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Synthesis of α_1-(Cbz-aminoalkyl)-α_2-(hydroxyalkyl)phosphinic esters

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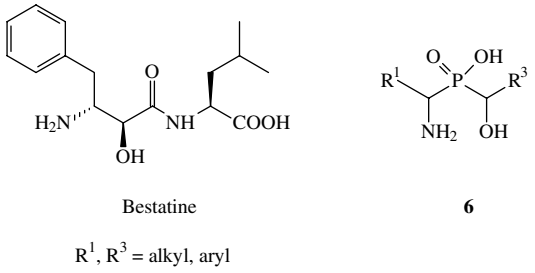
Abstract—A synthesis of α_1-(Cbz-aminoalkyl)-α_2-(hydroxyalkyl)phosphinic esters was achieved by the 1,2-addition of the appropriate aldehyde to Cbz-protected phosphinic analogues of amino acid esters in the presence of at least three equivalents of trimethylsilyl chloride and NEt_3. The complete deprotection of the product esters could be achieved in one step using 35% HBr in acetic acid.

Phosphinic peptides and pseudopeptides are interesting classes of compounds possessing broad biological activities. These compounds have attracted particular interest as inhibitors of transition state analogues of Zn-metalloproteases.[1,2]

In our investigations of the synthesis of new inhibitors of aminopeptidase N (CD13), which, according to some recent reports, may be implicated in the process of programmed cell death of cancer cells, we have focused on analogues of bestatine, a potent inhibitor of aminopeptidase N and an apoptosis inducer (Scheme 1).[3–5]

One group of such compounds, α_1-aminoalkyl-α_2-hydroxyalkylphosphinates **6**, possess an amino group attached to the α_1 carbon atom and a hydroxy group at the α_2 carbon atom (Scheme 1). Such structures represent very close structural analogues of bestatine, where the OH moiety is replaced by the more acidic P–OH fragment. We suggest that this modification will improve binding to the zinc ion in the active center of aminopeptidase N.



Bestatine

6

R^1, R^3 = alkyl, aryl

Scheme 1. Structure of bestatine and its phosphinic analogues **6**.

There are no previous reports of the synthesis of α_1-aminoalkyl-α_2-hydroxyalkylphosphinates. There is one example of the preparation of a similar compound, which possesses as an additional amino group at the β_2 position. This symmetrical pseudodipeptide was synthesized in 47% yield by a classical condensation of the Cbz-protected phosphinic analogue of phenylalanine with Cbz-phenylalaninal in the presence of NEt_3. After appropriate derivatization, the product proved to be a potent inhibitor of protease HIV.[6,7]

Herein we report a general synthetic approach to the synthesis of esters of α_1-(Cbz-aminoalkyl)-α_2-hydroxyalkyl phosphinic acids **5** starting from Cbz-protected phosphinic analogues **4** of amino acids esters, prepared according to well established procedures, in a few steps from the appropriate aldehyde and benzhydrylamine salt with hypophosphorous acid.[8,9] Deprotection of **1** in 40% HBr resulted in phosphinic amino acid analogue **2**.[8] Subsequent protection with a Cbz group gave phosphinic acid **3**, which was converted into the desired ester **4** by action with the appropriate alcohol in the presence of DCC and DMAP in THF (Scheme 2).[8,9]

In the final step, the desired esters **5** were obtained by a modified procedure, originally described by Thottathil

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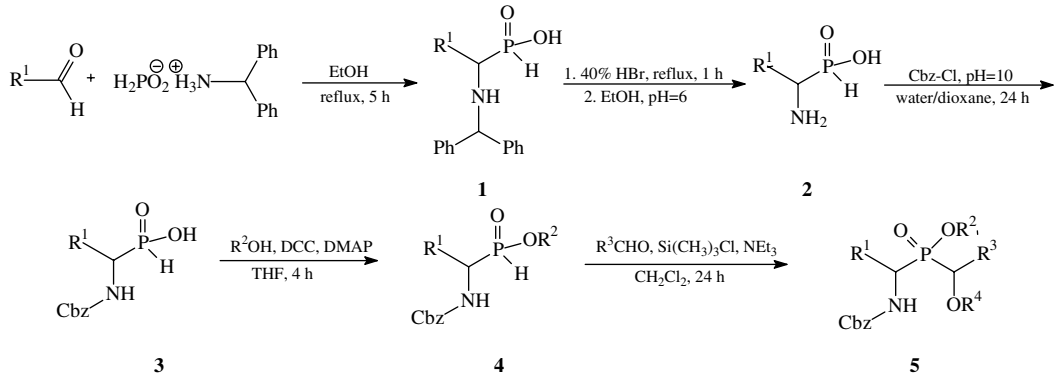


R^1=Ph, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$; R^2=Et, CH_2Ph; R^3=Ph, $(CH_2)_3CH_3$, $(CH_2)_2SCH_3$, $(CH_2)_2Ph$; R^4=H, $Si(CH_3)_3$

Scheme 2. Preparation of compounds **1**–**5**.

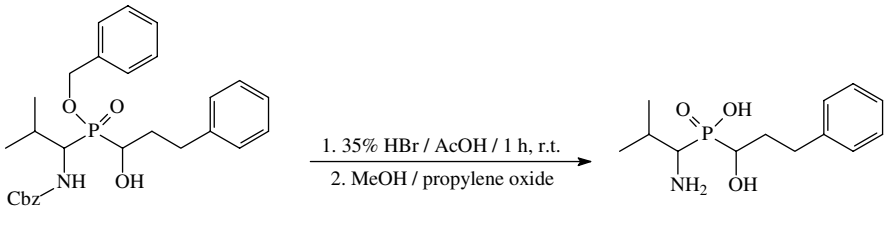
et al. for the 1,2-addition of crotonaldehyde to the ethyl ester of 4-phenylbutylphosphinic acid.[10] In our case the 1,2-addition of the appropriate aldehyde to the Cbz-protected phosphinic analogues **4** in the presence of at least three equivalents of trimethylsilyl chloride and NEt_3 in dichloromethane afforded the desired products in 70–86% yields.[11] The application of a large excess of trimethylsilyl chloride and NEt_3 resulted in complete conversion of the phosphinic substrate (Scheme 2), which could not be achieved by application of the conditions described in the original publication. Conversion to **5** was about 70–90%, and the reaction was accompanied by a side product, namely Cbz-protected phosphinic acid (about 10–30% according to the ^{31}P NMR spectra of the crude reaction mixture), which could be easily removed by washing with 5% aqueous $NaHCO_3$. Purification by column chromatography gave the desired product **5**.[12] Interestingly, in some cases (Table 1) the isolated product had a trimethylsilyl protected **5a** and **5d** derivates of protected hydroxy group, as confirmed by ^1H NMR, ^{13}C NMR and ESI analysis.[13] This is surprising considering the aqueous work-up and the expected low stability of the silyl ethers derivatives **5a** and **5d** to those conditions. This observation gave additional confirmation for the formation of a hydroxy group during the 1,2-addition of aldehydes to the *N*-Cbz-protected phosphinic esters **4** and further confirmed the structure of **5**.[14]

Full deprotection of compounds **5** could be easily accomplished by the action of 35% hydrogen bromide in acetic acid during 1 h at room temperature giving α_1-(aminoalkyl)-α_2-(hydroxyalkyl)phosphinic acids **6** as a mixture of two pairs of diastereomers, as exemplified for **5c** (Scheme 3).[15,16]

Recently, we have synthesized a large collection of compounds **6**, which were tested for their inhibitory activity toward aminopeptidase N (APN). Some of the tested compounds showed a significant effect towards APN as well as inducing apoptosis in vitro in some cancer cell lines. Currently we are studying the stereoselective

Table 1. Structural and synthetic data for compounds **5**

Entry	R^1	R^2	R^3	R^4	Yield (%)
5a	$(CH_3)_2CHCH_2$	CH_2Ph	CH_2CH_2Ph	$Si(CH_3)_3$	71
5b	$(CH_3)_2CHCH_2$	CH_2CH_3	$CH_2CH_2SCH_3$	H	80
5c	$(CH_3)_2CH$	CH_2Ph	CH_2CH_2Ph	H	75
5d	C_6H_5	CH_2CH_3	CH_3	$Si(CH_3)_3$	73
5e	C_6H_5	CH_2Ph	C_6H_5	H	86
5f	C_6H_5	CH_2Ph	CH_2CH_2Ph	H	86
5g	C_6H_5	CH_2Ph	$CH_2CH_2CH_2CH_3$	H	85



Scheme 3. An example of the deprotection of compounds **5**.

synthesis of diastereomers of **6** and any results will be published separately together with the biological studies, in due course.[17]

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7. Our preliminary experiments on the condensation of Cbz-Leu-P(O)(OEt)H with benzaldehyde in the presence of NEt_3 gave unsatisfactory results, repetition of the reaction in the presence of CH_2Cl_2 also failed. Improved results were achieved by condensation in the presence of KF in $DMF/CHCl_3$, but this method resulted in tedious separation of the desired product from the mixture.
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11. General procedure for the synthesis of compounds **5**. In a round bottom flask equipped with a magnetic stirrer was dissolved 2 mmol of the appropriate Cbz-protected phosphinic acid ester **4** in 15 mL of dry CH_2Cl_2. After cooling the mixture in an ice bath to 0 °C, dry triethylamine (6 mmol, 0.83 mL) and trimethylsilyl chloride (6 mmol, 0.75 mL) were added. After 0.5 h, 4 mmol of the appropriate aldehyde was added to the mixture. The reaction was left tightly closed for 24 h. After completion of the reaction, 3 mL of water was added. After 5 min, 20 mL of dichloromethane was added and the organic phase was separated, washed with 5% NH_4Cl_{aq} (10 mL), water (10 mL), $brine_{aq}$ (10 mL), then dried ($MgSO_4$) and evaporated in vacuo. Column chromatography on silica gel (70–200 mesh: 70 g) using hexane:AcOEt (1:1) gave the desired compound **5**.
12. The isolated compounds **4**and **5** always contained up to 1–3% by mass of DCU (*N*,*N*-dicyclohexyl urea—omitted from the ^1H NMR data), which remained from the esterification of **3**. Our attempts to eliminate this side product by several re-crystallizations from dichloromethane or hexane/AcOEt (1:1) and column chromatography were only partially successful.
13. The ^{31}P NMR spectra of non-silylated compounds **5** usually revealed the presence of small (1–2%) quantities of silylated derivatives (omitted from the ^{31}P NMR data). The susceptibility of these compounds to silylation and the stability of the silyl derivatives are unclear.
14. Compound **5a**: (yellow oil); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 49.69 (s, 34%), 50.20 (s, 13%), 50.16 (s, 15%) and 50.88 (s, 38%); ^1H NMR ($CDCl_3$, 300, 13 MHz) δ: 0.17 (m, 9H, $3\times CH_3$), 0.95 (m, 6H, $2\times CH_3$), 1.53–2.26 (m, 5H, $2\times CH_2$, CH), 2.52–2.87 (m, 2H, CH_2 Ph), 3.87–4.54 (m, 2H, NCHP, OCHP), 5.02–5.24 (m, 5H, CH_2OCO, OCH_2Ph, NH), 7.20–7.37 (m, 15H, ArH). MW = 581.8; MS (ESI) = 582.7 $(M)^+$, 604.8 $(M+Na)^+$, 620.8 $(M+K)^+$.
Compound **5b**: (beige semi-solid); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 49.68 (s, 42%), 49.84 (s, 35%), 50.72 (s, 11%) and 51.25 (s, 12%); ^1H NMR ($CDCl_3$, 300.13 MHz) δ: 0.93 (m, 6H, $2\times CH_3$), 1.26 (m, 3H, OCH_2CH_3), 1.34–2.00 (m, 5H, CH_2, CH_2, CH), 2.068, 2.089, 2.095 ($3\times$ s, 3H, SCH_3), 2.63–2.76 (m, 2H, SCH_2), 4.08–4.25 (m, 5H, NCHP, OCHP, OCH_2CH_3, NH), 5.09–5.23 (m, 3H, CH_2OCO, OH), 7.28–7.36 (m, 5H, ArH). MW = 417.4; MS (ESI) = 417.8 $(M)^+$, 439.9 $(M+Na)^+$, 455.9 $(M+K)^+$.
Compound **5c**: (white semi-solid); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 50.75 (s, 39%), 50.92 (s, 41%), 51.71 (s, 14%) and 52.41 (s, 6%); ^1H NMR ($CDCl_3$, 300.13 MHz) δ: 0.91–1.27 (m, 6H, $2\times CH_3$), 1.87–2.05 (m, 3H, CH_2, CH), 2.61–294 (m, 2H, CH_2), 3.76–4.19 (m, 2H, NCHP, OCHP), 5.00–5.16 (m, 5H, CH_2OCO, OCH_2 Ph, NH), 7.13–7.35 (m, 15H, ArH). MW = 495.5; MS (ESI) = 495.6 $(M)^+$, 517.7 $(M+Na)^+$, 533.6 $(M+K)^+$.
Compound **5d**: (yellow oil); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 46.06 (s, 15%), 46.27 (s, 42%), 47.39 (s, 25%) and 47.87 (s, 18%); ^1H NMR ($CDCl_3$, 300.13 MHz) δ: 0.16 (m, 9H, $3\times CH_3$), 1.02 (t, 3H, CH_3 (one diastereomer), $J = 7.1$ Hz), 1.19–1.38 (m, 6H, $2\times CH_3$, remaining three diastereomers ($3\times$ t) and CH_3 ($4\times$ dd)), 3.86–4.18 (m, 3H, OCHP, OCH_2CH_3), 5.02–5.33 (m, 3H, CH_2OCO, NCHP), 6.32 (m, 1H, NH), 7.28–7.47 (m, 10H, ArH). MW = 449.5; MS (ESI) = 450.1 $(M)^+$, 472.1 $(M+Na)^+$, 488.2 $(M+K)^+$.
Compound **5e**: (beige semi-solid), ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 43.88 (s, 45%), 44.49 (s, 15%), 45.39 (s, 8%) and 45.55 (s, 32%); ^1H NMR ($CDCl_3$, 300.13 MHz) δ: 4.64–5.10 (m, 7H, OCHP, OH, CH_2OCO, OCH_2Ph, NCHP), 7.03–7.50 (m, 20H, ArH). MW = 501.5; MS (ESI) = 502.5 $(M)^+$, 524.5 $(M+Na)^+$, 540.4 $(M+K)^+$.
Compound **5f**: (white semi-solid); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 47.78 (s, 47%, two tightly overlapping resonance signals), 48.06 (s, 34%) and 48.76 (s, 19%); ^1H NMR ($CDCl_3$, 300.13 MHz) δ: 1.82–2.00 (m, 2H, CH_2), 2.58–2.98 (m, 2H, CH_2), 3.76–4.40 (m, 2H, OCHP, OH), 4.72–5.11 (m, 4H, CH_2OCO, OCH_2Ph), 5.40 (m, 1H, NCHP), 7.05–7.35 (m, 20H, ArH); MW = 529.6; MS (ESI) = 530.5 $(M)^+$, 568.5 $(M+K)^+$.
Compound **5g**: (beige semi-solid); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 47.67 (s, 51%), 47.82 (s, 11%), 48.27 (s, 22%) and 48.72 (s, 16%); ^1H NMR ($CDCl_3$, 300.13 MHz) δ: 0.85 (m, 3H, CH_3), 1.18–1.96 (m, 6H, $3\times CH_2$), 3.44–4.35 (m, 3H, OCHP, OH), 4.73–5.15 (m, 4H, CH_2OCO, OCH_2Ph), 5.37 (m, 1H, NCHP), 7.28–7.36 (m, 15H, ArH). MW = 481.5; MS (ESI) = 482.2 $(M)^+$, 504.4 $(M+Na)^+$, 520.4 $(M+K)^+$.
15. 1 mmol of the appropriate compound **5** was treated with 1 mL of 35% HBr in acetic acid at rt for 1 h. The volatile products were removed in vacuo and the residue treated twice with dry Et_2O, which was decanted from the mixture. The remaining oil was dissolved in 2 mL of MeOH and the pH was adjusted to 6 by addition of propylene oxide. Precipitation started after cooling the mixture in a refrigerator. If the compound did not precipitate after 3 h, to the mixture was added 2 mL of dry Et_2O and the mixture was placed in the refrigerator again. Filtration and washing with dry Et_2O gave the desired compound **6** in almost quantitative yield.
Compound **6c**: (white powder): yield 94%, mp = 233.5–235.5 °C, ^{31}P NMR (D_2O, 121.5 MHz) δ: 39.26 (s, 49%) and 39.66 (s, 51%); ^1H NMR (D_2O, 300.13 MHz) δ: 0.91 (t, 6H, $2\times CH_3$, $J = 6.8$ Hz, diastereomeric), 0.93 (t, 6H, $2\times CH_3$, $J = 6.75$ Hz, diastereomeric), 1.78–1.94 (m, 2H, CH_2 CH_2Ph), 2.11–2.19 (m, 1H, CH), 2.50–2.60 and

2.71–2.78 (m, 2H, C$H_2$$CH_2$Ph), 3.19 (dd, 1H, NCHP, $^2J_{HP}$ = 9.9 Hz, $^3J_{HH}$ = 6.1 Hz, diastereomeric), 3.33 (dd, 1H, NCHP, $^2J_{HP}$ = 4.9 Hz, $^3J_{HH}$ = 4.9 Hz, diastereomeric), 3.70–3.79 (m, 1H, OCHP), 7.07–7.23 (m, 5H, ArH); ^{13}C NMR (D_2O, 75.46 MHz) δ: 17.20 (d, J = 3.9 Hz, CH_3, rotamer), 17.84 (d, J = 5.6 Hz, CH_3, rotamer), 19.47 (d, J = 8.2 Hz, CH_3, rotamer), 19.67 (d, J = 6.4 Hz, CH_3, rotamer), 26.7 (d, J = 7.1, $CH_2$$CH_2$Ph), 30.64 (s, $CH_2$$CH_2$Ph), 30.76 (s, $CH_2$$CH_2$Ph), 30.93 (s, CH), 31.12 (s, CH), 53.15 (d, $^1J_{CP}$ = 91.1 Hz, NCHP, diastereomeric), 53.49 (d, $^1J_{CP}$ = 90.7 Hz, NCHP, diastereomeric), 67.78 (d,$^1J_{CP}$ = 72.5 Hz, OCHP, diastereomeric), 69.31 (d, $^1J_{CP}$ = 73.0 Hz, OCHP, diastereomeric), 126.3 (s, arom.), 128.63 (s, ArH), 128.72 (s, ArH), 141.30 (s, ArH); IR (KBr, ν [cm^{-1}]) 1018.75 (s, P–OH), 1052.0 (s, C–O), 1161 (s, P=O), 1613.9 (m, N–H), 2872.1–3026.8 (ms, C–H), 3183 (ms, O–H).

16. The deprotection of **5** did not result in exchange of the hydroxy group by bromine, as confirmed by ^{1}H and ^{13}C NMR analysis. Our efforts to deprotect **5** in boiling 5 M HCl failed because of partial cleavage of the C–P bond.
17. This work is the subject of patent applications—P370190 and P372057.