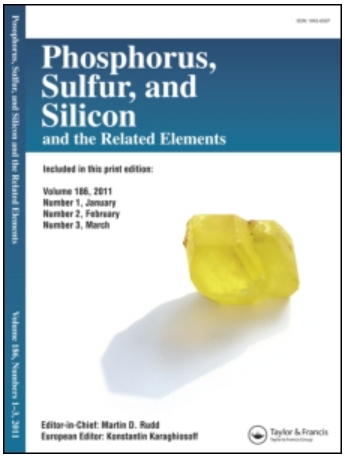


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# STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 82. SYNTHESIS OF SOME FUNCTIONALIZED 1,1-DIFLUOROMETHYLPHOSPHONATES

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# STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 82. SYNTHESIS OF SOME FUNCTIONALIZED 1,1-DIFLUOROMETHYLPHOSPHONATES

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A facile synthetic method leading to 3-amino-2-oxo-(hydroxy)-1,1-difluoroalkylphosphonates is reported. The stereochemistry involved in the suggested synthetic route is discussed.

*Key words:* Difluoromethylphosphonate; 3-amino-2-hydroxy derivatives; stereochemistry.



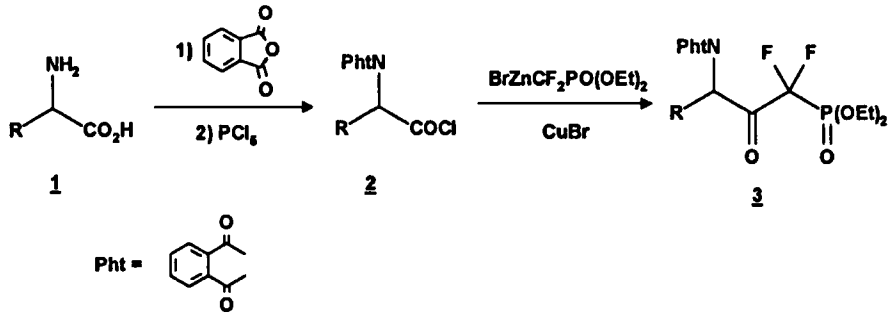
## INTRODUCTION

As an unusual amino acid, 3(*S*)-amino-2(*S*)-hydroxy-5-methyl-heptanoic acid (statine) is an essential component of pepstatin, a naturally occurring pentapeptide possessing inhibitory effect on proteolytic enzymes such as renin.[1-2] Some synthetic peptides derived from difluorostatine are potent renin inhibitors and show promising new therapeutic possibilities for the treatment of high blood pressure.[3] Recently, the difluoromethylphosphonate moiety has attacted much attention because it offered significant advantages over its nonfluorinated counterparts as enzyme inhibitors.[4-6] Chakravarty's communication[7] dealing with the synthetic and biological studies of phosphorus analogues of statone, namely, 3-amino-2-oxo-5-methylheptylphosphonates prompts us to investigate new methods for the synthesis of difuoromethylphosphonates bearing amino and hydroxy (or oxo) functional groups. These compounds can be regarded as difluoromethylphosphonate derivatives of statine or statone.

## RESULTS AND DISCUSSION

Our synthetic scheme is based on the direct introduction of the difluoromethylphosphonate moiety to a protected amino acid residue via a Reformatsky type reaction involving a reactive zinc reagent derived from 1-bromo-1,1-difluoromethylphosphonate[8] with *N*-phthaloylamino acid chloride using cuprous bromide as catalyst.

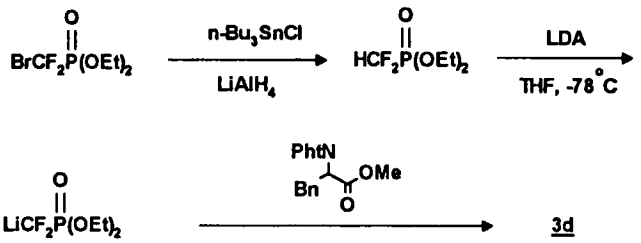
The key intermediate, diethyl 1-bromo-1,1-difuoromethylphosphonate was prepared from dibromodifluoromethane and triethylphosphite.[9] Upon reaction with zine powder in tetrahydrofuran the reactive zinc reagent, $BrZnCF_2P(O)(OEt)_2$ was obtained in good yield within six hours. It was found that in this type of reaction, tetrahydrofuran was a better choice as a solvent than ethylene glycol dimethyl ether (monoglyme or MG).[10] Reaction of the zinc reagent thus obtained with phthalimido acid chloride provided 3-*N*-phthalimido-2-oxo-1,1-difluoroalkyl-




| Entry | R | Yield(%) |
|---|---|---|
| 3a | S-i-Bu | 68 |
| 3b | S-Bn | 62 |
| 3c | R,S-Me | 51 |
| 3d | R,S-Bn | 52 |

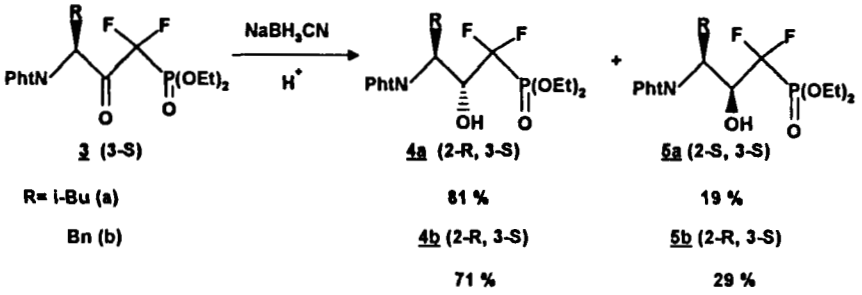
phosphonates (**3**). This reaction proceeded smoothly in the presence of cuprous bromide as catalyst. Since the solubility of cuprous bromide in tetrahydrofuran is very poor, addition of acetonitrile as co-solvent is necessary. Besides these, low temperature (<0°C) and anhydrous reaction conditions are essential, otherwise, a reduction product, 1,1-difluoromethylphosphonate will be formed. Depending on the stereoisomer of amino acids used, we can get *S*- or *R*,*S*-configuration of the R group on 3-position.

In addition, diethyl 1,1-difluoro-2-oxo-3-*N*-phthalimido-4-phenylbutylphosphonate (**3d**) can also be obtained by reaction of diethyl 1-lithium-1,1-difluoromethylphosphonate with 1-*N*-phthalimido-2-phenyalanine methyl ester by the following sequence of reactions:

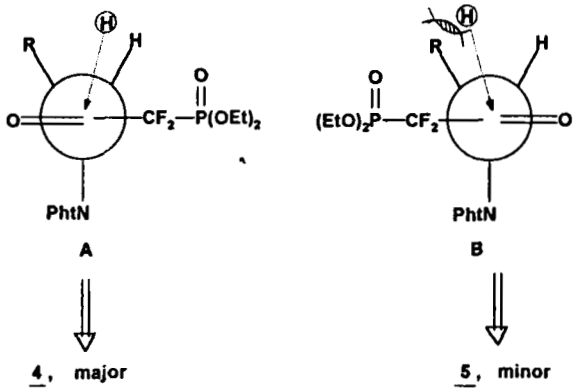



The stereochemistry of the reductive conversion of **3** into the corresponding hydroxy compound was examined. Stereoselectivity has to be expected during the nucleophilic attack on the carbonyl function located next to the chiral centre. As shown by us, in acidic condition, reaction of $NaBH_3CN$ with compound **3** having 3*S*-configuration offered a mixture of reduction products consisting of 2*R*,3*S*- (**4**) and 2*S*,3*S*- (**5**) stereoisomers, respectively.

The ratio of these isomers was conveniently determined by HPLC. The isomer with 2*R*,3*S*-configuration having a longer retention time constituted the major product, while the isomer with 2*S*,3*S*-configuration having shorter retention time was a minor component. The d.e. value of these reactions were estimated as 62% and 42% respectively by HPLC. The experimental phenomena could be ratio-



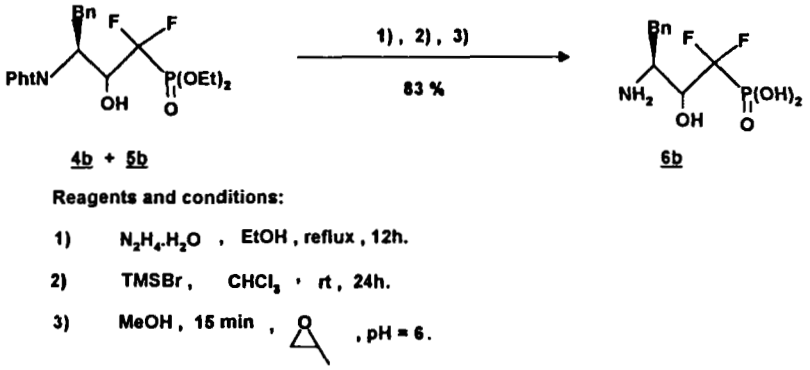

nalized by the Felkin-Ahn transition state model. By this model, two conformations **A** and **B** of the transition state describing the reduction process would be present.



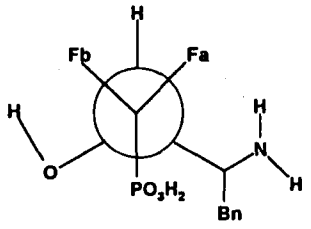

In conformer **A**, attack of a partially negative charged hydrogen of borane takes place from the sterically less hindered side during the reduction process, consequently, compounds **4** were formed as major products. However, conformer **B** provided compounds **5** as minor components which are associated with the approach of hydrogen from the bulky *R* side.

No significant difference exists between the $^{19}F$ NMR spectra of compounds **4** and **5**, but a typical AB splitting pattern was observed due to the magnetic non-equivalency of the two fluorine atoms.

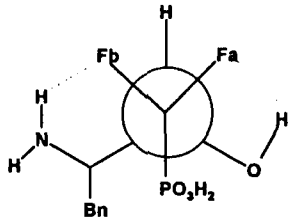
Diethyl 3-phthaloylimido-2-hydroxy-1,1-difluoro-4-phenylbutyl-phosphonate was successfully converted to 3-amino-2-hydroxy-1,1-difluoro-4-phenylbutylphosphonic acid in the usual manner.



Similarly, the $^{19}F$ NMR spectrum of **6b** showed typical AB splitting peaks. The coupling constants of these two nonequivalent fluorine atoms are 291.2 Hz and $^2J_{P,F}$ = 80.6 Hz, which are much smaller than that in **4b** and **5b**. Besides these, it is also noteworthy that the $^{19}F$ NMR spectra of **6b** showed identical coupling values (12.4 Hz) between the two nonequivalent fluorine atoms and the proton. It is logical to predict that in the stable configuration of product **6b**, the hydrogen atom at the 2-carbon is located in the middle of two fluorine atoms as shown in the scheme.




2 - R- 6b




2 - S -6b

## EXPERIMENTAL

Melting points were uncorrected. $^1H$-NMR specta were measured on a Varian EM-360L or a Bruker AM-300 spectrometer. $^{19}F$- and $^{31}P$-NMR spectra were taken on a Varian FX-90Q spectrophotometer. IR spectra were obtained with a Shimadzu IR-440 spectrophotometer. HPLC were conducted on a Hitachi-655 chromatographic instrument with a column of Hitachi 3056 (5, 4 × 250 mm), 65% and 90% methanol were employed as eluent for (**4a**, **5a**) and (**4b**, **5b**), respectively. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. THF was dried over KOH pellets for 2 days and then distillated from a sodium benzophenone ketyl. Zinc powder and cuprous bromide was purified according to Burton and Sprague.[10] Acetonitrile was dried by successive distillations from $P_2O_5$ and then from $K_2CO_3$. Diethyl bromodifluoromethylphosphonate was prepared according to the method described by Burton[9] with some modification: dibromodifluoromethane (24.1 g, 0.12 mol) and triethyl phosphite (18 ml, 0.11 mol) were stirred in a stainless steel autoclave at rt for 48 h. The product was then collected by vacuum distillation, bp 75–75.5°C/9 mmHg.

All of the processes described below were carried out under an atmosphere of dry nitrogen.

*(S) or (R,S) Diethyl 1,1-difluoro-2-oxo-3-phthalimidoalkylphosphonate* (**3**). *General procedure*: To a suspension of Zinc powder (0.8 g, 0.012 mol) in THF (6 ml) was added 1,2-dibromoethane (0.1 ml). After stirring for a few minutes, diethyl bromodifluoromethylphosphonate (3.2 g, 0.012 mol) was introduced in one portion and the mixture was stirred at rt for 6 h. The undissolved material was filtered off and then a mixture of CuBr (0.4) and acetonitrile (3 ml) was added to the filtrate followed by the addition of a solution of the corresponding phthaloylaminoalkyl acyl chloride in THF ($2.8 \times 10^{-3}$ M, 5 ml) at 0°C by a syringe. After stirring at 0°C for 4 h and rt for 8 h, the solution was concentrated under reduced pressure and the residue was dissolved in EtOAc (40 ml). The resultant organic solution was washed successively with $H_2O$ (2 × 20 ml), saturated $NaHCO_3$ aqueous solution (40 ml), $H_2O$ (20 ml) and saturated brine (40 ml). After being dried over sodium sulfate, the solvent was removed under reduced pressure and product **3** was separated by column chromatography (200–300 mesh silica gel, 1:2 EtOAc/petroleum ether).

**3a**: Yield 68%, $[\alpha]_D^{20} = -15.4°$ (12.5%, EtOH); IR (neat) $\nu$ = 1380, 1275 (P═O), 1020 (P—O—C) $cm^{-1}$; $^1H$ NMR (neat): $\delta$ = 0.6 (t, 6H, $J$ = 5 Hz), 0.8–1.1 (m, 6H), 1.2–1.5 (m, 3H), 4.2 (m, 4H), 5.7 (t, 1H, $J$ = 7), 7.5 (s, 4H); $^{19}F$ NMR ($CDCl_3$): 42.0 (d, $J_{P,F}$ = 100) ppm; $^{31}P$ NMR ($CDCl_3$): $\delta$ = 2.73 (t, $J_{F,P}$ = 95 Hz); EIMS (70 ev): m/z = 432 (M + 1).

**3b**: Yield 62%, $[\alpha]_D^{20} = -51.0°$ (11.7%, $CHCl_3$); IR (neat): $\nu$ = 1780, 1755, 1730, 1380, 1270 (P═O), 1020 (P—O—C) $cm^{-1}$; $^1H$ NMR ($CCl_4$): $\delta$ = 1.32 (t, 6H, $J$, 7 Hz), 3.55 (d, 2H, $J$ = 8 Hz), 4.0–4.5 (m, 4H), 5.0 (t, 1H, $J$ = 7), 7.15 (s, 5H), 7.75 (s, 4H); $^{19}F$ NMR ($CCl_4$/TFA): $\delta$ = 38 (d, $J_{P,F}$ = 100) ppm; $^{31}P$ NMR ($CDCl_3$): $\delta$ = 2.63 (t, $J_{F,P}$ = 100) ppm; EIMS: m/z = 466 (M + 1, 86%), 250 (100%), 232 (47%), 188 (23%), 131 (82%), 91 (22%).

**3c**: Yield 51%, IR (neat: $\nu$ = 1780, 1750, 1720, 1385, 1275 (P=O), 1020 (P—O—C) $cm^{-1}$; $^1H$ NMR ($CCl_4$): $\delta$ = 1.3–1.8 (m, 9H), 4.0–4.6 (m, 4H), 5.75 (m, 1H), 7.85 (s, 4H); $^{19}F$ NMR ($CCl_4$/TFA): $\delta$ = 35 (d, $J$ = 100) ppm; EIMS (70 ev): m/z = 390 (M + 1, 14%), 174 (100%).

**3d**: Yield 52%, mp 75–77°C (EtOAc/Hexane); IR (KCl disk.): $\nu$ = 1770, 1760, 1725, 1380, 1265 (P=O), 1020 (P—O—C) $cm^{-1}$; $^1H$ NMR ($CCl_4$): $\delta$ = 1.25 (t, 6H, $J$ = 7), 3.4 (d, 2H, $J$ = 8), 4.1–4.5 (m, 4H), 5.6 (t, 1H, $J$ = 7), 6.95 (s, 5H), 7.7 (s, 4H); $^{19}F$ NMR ($CCl_4$/TFA): $\delta$ = 37.5 (d, $J$ = 99) ppm; EIMS (70 ev): m/z = 466 (M + 1, 35.1%).

*Diethyl 1,1-difluoro-2(R,S)-hydroxy-3(S)-phthalimido-alkylphosphonate* (***4 and 5***). A solution of **3** (3 mmol), $NaBH_3CN$ (0.4 g, 6 mmol) and bromocresol green (4 mg) in ethanol (10 ml) was cooled to 0°C with an ice-water bath, and then a solution of HCl in ethanol (30%, 4 ml) was added slowly with efficient stirring. Any new addition is performed after indicator toning. After completion of the addition, the mixture was stirred at rt for 12 h. After removal of the precipitated sodium chloride by filtration, the filtrate was concentrated and the residue was stirred with 10% KOH (10 ml) at 0°C for 30 min, followed by extraction with dichloromethane (3 × 10 ml). The combined extracts were washed with saturated brine and dried ($Na_2SO_4$). After removal of the solvents, compounds **4a** and **5a** were obtained as a mixture of stereoisomers composed of 81% **4a** and 19% **5a**, chemical yield 81%, d.e. value 62% (HPLC). After being separated by column chromatography (200–300 mesh silica gel, 2:1 EtOAC/petroleum ether), the mixed stereoisomers **4a** and **5a** were obtained as colorless powder, mp 124–126°C; $[\alpha]^{20}$ = +9.7° (0.6%, $CHCl_3$).

IR (KCl disk.): $\nu$ = 3300 (O—H), 1770, 1710, 1380, 1255 (P=O), 1010 (P—O) $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ = 0.95 (d, 6H, $J$ = 3.5 Hz), 1.3 (t, 6H, $J$ = 7.2 Hz), 1.4–1.8 (m, 2H), 1.9–2.4 (m, 1H), 4.0–4.45 (m, 4H), 4.42–4.62 (br, 1H, OH), 4.64–5.10 (m, 2H, CHOH, CHN), 7.8 (s, 4H); $^{19}F$ NMR ($CDCl_3$): $\delta$ = 35.53–40.34 (AB; Fa; $^3J_{Fa,H}$ = 0; $^2J_{Fa,P}$ = 99.3 Hz; $^2J_{Fa,Fb}$ = 306.1 Hz), 50.11–55.22 (AB; Fb; $^3J_{Fb,H}$ = 20.7 Hz; $^2J_{Fb,P}$ = 99.3 Hz; $^2J_{Fb,Fa}$ = 306.2 Hz); $^{31}P$ NMR ($CDCl_3$): $\delta$ = 6.24 (t, $J$ = 100 Hz); Anal. Calc. for $C_{19}H_{26}F_2NO_6P$ (433.4): C 52.65, H 6.06, N 3.23%; Found: C 52.28, H 6.03, N 3.41%.

**4b** and **5b** were obtained as a mixture of stereoisomers with chemical yield 60%, d.e. value 42% (HPLC), mp 125–126°C (EtOAc/petroleum ether), $[\alpha]^{20}$ = −25°C (4%, $CHCl_3$); IR (KCl disk.): $\nu$ = 3250 (O—H), 1770, 1720, 1260 (P=O), 1040 (P—O—C) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.25–1.35 (m, 6H), 3.3 (d, 2H, $J$ = 8.2 Hz), 4.2–4.35 (m, 4H), 4.42 (m, 1H, CHN), 4.52 (m, 1H, CHOH), 5.05 (m, 1H, OH), 7.1–7.2 (m, 5H), 7.7 (s, 4H); $^{19}F$ NMR (90 MHz, Acetone-$d_6$): $\delta$ = 31.31–36.36 (AB, Fa; $^3J_{Fa,H}$ = 8 Hz; $^2J_{F,P}$ = 99 Hz; $^2J_{F,F}$ = 309.8 Hz), 45.20–50.05 (AB, Fb; $^3J_{Fb,H}$ = 20 Hz; $^2J_{F,P}$ = 99 Hz; $^2J_{F,F}$ = 309.8 Hz) ppm; EIMS (70 ev): m/z = 468 (M + 1, 24%), 188 (100%). Anal. Calc. For $C_{22}H_{24}F_2NO_6P$ (467.44): C 56.52, H 5.18, N 3.00; Found: C 56.69, H 5.02, N 2.88.

*1,1-difluoro-2(R,S)-hydroxy-3-amino-4-phenylbutylphosphonic acid* (**6b**): A solution of **4b** and **5b** (0.14 g, 0.3 mmol) in ethanol (2 ml) was refluxed with ethanolic hydrazine monohydrate (10%, 0.22 ml) for 12 h. After being concentrated under reduced pressure, the residue was triturated with diethyl ether and the undissolved material was removed under reduced pressure. After being dried in vacuo, the crude product thus obtained was directly treated with TMSBr (0.5 g) in dry and ethanol-free $CHCl_3$ (6 ml) at rt for 24 h. The volatile components were then removed on a rotatory evaporator and the residue was stirred with methanol (6 ml) at rt for 1 h, propyleneoxide was then added until pH6 was attained. The precipitated solid was collected by suction and washed thoroughly with ethanol, to give **6b** (0.07 g) in 83% yield. The product **6b** thus obtained is a colorless powder which is slightly soluble in water but easily soluble both in aqueous HCl or NaOH; **6b** gives a positive test with ninhydrin.

mp 268–270°C (dec); IR (KCl disk.): $\nu$ = 3700–2000, 1170 (P=O), 1055 (P—O) $cm^{-1}$; $^1H$ NMR (90 MHz, $D_2O$/NaOD): $\delta$ = 2.64 (d, 1H, $J$ = 9), 2.67 (d, 1H, $J$ = 6.8), 3.46 (d, 1H, $J$ = 8, CHN), 3.7 (d, 1H, $J$ = 14 Hz, CHOH), 7.2 (s, $5H_{aryl}$); $^{31}P$ NMR (90 MHz, $D_2O$/NaOD): $\delta$ = 4.45 (t, $J$ = 81 Hz) ppm; $^{19}F$ NMR (90 MHz, $D_2O$/NaOD): $\delta$ = 34.25–44.69 (AB, 2F; $^3J_{F,H}$ = 12.4 Hz; $^2J_{F,P}$ = 80.6 Hz; $^2J_{F,F}$ = 291.2 Hz) ppm; MS (FAB): m/z = 282 (M + 1), 254, 208, 190.

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## REFERENCES

1. H. Umezawa, T. Aoyagi, H. Morishma, M. Matsuzaki, M. Hamada and T. Takeuchi, *J. Antibiotics*, **23**, 259 (1970).

2. R. J. Workman and D. S. Burkitt, *Arch. Biochem. Biophys.*, **194,** 157 (1977).
3. S. Thaisrivongs, D. T. Pals, W. M. Kati, S. R. Turner and L. M. Thomasco, *J. Med. Chem.*, **28,** 1153 (1985).
4. G. M. Blackburn, *Chem. Ind. (London)*, 134 (1981).
5. S. Halazy, A. Ehrhard and C. Danzin, *J. Am. Chem. Soc.*, **113,** 315 (1991).
6. Z. Y. Yang and D. J. Burton, *J. Org. Chem.*, **57,** 4676 (1992).
7. P. K. Chakravarty, W. J. Greelee, W. H. Parsons, A. A. Patchett, P. Combs, A. Roth, R. B. Busch and T. N. Mellin, *J. Med. Chem.*, **32,** 1886 (1989).
8. D. J. Burton, T. Ishihara and M. Maruta, *Chem. Lett.*, 755 (1982).
9. D. J. Burton and F. M. Flynn, *J. Fluorine Chem.*, **16,** 329 (1977).
10. D. J. Burton and L. G. Sprague, *J. Org. Chem.*, **53,** 1523 (1988).