quenched [$NH_4Cl$(aq), 50 mL] and extracted with $Et_2O$ (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (20% EtOAc−hexanes) yielded **20** (5.60 g, 89%) as a 1:1 mixture of diastereomers [the diastereomeric ratio could be determined by conversion of the alcohols to their respective tosylates (1 equiv *n*-BuLi, 1.2 equiv of TsCl, THF, −78 °C) and integration of the tosyl methyl signals in the $^1$H NMR spectrum thereof]: $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.29 (s, 1 H), 4.63−4.61 (d, $J$ = 7 Hz, 1 H), 4.34−4.23 (app dquint, $J$ = 3, 7 Hz, 4 H), 4.13−4.10 (app d, $J$ = 10 Hz, 1 H), 4.01−3.97 (dd, $J$ = 7, 10 Hz, 1 H), 1.61 (s, 3 H), 1.49 (s, 9 H), 1.45 (s, 3 H), 1.40 (s, 3 H), 1.38−1.35 (t, $J$ = 7 Hz, 3 H), 1.37−1.34 (t, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.8, 94.2, 82.4, 77.8 (m), 64.54−64.48 (d, $J$ = 7 Hz), 64.35−64.29 (d, $J$ = 7 Hz), 64.1, 61.0, 28.2, 26.1, 23.8, 16.8, 16.30, 16.27. Anal. Calcd for $C_{17}H_{32}NO_7F_2P$: C, 47.33; H, 7.48; N, 3.25. Found: C, 47.40; H, 7.28; N, 3.29.

**Diethyl [(2*R*/*S*,3*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-1,1-difluoro-2,4-dihydroxy-3,4-(*N*,*O*-isopropylidene)-2-(*O*-methyloxalyl)-2-methylbutyl]phosphonate (35).** To a solution of tertiary alcohol(s) **20** (5.60 g, 13.0 mmol) in THF (130 mL) at −78 °C was added *n*-BuLi (9.26 mL, 13.0 mmol, 1.4 M in hexanes) dropwise via syringe. After 5 min, methyl oxalyl chloride (1.79 mL, 19.5 mmol) was added dropwise via syringe. The reaction mixture was stirred for 40 min at −78 °C and then for 45 min at 0 °C before being quenched with $NaHCO_3$ (aqueous, 60 mL). Following extraction with EtOAc (4 × 50 mL), the combined organics were dried ($MgSO_4$), filtered, and concentrated. The crude product was taken on directly to the next step. If desired, an analytical sample could be obtained by flash chromatography (20 → 40% EtOAc−hexanes): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.18 (br s, 1H), 4.37−4.23 (m, 5H), 4.18−4.15 (d, $J$ = 10 Hz, 1H), 4.00−3.95 (dd, $J$ = 7, 10 Hz, 1 H), 3.82 (s, 3 H), 1.65 (s, 3 H), 1.60 (s, 3 H), 1.47 (s, 3 H), 1.41 (s, 9 H), 1.39−1.33 (app q, $J$ = 7 Hz, 6 H). Anal. Calcd for $C_{20}H_{34}NO_{10}F_2P$: C, 46.42; H, 6.62; N, 2.71. Found: C, 46.69; H, 6.43; N, 2.74.

**Diethyl [(2*R*/*S*,3*S*)-3-[(*tert*-Butyloxycarbonyl)amino]-1,1-difluoro-4-hydroxy-3,4-(*N*,*O*-isopropylidene)-2-methylbutyl]phosphonate (21).** A solution of the crude ester **35**, $Bu_3SnH$ (5.23 mL, 19.5 mmol) and AIBN (2.13 g, 13.0 mmol), in toluene (80 mL) was purged with argon and then refluxed for 4 h. Evaporation and $SiO_2$ chromatography (0 → 10% EtOAc−hexanes) provided **21** (3.95 g, 73%) as a 5:1 mixture of diastereomers (determined by integration of the N*H* in the $^1$H NMR spectrum of **22a**,**b** after Dowex deprotection, vide infra): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.28−4.22 (app quint, $J$ = 7 Hz, 4 H), 3.94−3.87 (br m, 3 H), 2.61−2.42 (m, 1 H), 1.57 (s, 3 H), 1.52 (s, 3 H), 1.46 (s, 9 H), 1.39−1.35 (app t, $J$ = 7 Hz, 6 H), 1.20−1.18 (br d, 7 Hz, 3 H); $^{13}$C NMR (125 MHz, DMSO; *listed NMR peaks are common to both diastereomers unless indicated by major and minor*) $\delta$ 151.5, 124.9−118.8 (m), 92.9, 79.3, 68.5 (*major*), 67.6 (*minor*), 64.3 (d, $J$ = 7 Hz, *major*), 64.2 (d, $J$ = 7 Hz, *major*), 64.1 (d, $J$ = 6 Hz, *minor*), 63.9 (d, $J$ = 6 Hz, *minor*), 55.0 (*major*), 54.3 (*minor*), 41.9- 41.5 (m), 27.9, 27.8, 27.7, 16.6 (2 C, *minor*), 16.10 (*major*), 16.07 (*major*), 10.6; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{17}H_{32}NO_6F_2PLi$ $(M + Li)^+$ 422.2095, obsd 422.2095.

**L-*N*-(*tert*-Butyloxycarbonyl)-3-deoxy-3-[1′,1′-difluoro-(diethylphosphono)methyl]allothreoninol (22a).** To starting *N*,*O*-acetal(s) **21** (4.80 g, 11.6 mmol) in methanol (150 mL) was added Dowex 50 × 8 resin (14 g, rinsed with 50 mL of MeOH before use) and stirring continued at rt for 3 d. The resin was removed by filtration and rinsed with MeOH (2 × 30 mL). The combined filtrates were concentrated and subjected to flash chromatography (40 → 100% EtOAc−hexanes) to give, in the following order: (a) recovered **21** (1.40 g, 29%),

(b) **22b** (337 mg, 8.5%) (see below for spectral characterization), and (c) **22a** (1.85 g, 42.5%) [51% overall isolated yield of **22a,b** as a 5:1 ratio of diasteromers (72% overall yield based upon recovered starting material)]. For **22a**: $[\alpha]_D$ (93% ee) −8.6° (*c* 4.0, EtOAc); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.13−5.11 (d, $J$ = 8.7, 1 H), 4.27−4.17 (app dquint, $J$ = 7 Hz, 4 H), 4.04−4.03 (m, 1 H), 3.68−3.66 (m, 1 H), 3.58−3.56 (m, 1 H), 2.61-2.54 (br m, 1 H), 1.39 (s, 9 H), 1.34−1.30 (app t, $J$ = 7.2 Hz), 1.15−1.13 (d, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.0, 124.9−119.0 (dt, $J$ = 213, 265 Hz), 79.5, 64.7−64.6(d, $J$ = 7 Hz), 64.6−64.5 (d, $J$ = 7 Hz), 63.4, 51.8, 39.0−38.7 (app q, $J$ = 17 Hz), 28.3, 16.3, 16.2, 9.1. Anal. Calcd for $C_{14}H_{28}NO_6F_2P$: C, 44.80; H, 7.52; N, 3.73. Found: C, 44.64; H, 7.36; N, 3.75. Optical Purity. **22a** was judged to be 93% ee from the $^1$H NMR spectrum (500 MHz, $CDCl_3$) of its Mosher ester [(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride,[36] $NEt_3$, DMAP, $CH_2Cl_2$]. [See the supporting information for copies of this $^1$H NMR spectrum and of the corresponding reference spectrum obtained using (±)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.

**L-*N*-(*tert*-Butyloxycarbonyl)-3-deoxy-3-[1′,1′-difluoro-(diethylphosphono)methyl]allothreonine (6).** A solution of **22a** (995 mg, 2.65 mmol) and PDC (4.99 g, 13.3 mmol) in DMF (9 mL) was stirred at rt for 12 h. After $H_2O$ (20 mL) and 1 N HCl (2 mL) were added, the crude reaction mixture was extracted with EtOAc (2 × 50 mL) and $CH_2Cl_2$ (100 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (0 → 10% MeOH−EtOAc) yielded **6** (799 mg, 77%): $[\alpha]_D$ (93% ee) +7.3° (*c* 3.5, EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.90−9.50 (br s, 1H), 5.17−5.14 (d, $J$ = 9 Hz, 1 H), 4.87−4.84 (d, $J$ = 9 Hz, 1 H), 4.32−4.23 (m, 4 H), 3.00−2.83 (m, 1 H), 1.43 (s, 9 H), 1.397−1.350 (t, $J$ = 7 Hz, 3 H), 1.391−1.344 (t, $J$ = 7 Hz, 3 H), 1.19−1.17 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.1, 155.4, 121.8 (dt, $J$ = 213, 265 Hz), 80.1, 65.1−64.9 (m), 52.0, 34.5 (app q, $J$ = 17 Hz), 28.3, 16.30, 16.27, 8.7; HRMS (FAB, 3-NOBA) calcd for $C_{14}H_{27}NO_7F_2P$ $(M + H)^+$ 390.1493, obsd 390.1500.

**Cyclic Phosphonates 23a and 23b.** To **22a** (50 mg, 133 μmol) in THF (1.0 mL) at −78 °C was added *n*-BuLi (38 μL, 53 μmol, 1.4 M in hexanes) dropwise via syringe. After the mixture was stirred at −78 °C for 1 h and then at 0 °C for 1 h, $NH_4Cl$ (aqueous, 2 mL) was added. Following extraction with $Et_2O$ (3 × 2 mL), the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5 → 10% EtOAc−hexanes) yielded **23a** (13 mg) in a first fraction and diastereomer(s) **23b** (12 mg) in a second fraction (50% combined yield).

**23a**: $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.71−4.66 (m, 1H), 4.39−4.31 (app quint, $J$ = 7 Hz, 2 H), 4.31−4.24 (m, 1H), 4.19−4.24 (m, 1 H), 3.96−3.90 (m, 1 H), 2.55−2.44 (m, 1 H), 1.43 (s, 9 H), 1.43−1.39 (t, $J$ = 7 Hz, 3 H), 1.21−1.19 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.0, 80.5, 68.8, 68.7, 66.1, 50.6, 43.7−43.3 (dt, J = 13, 20 Hz), 28.2, 16.4, 16.3, 8.3; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{12}H_{22}NO_5F_2PLi$ $(M + Li)^+$ 336.1364, obsd 336.1360.

**23b**: $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.74−4.71 (br d, $J$ = 7 Hz, 1 H), 4.45−4.37 (m, 1 H), 4.39−4.31 (app quint, $J$ = 7.2 Hz, 2 H), 4.16−4.08 (app q, $J$ = 9 Hz, 1 H), 3.85−3.78 (m, 1 H), 2.57−2.47 (m, 1 H), 1.43 (s, 9 H), 1.42−1.39 (t, $J$ = 7.2 Hz, 3 H), 1.26−1.25 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.8, 80.5, 69.2, 65.23, 65.19, 51.4, 43.6−43.4 (m), 28.3, 16.5, 16.4, 9.4; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{12}H_{22}NO_5F_2PLi$ $(M + Li)^+$ 336.1364, obsd 336.1352.

**Cyclic phosphonates 24a and 24b.** Diastereomer **22b** (28 mg, 75 μmol) was cyclized in an analogous manner [flash chromatography (5% EtOAc−hexanes)] to provide **24a** (10 mg) in a first fraction and **24b** (4 mg) in a second fraction (56% combined yield).

**24a:** $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.09−5.07 (br d, $J$ = 9 Hz, 1 H), 4.39−4.30 (app quint, $J$ = 7 Hz, 2 H), 4.35−4.28 (buried m, 2 H), 4.02−4.00 (app d, $J$ = 9 Hz, 1 H), 2.65−2.53 (m, 1 H), 1.44 (s, 9 H), 1.42−1.39 (t, $J$ = 7 Hz, 3 H), 1.21−1.19 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 80.4, 72.9, 65.3, 51.3, 41.9−41.5 (dt, $J$ = 9, 19 Hz), 28.3, 16.4, 7.8; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{12}H_{22}NO_5F_2PLi$ $(M + Li)^+$ 336.1364, obsd 336.1352.

**24b:** $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.07−5.04 (br d, $J$ = 11 Hz, 1 H), 4.60−4.55 (dd, $J$ = 3, 12 Hz, 1 H), 4.40−4.34 (app quint, $J$ = 7.0 Hz, 2 H), 4.31−4.21 (m, 1 H), 4.06−4.02 (m, 1 H), 2.83−2.73 (m, 1 H), 1.44 (s, 9 H), 1.44−1.41 (t, $J$ = 7 Hz, 3 H), 1.20−1.18 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (500 MHz, $CDCl_3$) $\delta$ 155.0, 80.4, 72.0, 65.8, 51.7, 41.4−41.0 (dt, $J$ = 11, 20 Hz), 16.4, 7.6; HRMS (FAB, 3-NOBA/LiI) calcd for $C_{12}H_{22}NO_5F_2PLi$ $(M + Li)^+$ 336.1364, obsd 336.1365.

A double quantum-filtered phase sensitive 2-D COSY experiment (see the supporting information) revealed a coupling constant $J$ = 11.7 ± 1 Hz between the C*H*$CF_2$, and C*H*NHBoc for **23b**. The analogous experiment performed a mixture of **24a** and **24b** furnished a value of $J$ = 3.6 ± 0.5 Hz for the corresponding vicinal coupling constant in this system. These results demonstrate that **22a** has the allothreo relative stereochemistry, while **22b** has the threo relative stereochemistry (see Scheme 7).

**Synthesis of L-Phosphothreonine Analogue 7. Methyl (*S*)-3-*O*-(*tert*-Butyldimethylsilyl)-2-*O*-[(*R*,*S*)-tetrahydropyranyl]glycerate (25).** To a solution of methyl (*S*)-3-(*O*-*tert*-butyldimethylsilyl)glycerate[37] (11.5 g, 49.5 mmol) in $CH_2Cl_2$ (200 mL) at rt was added 3,4-dihydro-2*H*-pyran (20 mL, 219 mmol) and PPTS (622 mg, 2.47 mmol). After being stirred for 24 h at rt, the reaction mixture was partitioned between $NaHCO_3$ (aqueous, 50 mL) and EtOAc (75 mL). The aqueous layer was further extracted with EtOAc (2 × 100 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5 → 10% EtOAc−hexanes) gave **25** (13.3 g, 85%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$; *listed NMR peaks are common to both diastereomers unless labeled as major or minor; a diastereomeric ratio of 1.4:1 was established by integration of $C_2$-H*) $\delta$ 4.75−4.74 (t, $J$ = 3 Hz, 1 H; *major*), 4.72−4.70 (t, $J$ = 3 Hz, 1 H; *minor*), 4.37−4.35 (app t, $J$ = 5 Hz, 1 H; *minor*), 4.19−4.17 (dd, $J$ = 5, 7 Hz, 1 H; major), 3.89−3.76 (2 H, m), 3.69 (s, 3 H), 1.83−1.80 (m, 1 H), 1.70−1.66 (m, 2 H), 1.56−1.46 (m, 3H), 0.84 (s, 9 H; *minor*), 0.83 (s, 9 H; *major*), 0.03 (s, 3 H; *minor*), 0.02 (s, 3 H; *minor*), 0.010 (s, 3 H; *major*), 0.007 (s, 3 H, *major*); $^{13}$C NMR (125 MHz, $CDCl_3$; *listed as mixture of diastereomers*) $\delta$ 171.5, 171.4, 99.6, 96.8, 77.8, 75.1, 64.3, 64.0, 62.1, 61.6, 51.7, 51.6, 30.2, 30.1, 25.70, 25.65, 25.3, 25.2, 18.9, 18.6, 18.2 (*common*), −5.47 (2 C), −5.52, −5.59; MS (FAB, 3-NOBA/NaI) 341 (100), 285 (1), 235 (4). Anal. Calcd for $C_{15}H_{30}SiO_5$: C, 56.57; H, 9.49. Found: C, 56.70; H, 9.32.

**Diethyl [(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,1-difluoro-3-[(*R*,*S*)-tetrahydropyranyloxy]-2-ketobutyl]phosphonate (16).** From ester **25** (13.3 g, 42.0 mmol), following general procedure A, was obtained **16** (17.2 g, 87%) after purification by flash chromatography (20% EtOAc−hexanes) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.92−4.90 (app t, $J$ = 4 Hz, 1 H; *major*), 4.75−4.73 (app t, $J$ = 3 Hz, 1 H; *minor*), 4.68−4.66 (dd, $J$ = 3, 7 Hz, 1 H; *minor*), 4.59−4.57 (app t, $J$ = 3 Hz, 1 H; *major*), 4.32−4.24 (m, 4 H), 4.01−3.68 (m, 3 H), 3.51−3.34 (m, 1 H), 1.86−1.77 (m, 1 H), 1.70−1.68 (m, 2 H), 1.57−1.49 (m, 3 H), 1.39−1.32 (m, 6 H), 0.85 (s, 9 H; *major*), 0.84 (s, 9 H; *minor*), 0.044 (s, 3 H; *minor*), 0.037 (s, 3 H; *major*), 0.031 (s, 3 H; *major*), 0.027 (s, 3 H; *minor*); $^{13}$C NMR (125 MHz, $CDCl_3$; mixture of THP-diastereomers): $\delta$ 100.4, 98.1, 79.7, 78.6, 66.0−65.98 (d, $J$ = 7 Hz), 66.0−65.9 (d, $J$ = 7 Hz), 64.0, 63.8, 62.7, 62.6, 30.71, 30.65, 26.4, 25.9, 25.7, 19.7, 19.5, 18.9, 16.94, 16.90, −4.8, −4.86, −4.9 (2C); MS (FAB, 3-NOBA/LiI): 481 (100), 417 (7), 397 (28), 391 (29), 361 (8); HRMS (FAB, 3-NOBA, LiI) calcd for $C_{19}H_{37}O_7F_2SiPLi$ $(M + Li)^+$ 481.2174, obsd 481.2177.

**Diethyl [(2*R*/*S*,3*S*)-4-*O*-(*tert*-Butyldimethylsilyl)-1,1-difluoro-2-methyl-3-*O*-[(*R*,*S*)-tetrahydropyranyl]-2,3,4-trihydroxybutyl]phosphonate (26).** To a solution of **26** (17.2 g, 36.4 mmol) in $Et_2O$ (200 mL) at −78 °C was added MeMgBr (18.3 mL, 3 M in $Et_2O$, 54.7 mmol) dropwise via syringe. The reaction mixture was allowed to warm to 0 °C over 3 h, and then $NH_4Cl$ (aqueous, 10 mL) was added and the pH adjusted to 5 with 1 N HCl. The aqueous layer was extracted with

(37) (a) Mukaiyama, T.; Shiina, I.; Sakata, K.; Emura, T.; Seto, K.; Saito, M. *Chem. Lett.* **1995**, 179−180. (b)Shapira, M.; Gutman, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1689−1700.

EtOAc (3 × 200 mL). The organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10 → 25% EtOAc−hexanes) provided two separable pairs of diastereomers as colorless oils in a 2:1 ratio by $^1$H NMR. It is presumed that the diastereomers within each pair differ only in the stereochemistry at the THP-derived center. The overall yield was (15.2 g, 85 %).

**26a,b** (first-eluting THP pair): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.959 (s, 1 H; *one diastereomer*), 4.955 (s, 1 H; *other diastereomer*), 4.68 (s, 1 H; *one diastereomer*), 4.67 (s, 1 H, *other diastereomer*), 4.31−4.23 (m, 4 H), 4.16−4.13 (dd, $J$ = 4, 8.5 Hz, 1 H), 4.07−4.04 (dd, $J$ = 4, 10 Hz), 3.91−3.87 (app t, $J$ = 10 Hz, 1 H), 3.88−3.85 (m, 1 H), 3.51−3.46 (m, 1 H), 1.79−1.74 (m, 1 H), 1.71-1.65 (m, 1 H), 1.53−1.49 (m, 4 H), 1.494 (s, 3 H; *one diastereomer*), 1.490 (s, 3 H; *other diastereomer*), 1.37−1.33 (app q, $J$ = 7 Hz, 6 H), 0.88 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$; *first pair reported as a mixture of diastereomers*) $\delta$ 101.8, 76.62, 76.59, 76.5, 64.4−64.3, 64.2−64.1, 64.0, 63.5, 30.7, 25.7, 25.3, 20.2, 16.32, 16.28, −5.68, −5.74; MS (FAB, 3-NOBA/NaI) *t*513 (100), 407 (14), 349 (3), 176 (17). Anal. Calcd for $C_{20}H_{41}O_7F_2SiP$: C, 48.96; H, 8.42. Found: C, 48.80; H, 8.22.

**26c,d** (second-eluting THP pair): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.93 (br s, 1 H), 4.53−4.51 (d, $J$ = 6 Hz, 1 H), 4.32−4.21 (m, 4 H), 4.09−4.07 (d, $J$ = 9 Hz, 1 H), 3.99−3.96 (d, $J$ = 11 Hz, 1 H), 3.85−3.83 (d, $J$ = 11 Hz, 1 H), 3.51−3.46 (m, 2 H), 1.88−1.83 (m, 2 H), 1.53−1.44 (m, 4 H), 1.37-1.33 (m, 6 H), 1.33 (s, 3 H, *one diastereomer*), 1.32 (s, 3 H, *other diastereomer*), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 103.6, 83.9, 65.9, 64.4−64.3 (7 Hz), 64.2−64.1 (5.5 Hz), 63.0, 62.9, 31.1, 25.8, 24.9, 21.7, 18.1, 17.3, 16.4, 16.3, −5.4, −5.5; MS (FAB, 3-NOBA/NaI) 513 (100), 407 (4), 176 (2). Anal. Calcd for $C_{20}H_{41}O_7F_2SiP$: C, 48.96; H, 8.42. Found: C, 49.12; H, 8.16.

**Diethyl [(2*R*/*S*,3*R*)-4-*O*-(*tert*-Butyldimethylsilyl)-1,1-difluoro-3,4-dihydroxy-2-methyl-3-*O*-[(*R*,*S*)-tetrahydropyranyl]butyl]phosphonate (27).** To **26** (7.50 g, 9.38 mmol) in THF (40 mL) at −78 °C was added *n*-BuLi (7.6 mL, 1.6 M, 12.2 mmol) dropwise via syringe. After 5 min, methyl oxalyl chloride (1.29 mL, 14.1 mmol) was added, and the reaction was allowed to warm to 0 °C over 2 h. The reaction mixture was then partitioned between $NaHCO_3$ (aqueous, 40 mL) and EtOAc (75 mL). After further extraction with EtOAc (2 × 100 mL), the organics were dried ($MgSO_4$), filtered, and concentrated. The crude methyl oxalyl ester was taken up in $PhCH_3$ (50 mL), and $Bu_3SnH$ (3.50 mL, 13.0 mmol) and AIBN (490 mg, 3.0 mmol) were added. The reaction mixture was purged with argon and then heated at 110 °C for 2 h. Following evaporation of the volatiles, $SiO_2$ column chromatography (20% EtOAc−hexanes) provided **27** (6.61 g, 65%) as an oil. [By $^1$H NMR, **27** was obtained as a mixture of four diastereomers in a ratio of 2.3:1.3:1.0:1.5, as estimated from the integrals of the acetal protons of each THP group. Analytical samples of the first-eluting diastereomer (**27a**) and of the last-eluting diastereomer (**27d**) could be obtained by standard $SiO_2$ chromatography. Furthermore, **27a** and **27d** were the sole products obtained upon reprotection (DHP, PPTS) of allothreo alcohol **28**. This result indicates that **27a** and **27d** are a pair of allothreo diastereomers differing only in stereochemistry at the THP center.]

**27a**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.87 (br s, 1 H), 4.30−4.21 (app dquint, $J$ = 1.4, 7 Hz, 4 H), 4.23−4.16 (buried, 1 H), 3.95−3.88 (m, 1 H), 3.70−3.65 (dd, $J$ = 6, 10 Hz, 1 H), 3.58−3.53 (dd, $J$ = 6, 10 Hz), 3.51−3.43 (m, 2 H), 2.63−2.50 (m, 1 H), 1.84−1.46 (m, 6 H), 1.38−1.33 (t, $J$ = 7 Hz, 3 H), 1.37−1.33 (t, $J$ = 7 Hz, 3 H), 1.22−1.20 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 96.8, 72.2, 64.30, 64.26, 62.9, 61.9, 38.8−38.3 (q, $J$ = 15 Hz), 30.8, 25.8, 25.6, 20.2, 19.0, 16.4, 16.3, 8.0, −5.5, −5.6. Anal. Calcd for $C_{20}H_{41}O_6SiF_2P$: C, 50.62; H, 8.71. Found: C, 50.54; H, 8.69.

**27d**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.61 (br s, 1 H), 4.26−4.19 (m, 4 H), 4.18−4.15 (dd, $J$ = 6,9 Hz, 1 H), 3.86−3.83 (m, 1 H), 3.79−3.76 (dd, $J$ = 5, 9 Hz, 1 H), 3.46−3.42 (app t, $J$ = 10 Hz, 2 H), 2.66−2.57 (m, 1 H), 1.74−1.73 (m, 1 H), 1.66−1.58 (m, 2 H), 1.48-1.43 (m, 3 H), 1.34−1.32 (app t, $J$ = 7 Hz, 6 H), 1.12−1.11 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 100.7, 75.2, 64.2, 64.1, 63.2, 62.2, 37.4−37.0 (dt, $J$ = 15, 18.5 Hz), 30.8, 25.7, 25.3, 20.2, 18.0, 16.31, 16.26, 5.8, −5.5, −5.7. Anal. Calcd for $C_{20}H_{41}O_6SiF_2P$: C, 50.62; H, 8.71. Found: C, 50.55; H, 8.81.

**Diethyl [(2*R*,3*R*)-4-*O*-(*tert*-Butyldimethylsilyl)-1,1-difluoro-3,4-dihydroxy-2-methylbutyl]phosphonate (28).** To **27** (mixture of four diastereomers, 8.12 g, 17.1 mmol) in $CH_2Cl_2$ (120 mL) at −40 °C were added ethanethiol (6.0 mL, 82 mmol) and $BF_3{\cdot}Et_2O$ (100 mg) in $Et_2O$ (2 mL). After the mixture was warmed slowly to 0 °C over 2 h, $NaHCO_3$ (aqueous, 10 mL) was added and the stirring continued for 10 min. Following extraction with $CH_2Cl_2$ (2 × 50 mL), the organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (6 → 20% EtOAc−hexanes) afforded **28** (4.10 g, 61%) as an oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.32−4.17 (app quint, $J$ = 7 Hz, 4 H), 4.13−4.09 (app t, $J$ = 6 Hz, 1 H), 3.65−3.60 (dd, $J$ = 6, 10 Hz, 1 H), 3.49−3.43 (dd, $J$ = 8,10 Hz, 1 H), 2.58−2.37 (m, 1 H), 1.38−1.33 (app t, $J$ = 7 Hz, 6 H), 1.11−1.08 (d, $J$ = 7 Hz, 3 H), 0.86 (s, 9 H), 0.03, (s, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 68.1, 65.0 (d, $J$ = 7 Hz), 64.5 (d, $J$ = 7 Hz), 63.7, 41.6−41.2 (m), 25.8, 16.3, 5.9, −5.4, −5.5. Anal. Calcd for $C_{15}H_{33}O_5F_2SiP$: C, 46.14; H, 8.52. Found: C, 46.30; H, 8.33.

**Diethyl [(2*R*,3*S*)-3-Azido-4-[(*tert*-butyldimethylsilyl)-oxy]-1,1-difluoro-2-methylbutyl]phosphonate (29).** To **28** (201 mg, 515 $\mu$mol) in $CH_2Cl_2$ (10 mL) at −40 °C were added 2,6-di-*tert*-butyl-4-methylpyridine (212 mg, 1.05 mmol) and $Tf_2O$ (140 $\mu$L, 0.83 mmol). The resulting reaction mixture was allowed to warm to −5 °C over 1 h and then quenched by the addition of MeOH (70 $\mu$L, 1.7 mmol) at −40 °C. Following addition of DMF (5 mL) and sodium azide (300 mg, 4.62 mmol), the $CH_2Cl_2$ was carefully removed with stirring, in vacuo. The reaction mixture was allowed to slowly warm to rt over the course of 1 h and then partitioned between $H_2O$ (20 mL) and $Et_2O$ (2 × 40 mL). The organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10 → 20% EtOAc−hexanes) provided the **29** (114 mg, 54%) [on a larger scale, **28** (3.26 g, 1.80 mmol) gave **29** (1.36 g, 39%)]: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.29−4.22 (m, 4 H), 3.91−3.89 (dd, $J$ = 2, 10.5 Hz, 1 H), 3.86−3.83 (m, 1 H), 3.72−3.68 (dd, $J$ = 8.5, 10.5 Hz, 1 H), 2.61−2.46 (m, 1 H), 1.38−1.35 (app t, $J$ = 7 Hz, 6 H), 1.12−1.11 (d, $J$ = 7 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 64.63, 64.57, 63.9, 62.2, 40.4-40.0 (dt, $J$ = 15, 19 Hz), 25.7, 18.2, 16.33, 16.30, 8.6, −5.61, −5.64; IR (atr) 2929.3 (s), 2856.1 (s), 2137.7 (s), 2094.3 (s). Anal. Calcd for $C_{15}H_{32}N_3O_4F_2SiP$: C, 43.36; H, 7.76; N, 10.11. Found: C, 43.52; H, 7.82; N, 10.05.

**L-*O*-(*tert*-Butyldimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)-3-deoxy-3-[1′,1′-difluoro(diethylphosphono)methyl]-threoninol (30).** To **29** (246 mg, 592 $\mu$mol), $Boc_2O$ (258 mg, 1.18 mmol). and 10% Pd on carbon (25 mg) in EtOAc (10 mL) was added $NEt_3$ (330 $\mu$L, 2.37 mmol). The resulting reaction mixture was hydrogenated at 40 psi for 8 h in a Parr apparatus. Filtration (Celite), concentration, and flash chromatography (5 → 20% EtOAc−hexanes) yielded **30** (241 mg, 83%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.16−5.13 (br d, $J$ = 7 Hz, 1 H), 4.30−4.20 (app dquint, $J$ = 2, 7 Hz, 4 H), 3.99−3.95 (m, 1 H), 3.71−3.69 (app d, $J$ = 5 Hz, 2 H), 2.75−2.54 (m, 1 H), 1.41 (s, 9 H), 1.38−1.33 (app t, $J$ = 7 Hz, 6 H), 1.19−1.16 (d, $J$ = 7 Hz, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.4, 79.1, 64.6, 64.5, 63.0, 51.9, 39.5 (m), 28.4, 25.8, 18.1, 16.4, 16.3, −5.6; MS (FAB, 3-NOBA/LiI) 496 [100, $(M + Li)^+$], 440 (17), 203 (6). Anal. Calcd for $C_{20}H_{42}NO_6F_2SiP$: C, 49.06; H, 8.65; N, 2.86. Found: C, 49.07; H, 8.41; N, 2.98.

**l-*N*-(*tert*-Butyloxycarbonyl)3-deoxy-3-[1′,1′-difluoro(diethylphosphono)methyl]threoninol (22b).** A tightly sealed test tube containing **30** (200 mg, 409 $\mu$mol) in $CH_3OH/CCl_4$ (1.6 mL, 1:1 v/v) was sonicated in an ultrasonic laboratory cleaning bath for 9 h. Evaporation of the volatiles and flash chromatography (30 → 100% EtOAc−hexanes) provided **22b** as an oil (114 mg, 75%): $[\alpha]_D$ (91% ee) +7.4° (*c* 1.9, EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.40−5.39 (br d, $J$ = 8 Hz, 1 H), 4.24−4.17 (app sextet, $J$ = 7 Hz, 4 H), 3.87 (br s, 1 H), 3.71−3.69 (m, 1 H), 3.62−3.60 (m, 1 H), 3.39 (br s, 1 H), 2.70−2.54 (m, 1 H), 1.36 (s, 9 H), 1.32−1.29 (app t, $J$ = 7 Hz, 6 H), 1.12−1.11 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.2,

125.9−120.0 (dt, $J$ = 213, 266 Hz), 79.3, 64.7, 64.6, 62.9, 52.9, 39.6−39.2 (m), 28.2, 16.2, 10.1; MS (FAB, 3-NOBA/LiI) 382 [100, $(M + Li)^+$], 326 (28), 160 (35). Anal. Calcd for $C_{14}H_{28}NO_6F_2P$: C, 44.80; H, 7.52; N, 3.73. Found: C, 44.96; H, 7.62; N, 3.88.

**L-*N*-(*tert*-Butyloxycarbonyl)-3-deoxy-3-[1′,1′-difluoro-(diethylphosphono)methyl]threonine (7).** To **22b** (42.0 mg, 112 $\mu$mol) in DMF (1 mL) was added PDC (210 mg, 560 $\mu$mol) and the resulting reaction mixture stirred at rt for 24 h. The reaction was quenched with $H_2O$ (5 mL) and 1 N HCl (0.5 mL) and extracted with EtOAc (3 × 10 mL). Organics were combined, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (0 → 10% MeOH−EtOAc) provided **7** (22.0 mg, 50%): $[\alpha]_D$ (91% ee) +21.0° (*c* 1.1, MeOH); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.43−5.41 (d, $J$ = 9 Hz, 1 H), 4.58−4.56 (dd, $J$ = 3, 9 Hz, 1 H), 4.31−4.25 (m, 4 H), 3.11−3.04 (m, 1 H), 1.42 (s, 9 H), 1.27−1.25 (d, $J$ = 7 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 171.7, 155.2, 103.8, 78.3, 64.3 (m), 64.2 (m), 53.3, 28.0, 16.1, 16.0, 10.9; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{14}H_{26}NO_7F_2PNa$ $(M + Na)^+$ 412.1313, obsd 412.1298. Optical Purity. **7** was judged to be 91% ee from the $^1$H NMR spectrum (500 MHz, $CDCl_3$) of its Mosher amide, obtained via the following sequence: (a) $CH_2N_2$; (b) HCl, EtOAc;[35] (c) (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride,[36] $NEt_3$, DMAP, $CH_2Cl_2$ [see the supporting information for copies of this $^1$H NMR spectrum and of the corresponding reference spectrum obtained using (±)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.]

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**Note Added in Proof:** New methods for the synthesis of α,α-difluorinated phosphonate analogues of (i) secondary phosphates and (ii) aryl phosphates, respectively, appeared subsequent to submission of this manuscript: (i) Pietre, S. *Tetrahedron Lett.* **1996**, *37*, 2233−2236. (ii) Qiu, W.; Burton, D. J. *Ibid.* **1996**, *37*, 2745−2748.

**Supporting Information Available:** $^1$H NMR spectra for compounds **5**−**7**, **11**−**16**, **18**−**21**, **22a**,**b**, **23a**,**b**, **24a/b**, **25**, **26a/b**, **26c/d**, **27**, **27a**,**d**, **28**−**30**, and **33**−**35**, $^1$H NMR spectra for Mosher amides or esters used to assess the enantiomeric purity of **5-7**, and double quantum-filtered phase sensitive COSY spectral data for **23b** and **24a/b** (50 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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