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# Solid-phase synthesis of α-hydroxy phosphonates and hydroxystatine amides. Transition-state isosteres derived from resin-bound amino acid aldehydes

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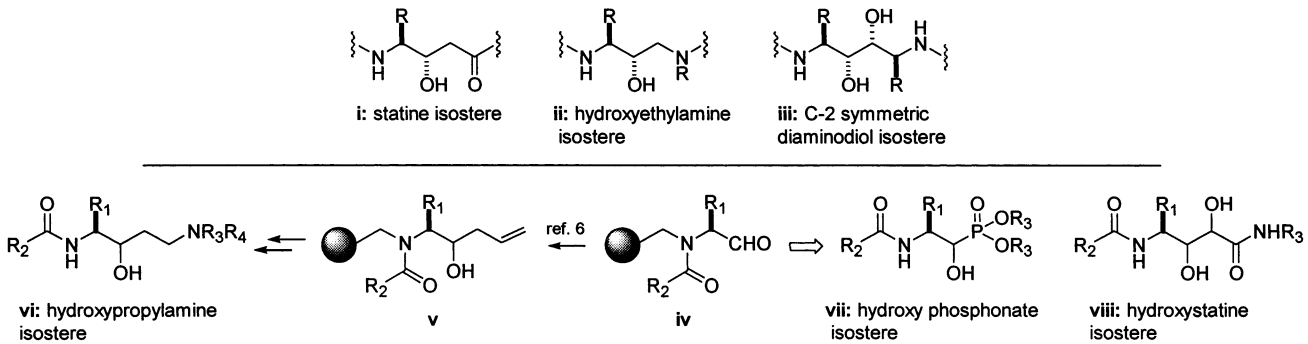
**Abstract**—Resin-bound *N*-acylated amino acid aldehydes **iv** were converted in a single step to α-hydroxy phosphonates **vii** (Pudovik reaction) and in six-steps to hydroxystatine amides **viii**, demonstrating the utility of intermediates **iv** for constructing multiple aspartic acid transition-state isosteres. 

The incorporation of stable transition-state isosteres into pseudopeptide templates is an effective strategy for inhibiting aspartic acid proteases.[1] Nearly two dozen isosteres have been reported in the literature, synthesized primarily in conjunction with the development of clinically efficacious inhibitors of renin and HIV protease.[1,2] Several isosteres, notably statine **i**,[3] hydroxyethylamine **ii**,[4] and the C-2 symmetric diaminodiol **iii**,[5] have served as pharmacophores in chemical libraries. These libraries successfully yielded highly potent and selective inhibitors of HIV protease, human cathepsin D, and malarial plasmepsin II. In seeking a versatile approach to construct encoded combinatorial libraries with broad utility for the discovery of aspartyl protease inhibitors, amino acid aldehydes **iv** were envisaged as pivotal intermediates from which multiple transition-state isosteres may be obtained. We recently reported an efficient five-step conversion of β-amino homoallylic alcohols **v** to the hydroxypropylamine isostere **vi** on solid support.[6] Intermediates **v** were derived via the addition of allylindium or allylboronic acid pinacolate to resin-bound *N*-acyl amino acid aldehydes **vi**. Herein we describe the solid-phase synthesis of α-hydroxy phosphonates (Scheme 1) **vii** and α-hydroxystatines (Scheme 2) **viii** from **iv**.

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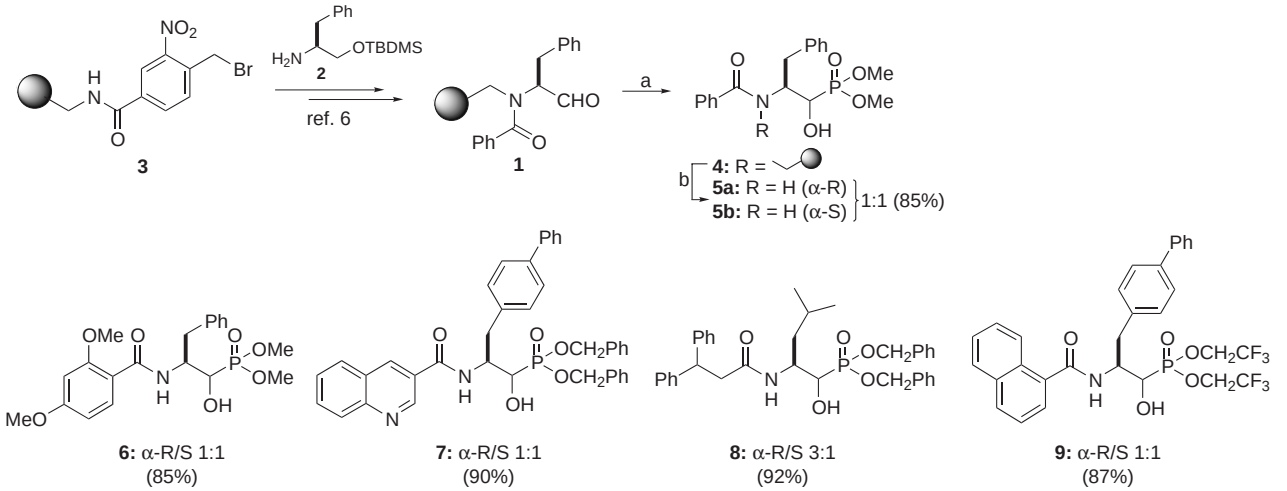
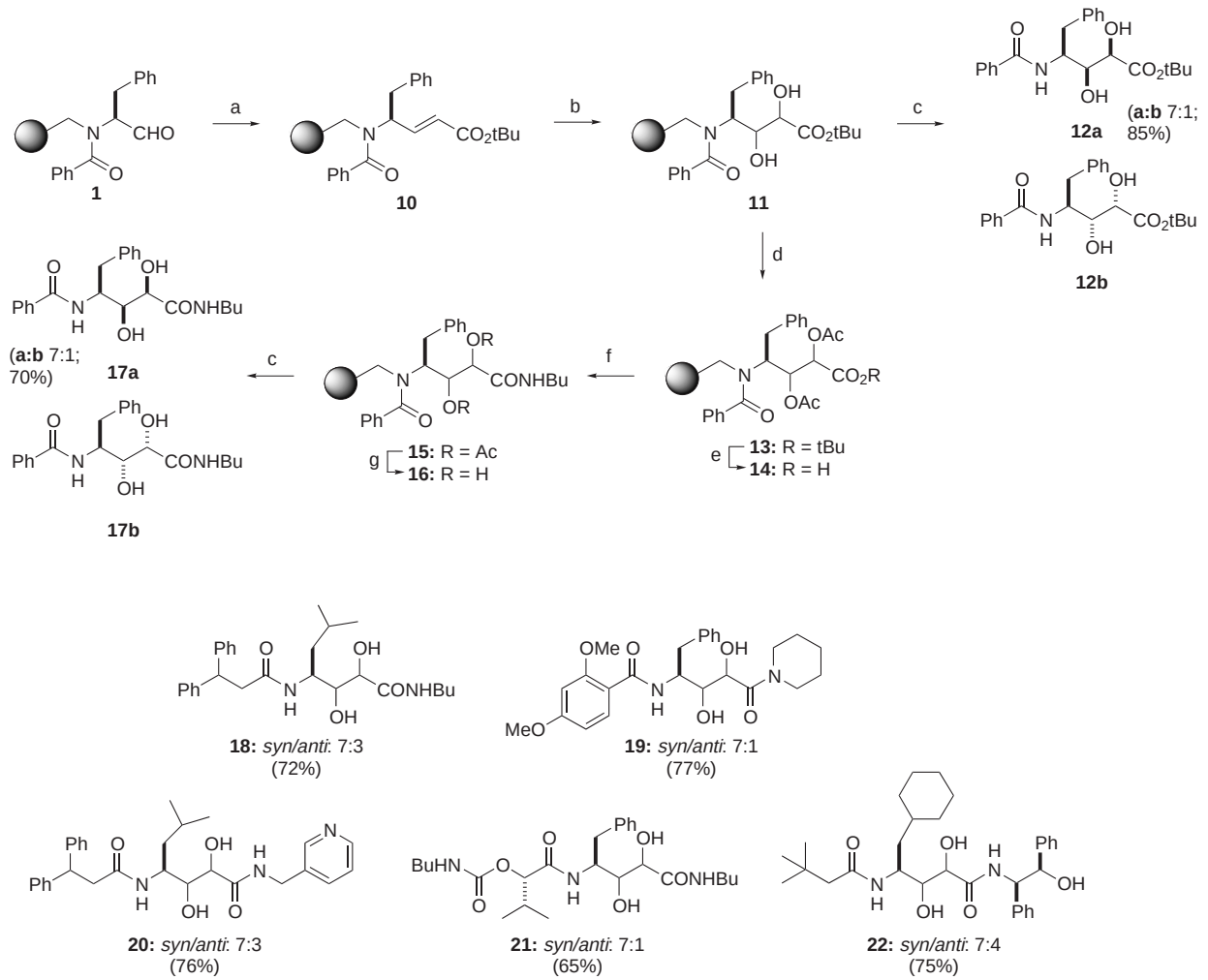



**Scheme 1.** Solid-phase synthesis of α-hydroxy phosphonates. *Reagents and conditions*: (a) 10 equiv. each $HP(O)(OMe)_2$ and $Et_3N$, $CH_2Cl_2$, 12 h; (b) $h\nu$ (365 nm), MeOH, 3 h, 40°C.




**Scheme 2.** Solid-phase synthesis of hydroxystatines. *Reagents and conditions*: (a) 4 equiv. $Ph_3PCHCO_2tBu$, THF, 12 h; (b) 0.2 equiv. $OsO_4$, 3 equiv. morpholine *N*-oxide, acetone–water (1:1), 12 h; (c) $h\nu$ (365 nm), MeOH, 3 h, 40°C; (d) 30 equiv. $(MeCO)_2O$, cat. DMAP, pyridine, 12 h; (e) 50% TFA–$CH_2Cl_2$, 8 h; (f) i. 8 equiv. pentafluoro phenyl trifluoroacetate and 10 equiv. pentafluorophenol, DMF–pyridine (1:1); ii. DMF wash; iii. 3 equiv. $BuNH_2$, DMF, 12 h; (g) 10% $H_2NNH_2$–MeOH, 2 h.

Resin-bound aldehyde **1** was prepared via coupling of phenylalaninol-*O*-*t*-butyldimethylsilylether **2** to Tentagel resin **3** derivatized with 4-bromomethyl-3-nitrobenzoic acid (photo-labile linker), benzoylation, desilylation, and oxidation with iodoxybenzoic acid as previously described.[6] Treatment of **1** with 10 equiv. of a 0.2 M solution of dimethyl phosphite in $CH_2Cl_2$ containing 10 equiv. of $Et_3N$ (12 h, 25°C; **1**–**4**) followed by photolysis furnished the α-hydroxy dimethylphosphonates **5a**,**b** as a 1:1 mixture of diastereomers. Purity (HPLC) of the crude cleavage product was in excess of 95% and **5a**,**b** were isolated in ca. 45% yield, respectively, from **1**.[7] Optical purity of the isolated materials was >95% via chiral HPLC indicating racemization at the α-center in **1** was negligible. A survey of the reaction of other amino acid aldehydes (e.g. alanine, leucine, substituted phenyalanine acylated with electron-rich/deficient aroyls, heteroaroyls, substituted acyls) with commercially available dialkyl- and dibenzyl-phosphites gave similarly clean conversions (>85% purity by HPLC, >80% isolated yield) to α-hydroxy phosphonates **vii** (e.g., **6**–**9**). Diastereomeric ratios ranged from 1:1 to 3:1 ($^{31}P$ NMR) in favor of the α-*S* stereochemistry (*syn* with respect to the amino acid side chain), analogous to solution-phase results.[8] The only exception being the reaction of the ethylene cyclic phosphite with intermediates **iv** which proceeded in poor yield (<10%).

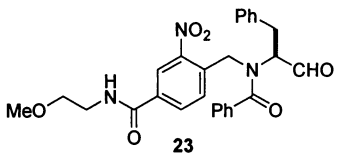
In contrast to the single step conversion of **iv** to the hydroxy phosphonate isostere, elaboration of **iv** to hydroxystatine required a two-carbon homologation and installment of the diol. Two-carbon homologation was straightforward via Wittig condensation of **1** with *t*-butyl triphenylphosphoranylidene)acetate (4 equiv.) in THF at room temperature for 3 h producing **10**.[9a] Dihydroxylation of **10** using a catalytic amount of $OsO_4$ and NMO afforded diol **11**. This reaction occurred in high yield and purity as established by photolytic cleavage of **11**, yielding **12a**,**b** as a 7:1 mixture of diastereomers.[9b] The diol stereochemistry (major diastereomer—diol *syn* with respect to the amino acid side chain) was tentatively assigned based on literature precedent for this reaction in solution[10] and on the basis of biological activity.[11] To complete the synthesis of the desired hydroxystatine amide isostere, it was found necessary to protect the diol **11** as its corresponding diacetate diester **13** (30 equiv. $Ac_2O$, pyridine, cat. DMAP) to permit clean ester to amide conversion.[12] Treatment of resin-bound ester **13** with 50% TFA–$CH_2Cl_2$ for 8 h gave acid **14**. Several conventional carboxylate activation methods including the HATU, DIC/HOBt or PyBroP either gave very slow conversions when *n*-butylamine was added with the activating agent or multiple by-products when the carboxylate was pre-activated. The mixed anhydride derived from isobutyl chloroformate gave somewhat purer product and the formation of the pentafluorophenyl ester with pentafluorophenyl trifluoroacetate[13] further improved the coupling. Optimizing the latter method, the last trace of unidentified by-products was removed by adding 2 additional equiv. of pentafluorophenol to the pentafluorotrifluoroacetate to ensure that the initially formed mixed anhydride was completely converted to the pentafluorophenyl ester before the addition of amine. Under these conditions, the two-step coupling provided clean high yield conversion to amide **15**.[14] Deprotection of the diacetate (**15** to **16**) with hydrazine in methanol was rapid requiring 2 h on solid support (<1 h in solution[9a]). Photolysis of **16** afforded hydroxystatine amide **17a**,**b** as a 7:1 mixture of diastereomers in 70% overall yield from **1**. The utility of this chemistry to generate hydroxystatine amides is further exemplified in the solid-phase synthesis of **18**–**22**.

In summary, resin-bound amino acid aldehydes are useful intermediates for generating multiple transition-state isosteres, specifically hydroxy phosphonates **vii**, hydroxystatine esters and amides **viii**, and hydroxypropylamines **vi**.[6] Further application of these chemistries in the preparation of encoded combinatorial libraries targeted for aspartic acid proteases will be forthcoming.

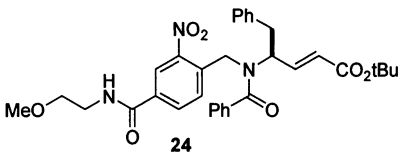
## References


1. Rich, D. H. In *Proteinase Inhibitors*; Barrett, A. J., Salvensen, G., Eds.; Elsevier Science: Amsterdam, 1986; Chapter 5.
2. (a) Abdel-Meguid, S. S. J. *Med. Res. Rev.* **1993**, *13*, 731; (b) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305; (c) Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 173.
3. (a) Carroll, C. D.; Patel, H.; Johnson, T. O.; Guo, T.; Orlowski, M.; He, Z.-M.; Cavallaro, C. L.; Guo, J.; Oksman, A.; Gluzman, I. Y.; Connelly, J.; Chelsky, D.; Goldberg, D. E.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2315–2320; (b) Carroll, C. D.; Johnson, T. O.; Tao, S.; Lauri, G.; Orlowski, M.; Gluzman, I. Y.; Goldberg, D. E.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3203–3206; (c) Owens, R. A.; Gesellchen, P. D.; Houchins, B. J.; DiMarchi, R. D. *Biochem. Biophys. Res. Commun.* **1991**, *181*, 402.
4. Haque, T. S.; Skillman, A. G.; Lee, C. E.; Habashita, H. G.; Ilya, Y.; Ewing, T. J.; Goldberg, D. E.; Kuntz, I. D.; Ellman, J. A. *J. Med. Chem.* **1999**, *42*, 1428.
5. Wang, G. T.; Li, S.; Wideburg, N.; Krafft, G. A. *J. Med. Chem.* **1995**, *38*, 2995.
6. Cavallaro, C. L.; Herpin, T.; McGuinness, B. F.; Shimshock, Y. C.; Dolle, R. E. *Tetrahedron Lett.* **1999**, *40*, 2741.
7. All new compounds gave physical and spectroscopic data consistent with their structure. Yields reported herein are cleaved, purified yields derived from **1**. The isolated yield of **1** is 40% based on theoretical resin loading: see reference 6. The optimized reaction conditions were established based on a survey of up to 30 substrates.
8. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W.; Lynn, W.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, Jr., E. W. *J. Med. Chem.* **1995**, *38*, 4557. The addition of aldehydes to resin-bound phosphites has been reported: Cao, X.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 6037.

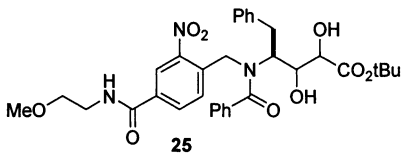
9. (a) Solid-phase transformations in Scheme 2 were first investigated and optimized in solution using substrate **23**; (b) Dihydroxylation of **24** afforded **25** as a 7:1 mixture of diastereomers. Attempts to use chiral ligands in the asymmetric osmylation reaction did not significantly change the diastereomeric ratio.
10. Reetz, M. T.; Strack, T. J.; Mutulis, F.; Goddard, R. *Tetrahedron Lett*. **1996**, *37*, 9293.
11. The minor diastereomers of **18–22** display inhibitory activity against the aspartyl protease cathepsin D and/or plamepsin II while the major diastereomers are inactive (unpublished observation). These results provide additional support that the amino acid side chain and the adjacent hydroxyl are disposed in an *anti* relationship in the minor isomer, as this is the stereochemical configuration required for aspartyl protease affinity (see references 1–3).
12. As originally planned, ester **10** would be converted to α,β-unsaturated amide **26** on resin and then dihydroxylated as a final reaction step before cleavage. However, amide **27** was a poor substrate for dihydroxylation (ca. 50% conversion to diol **28** under vigorous conditions) owing to the difficulty in hydrolyzing the intermediate osmate ester. This result was even more pronounced on solid-phase; hence, this route was abandoned in favor of the diol protection–deprotection (diacetate) sequence.
13. Ni, Z.-J.; Maclean, D.; Holmes, C. P.; Murphy, M. M.; Ruhland, B.; Jacobs, J. F.; Gordon, E. M.; Gallop, M. A. *J. Med. Chem*. **1996**, *39*, 1601.
14. (a) In some instances, partial de-acetylation was also observed during amide formation; (b) A broad survey of amines was conducted in this coupling step, anilines were noted as poor partners.



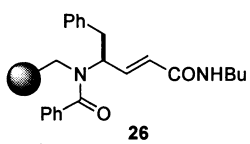

**23**



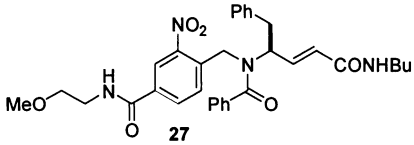

**24**



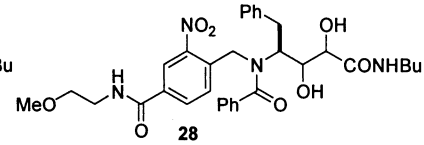

**25**




**26**




**27**




**28**