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THE ENANTIO- AND DIASTEREOSELECTIVE SYNTHESIS OF THE FIRST PHOSPHO-STATINE DERIVATIVE

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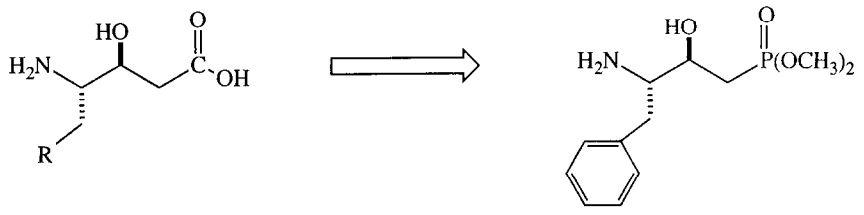
Abstract: The title compound was synthesized by the diastereoselective addition of the lithium or sodium anion of dimethyl methylphosphonate to N-trityl-L-phenylalaninal.

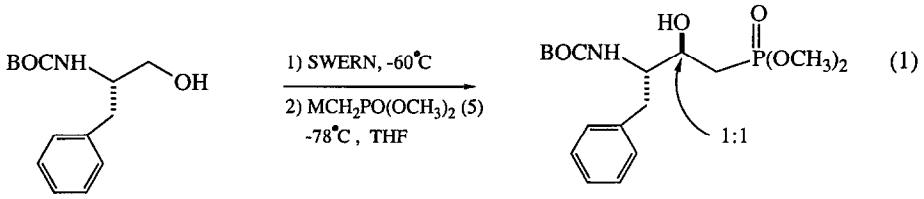
Inhibition of renin, an aspartic proteinase, is a current area of intense research.[1] Incorporation of statine (**1**) (R = i - pr), and derivatives thereof, into an appropriate peptide sequence has led to the discovery of very potent renin inhibitors.[2] We wished to investigate the effect of replacing the C_1-carboxyl of statine with a phosphonyl group. In considering



1 **2**

synthetic approaches to these derivatives one would ideally wish to control both the relative and absolute sense of asymmetry at the C_2-hydroxy and C_3-amino centers. In this letter we wish to report the first diastereo- and enantioselective preparation of a phospho-statine derivative.

It was hoped that **2** could be prepared by analogy to the literature syntheses of statine.[3a] Preliminary investigations were begun with BOC-L-phenylalininol (**3**) to take advantage of the UV tag during isolation of the products. Swern oxidation[4] of **3** (reaction was run and quenched at -60°C) provided BOC-L-phenylalininal (**4**) which was immediately added in dry tetrahydrofuran (THF) to a -78°C solution of the lithium or sodium anion of dimethyl methyl phosphonate (**5**) (1.1 eq. n-BuLi or NaHMDS, 1.2 eq. $CH_3PO(OCH_3)_2$, THF, -78°C, 0.5 h) (eqn. 1).[3b] After 0.25 h at -78°C the reaction was quenched (excess satd. aq. NH_4Cl) and the products isolated by a typical extractive process to provide consistently modest yields (15-30%)[5] of the desired phospho-

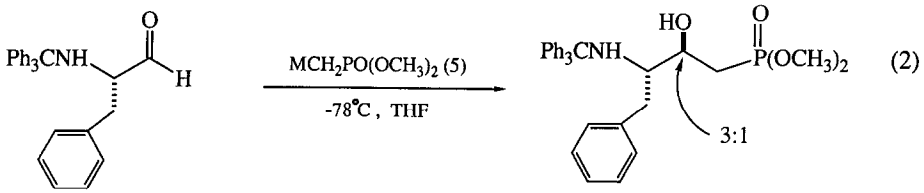


(1)

3 **6**

statine derivatives (**6**)[6] as a 1:1 diastereomeric mixture at the C_2-hydroxyl center. Further attempts to improve the yield (i.e., addition sequence, metal counterion, solvent, stoichiometry, and temperature) were unsuccessful. The balance of the products from these reactions typically consisted of ca. 50% dimethyl methylphosphonate (**7**), a complex mixture of unidentified non-polar products, and none of the starting aldehyde **4**.

These results implied that a potential complication involved anion **5** deprotonating the aminourethane proton competitively with addition to the aldehyde carbonyl.[7] To alleviate this potential problem the condensation was carried out analogously with N-trityl-L-phenylalinal (**8**) (prepared by Swern oxidation of the corresponding alcohol) to afford a 67% yield of a 3:1 diastereomeric mixture at C_2 of the corresponding β-hydroxy phosphonates (**9**) (eqn. 2).



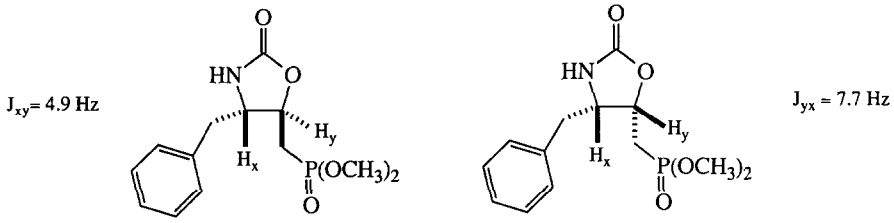
(2)

8 **9**

Chromatographic conditions to separate the diastereomers could not be identified and further characterizations were carried out on the mixture.

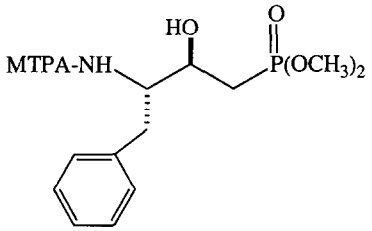
Conversion of **9** to the corresponding oxazolidinones (**10a** and **10b**) (1) 50% aq. HOAc; 2) 10% Cl_2CO in $PhCH_3$, excess Et_3N, 0°C) permitted assignment of the relative stereochemistry between C_2 and C_3 by ^1H NMR arguments.[8] The major diastereomer, **10a**, bore the desired anti-relationship (J_{XY} = 4.9 Hz) while the minor diastereomer, **10b**, contained the unwanted syn stereorelationship (J_{XY} = 7.7 Hz). The observed diastereoselectivity is not consistent with the Felkin[9] model for asymmetric induction. However, these results are consistent with the Cram[10,11] model for

asymmetric induction when one employs the benzyl moiety as the "large" group. Further investigations to determine the basis and generality of the observed stereochemical outcome are in progress and will be reported in due course.



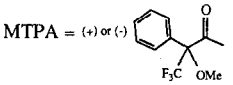
10a **10b**

The optical integrity of the C_3-amino center was examined by converting **9** to the corresponding (+)- and (-)-Mosher amides[12] (**11a** and **11b** respectively) (1) 50% aq. AcOH; 2) (+)-



11a = (+) - MTPA

11b = (-) - MTPA



or (-)-MTPA-Cl, Et_3N, CH_2Cl_2, 0°C). Neither of the (3R)-diastereomers could be detected in the 300 MHz ^1H NMR spectra of **11a** and **11b**, thus establishing the minimum enantiomeric excess in **9** to be 90% ee.

Thus we have demonstrated the first enantio- and diastereoselective synthesis of a phosphostatine derivative. Incorporation of **9** into an appropriate peptide sequence[13] has provided potent renin inhibitors (IC_{50} = 15-50 nm). These results will be presented in due course.

REFERENCES AND FOOTNOTES

1. Boger, J. Ann. Rep. Med. Chem. **1985**, 257 and references cited therein.

2. Bock, M.G.; DiPardo, R.M.; Evans, B.E.; Rittle, K.E.; Boger, J.S.; Freidinger, R.M.; Veber, D.F. J. Chem. Soc., Chem. Commun. **1985**, 109.

3. a) Woo, P.W.K. Tetrahedron Lett. **1985**, 26, 2973 and references cited therein.
b) Mikolajczyk, M.; Balczewski, P. Synthesis **1984**, 691.

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

5. All yields refer to chromatographically purified (flash or mplc) substances.

6. Satisfactory combustion analyses and spectral data (NMR, IR, MS) were obtained for all new compounds reported herein.

7. Kinetic NH deprotonation of acylaminoketones has been proposed recently: Hoye, T.R.; Duff, S.R.; King, R.S. Tetrahedron Lett. **1985**, 26, 3433.

8. The relevant portions of the 300 MHz ^{1}H NMR spectra of **10a** and **10b** in $CDCl_3$ with TMS as the internal standard are: **10a** δ 4.51 (d, d, d, d; J = 4.8, 5.4, 7.9, 8.6 Hz; Hy), 3.95 (d, d, d; J = 4.9, 5.0, 8.8 Hz; Hx), 3.00 (ABX; J = 5.0, 13.4 Hz; PhCHH), 2.79 (ABX; J = 8.8, 13.4 Hz; PhCHH), 2.27 (ABX_2; J = 5.6, 15.2, 19.3 Hz; OPCHH), 2.13 (ABX_2; J = 7.8, 15.2, 18.5 Hz; OPCHH); **10b** δ 5.05 (d, d, d, d; J = 7.5, 7.5, 7.5, 7.5 Hz; Hy), 4.05 (d, d, d,; J = 5.8; 7.5; 12 Hz; Hx), 3.08 (ABX; J = 3.3, 12.8 Hz; PhCHH), 2.56 (ABX; J = 12, 12.8 Hz; PhCHH), 2.43 (ABX_2; J = 7.5, 15.4, 19.6 Hz; OPCHH), 2.27 (ABX_2; J = 7.5, 15.4, 19.6 Hz; OPCHH).

9. Cherest, M.; Felkin, H.; Prudent, N. Tetrahedron Lett. **1968**, 2199. The N-trityl amino group was assumed to be the "large" group based on a further refinement of this model by Ahn (ref. 14).

10. Cram, D.J.; Abd. Elhalez, F.A. J. Am. Chem. Soc. **1952**, 74, 5828.

11. It has been assumed that the cyclic Cram model is inoperable on the basis of steric congestion at nitrogen, and that the sodium or lithium phosphonate anions provide identical diastereoselectivities.

12. Dale, J.A.; Dull, D.A.; Mosher, H.J. J. Org. Chem. **1969**, 34, 2543.

13. The (2S,2R)-diastereomers were separable when in the full peptide inhibitor.

14. a) Ahn, N.T.; Eisenstein, O. Nouv. J. Chim. **1977**, 1, 61. b) Ahn, N.T. Top. Current Chem., **1980**, 88, 145.

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