Pergamon

Tetrahedron Letters 43 (2002) 6325–6328

TETRAHEDRON LETTERS

New organometallic approach to derivatives of α-substituted statines from *N*,*N*-dibenzylaminoaldehydes

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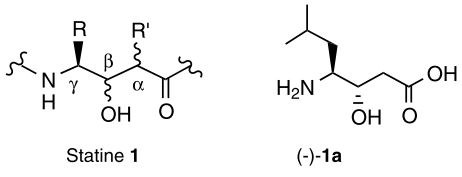
Received 10 May 2002; revised 10 July 2002; accepted 12 July 2002

Abstract—α-Substituted statines derivatives were synthesized via the zinc-mediated allylation of *N*,*N*-dibenzyl α-aminoaldehydes followed by ozonolysis of the intermediate homoallylic alcohols.

In recent years, β-hydroxy-γ-aminoacids **1** (statines) have received much attention since these aminoacids are key units in peptidomimetic protease inhibitors (Fig. 1).[1] Particularly aspartic proteases including pepsin, renin, HIV-1 and HIV-2 proteases, plasmepsin, cathepsin D and β-secretase are targets for peptidomimetic inhibitors.[2] The majority of protease inhibitors are based on transition-state analogues as replacements for the dipeptide subunit at the cleavage bond of the substrate. The statine moiety replaces this subunit that contains the scissile amide bond (P_1–P'_1 residues). The critical hydroxyl group of statines acts as transition-state mimic which interacts with the two catalytic aspartates.[2,3] Furthermore, the configuration of the C_β chiral center influences the binding affinity of the inhibitors.[4,5] So, statines act as isosteres for a restricted conformation of a dipeptide unit.

In order to replace the missing P'_1 side chain, it would be of interest to introduce a substituent at the α-position of statines.[6] Synthesis of statine, (–)-(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid **1a**, and its *N*-protected ester derivatives are well described.[7] On the other hand, only a few examples of α-substituted statines have appeared in the literature, mainly via ring-opening of α,β-epoxy ester[6,8] and aldol-type reactions.[9,10]



Statine **1** (-)-**1a**

Figure 1.

In our ongoing studies to synthesize new statines functionalized at the C_α position[10], we report here on an expeditious synthetic route to these isosteres via the well described metal-mediated allylation of *N*-protected α-aminoaldehydes[11,12] followed by the ozonolysis of the double-bond (Scheme 1).

The *N*,*N*-dibenzylaminoaldehydes **3** were selected as starting materials for they are easily prepared in enantiomeric pure form from α-amino acids **2** and are useful chiral building blocks in C–C bond forming reactions.[12] Particularly the addition of organometallic allylic reagents (Mg[13], Ti[13], B[14], Zn[15], Cr[16], In[17]) to these derivatives has been described to give homoallylic alcohols with a high *anti* diastereoselectivity.[12,18] Barbier-type zinc-mediated allylation in aqueous media was chosen for this last reason and for its procedure convenience.[19]

Thus, *N*,*N*-dibenzylaminoaldehydes **3a**–**c** derived from alanine, leucine and phenylalanine **2a**–**c**, respectively, were prepared according to the Reetz procedure.[12] Treatment of these aldehydes **3a**–**c** with organozinc reagents generated in situ from allyl and crotyl bromide in NH_4Cl aqueous medium following a modified reported procedure[20] afforded homoallylic alcohols **4**.

Keywords: α-aminoaldehydes; organozinc reagents; homoallylic alcohols; statines.

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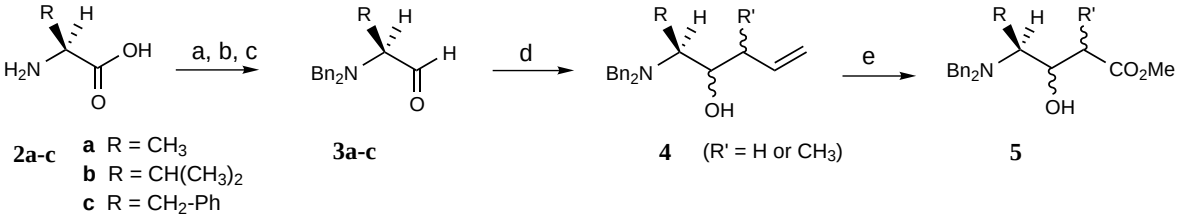
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01401-6



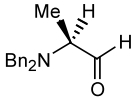
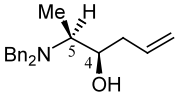
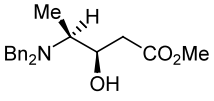
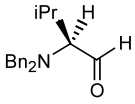
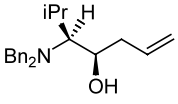
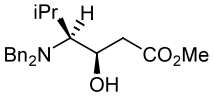
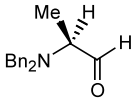
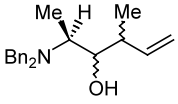
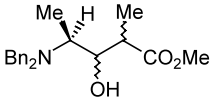
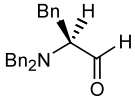
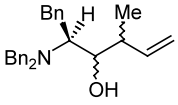
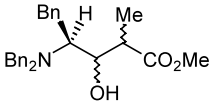
Scheme 1. *Reagents and conditions*: (a) K_2CO_3, BnBr; (b) $LiAlH_4$, THF; (c) $COCl_2$, NEt_3, DMSO; (d) R′-CH=CH-CH_2Br, Zn, THF, NH_4Cl; (e) O_3, NaOH, CH_3OH, CH_2Cl_2, −78°C.

Ozonolysis of the double bond was carried out in CH_2Cl_2–MeOH in the presence of sodium hydroxide.[21] Under these conditions the intermediate ozonides were directly transformed to the statine methyl esters **5** (Scheme 1, Table 1).

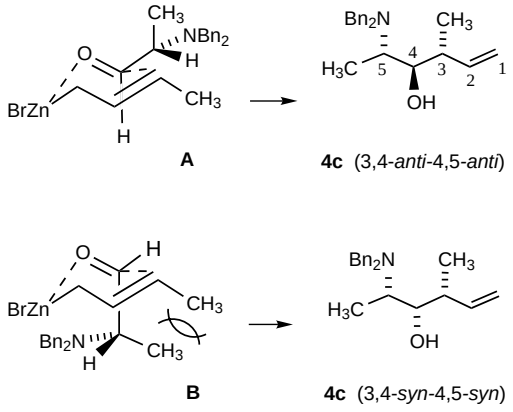
The addition of allylzinc bromide to *N*,*N*-dibenzyl-aminoaldehydes **3a**,**b** (entries 1, 2) gave the *anti* homoallylic alcohols **4a**,**b** practically as unique diastereomers (*anti*/*syn*>97/3) as already described.[15] This very high *anti* diastereoselectivity has been explained by allylation from the less hindered *re* face of the carbonyl group following a non-chelated Felkin–Anh model.[15,20,22] Ozonolysis then gave the β-hydroxy-esters **5a**,**b** with moderate unoptimized yields.

The addition of crotylzinc bromide to aminoaldehyde **3a** (entry 3) afforded alcohol **4c** as a mixture 78:22 of two of the four possible diastereomers to which the stereochemistry 3,4-*anti*–4,5-*anti* and 3,4-*syn*–4,5-*syn* were attributed, respectively (Scheme 2).[23] These assignments resulted from the analysis and comparison of their ^1H and ^{13}C NMR spectra with the ones of the four diastereomers of alcohol **4c** which have been already prepared by Hoffmann et al.[14] The major diastereomer **4c** (3,4-*anti*–4,5-*anti*) was the expected

Table 1. Synthesis of statine methyl esters **5**

Entry	α-Amino aldehydes **3a-c**	Homoallylic alcohols **4**	Yield **4** (%)[a]	(*anti*/*syn*)$_{4,5}$[b] **4a-b**	Diastereo-selectivity[c] **4c-d**	Statine derivatives **5**	Yield **5** (%)[a]
1	 **3a**	 **4a**	55	100 / 0		 **5a**	42
2	 **3b**	 **4b**	52	97/3		 **5b**	43
3	 **3a**	 **4c**	57		2 dia (78/22)	 **5c**	40
4	 **3c**	 **4d**	59		2 dia (~80/20)	 **5d**	52

[a] Yield of purified product after flash-chromatography.
[b] *anti*/*syn* Ratio estimated by GLC analysis.
[c] Diastereomeric ratio estimated by ^1H NMR spectroscopy



Scheme 2.

one and resulted from the chairlike transition state **A** where both the γ-methyl group of the crotyl reagent and the chiral residue of the aminoaldehyde **3a** are in pseudo-equatorial position.[18] The minor one should emerge from the less favored transition state **B** in which the latter group is in the axial position (Scheme 2). The subsequent ozonolysis gave the statine **5c** as a mixture from which the major diastereomer could be obtained pure by chromatography.[24]

Crotylzinc bromide reacted likewise with α-aminoaldehyde **3c** (entry 4). It gave the homoallylic alcohol **4d** also as a mixture of two diastereomers (ratio 80:20; supposed to be the *anti–anti* and *syn–syn* diastereomers by analogy with alcohol **4c**) as shown by analysis of its ^{1}H and ^{13}C NMR spectra. The corresponding β-hydroxyester **5d** was further obtained by ozonolysis of the terminal double bond.

In summary, we have demonstrated that α-substituted statine derivatives can be obtained by the diastereoselective zinc-mediated condensation of allylic bromides to *N*,*N*-dibenzyl α-aminoaldehydes followed by ozonolysis of the intermediate homoallylic alcohols.

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23. **Typical procedure** (entry 3). Crotyl bromide (1.4 g, 10.4 mmol, 2 equiv.) was slowly added to a suspension of *N*,*N*-dibenzylaminoaldehyde **3a** (1.31 g, 5.2 mmol) and Zn (1.37 g, 20.8 mmol, 4 equiv.) in THF (15 mL)/saturated aqueous NH_4Cl (3 mL) maintained at 0°C. After stirring for 6 h, another equivalent of crotyl bromide was added. The mixture was stirred at room temperature overnight, diluted with water and extracted with AcOEt. The solvents were evaporated to afford a crude residue that was purified by flash-chromatography on silica gel with hexane/AcOEt (90/10). 5-Dibenzylamino-3-methyl-hexen-4-ol **4c** (908 mg, 57%) was obtained as a mixture 78/22 of two diastereomers. R_f (SiO_2, PE/Et_2O: 50/50) = 0.72. IR (neat), cm^{-1}: 3452, 3063, 2965, 2803, 1635, 1602, 1494, 1453, 1377, 1242, 1111, 1073, 1028, 998, 970, 913, 828. Spectral data for **4c** (*anti–anti*): ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 0.95 (d, J = 7.0 Hz, 3H, 3-C-CH_3); 1.14 (d, J = 6.7 Hz, 3H, 6-CH_3); 1.45 (br.s, 1H, OH); 2.74 (quint, J = 6.7 Hz, 5-CH-N); 3.4–3.5 (m, 1H, 4-CH-O); 3.51 and 3.78 (syst. AB, J = 13.7 Hz, 4H, 2×CH_2-N); 4.90 (dd, J = 17.3 and 1.9 Hz, 1H, 1-CH); 5.0 (m, 1H, 1-CH); 5.43 (ddd, J = 17.3, 10.6 and 7.1 Hz, 1H, 2-CH); 7.2–7.4 (m, 10H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 8.6 (6-C); 16.6 (3-C-CH$_3$); 39.3 (3-C); 54.6 (2×CH$_2$-N); 55.0 (5-CH-N); 76.8 (4-CH-O); 116.8 (1-C); 126.9, 128.3 and

129.0 (3×*C* Ar.); 139.0 (2-*C*), 140.4 (*C* Ar.). **4c** (*syn–syn*): ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 0.62 (d, $J=6.8$ Hz, 3H, 3-C-CH_3); 1.16 (d, $J=6.6$ Hz, 3H, 6-CH_3); 2.77 (quint, $J=6.7$ Hz, 5-C*H*-N); 3.7–3.8 (m, 1H, 4-C*H*-O); 3.46 and 3.76 (syst. AB, $J=13.6$ Hz, 4H, 2xCH_2-N); 4.80–5.0 (m, 1H, 1-C*H*); 5.0–5.2 (m, 1H, 1-C*H*); 5.77 (ddd, $J=17.7$, 10 and 6.7 Hz, 1H, 2-C*H*); 7.2–7.4 (m, 10H, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 8.7 (6-*C*); 11.8 (3-C-*C*H$_3$); 39.1 (3-*C*); 54.4 (5-*C*H-N); 54.6 (2×*C*H$_2$-N); 76.2 (4-*C*H-O); 114.6 (1-*C*); 127.0, 128.3, 129.1 and 140.2 (4×*C* Ar.); 142.4 (2-*C*). These ^{1}H and ^{13}C NMR data were in very good agreement with the ones described by Hoffmann et al. for the *anti–anti* and *syn–syn* diastereomers.[14]

24. Methyl 4-dibenzylamino-2-methyl-3-hydroxypentanoate **5c**. Ozone was allowed to bubble into a stirred solution maintained at −78°C of alcohol **4c** (308 mg, 1 mmol) in 2.5 M methanolic sodium hydroxide (2 mL) and CH_2Cl_2 (8 mL) until the solution became blue (~90 min). The solution was warmed up, diluted with ether and hydrolyzed. After extraction with ether and drying on Na_2SO_4, the solvents were evaporated under vacuo. The crude residue was purified by flash-chromatography (PE/Et_2O: 40/60) to give the β-hydroxyaminoester **5c** (136 mg, 40%). A second chromatography afforded the major diastereomer of **5c** as a colorless oil. R_f (SiO_2, hexane/Et_2O: 20/80 = 0.38). $[\alpha]_D^{20}$ −8 (*c* 1, CH_2Cl_2). IR (neat) cm^{-1}: 3380, 3062, 3029, 2978, 2949, 1737, 1616, 1496, 1454, 1200. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 0.82 (d, $J=7$ Hz, 3H, 2-C-CH_3); 1.37 (d, $J=7$ Hz, 3H, 5-CH_3); 2.35 (m, 1H, 2-C*H*); 2.62 (m, 1H, 4-C*H*-N); 3.33 and 3.85 (syst. AB, $J=13.3$ Hz, 4H, 2×CH_2-N); 3.48 (m, 1H, 3-C*H*-O); 3.69 (s, 3H, O-CH_3); 5.50 (s, 1H, O*H*); 7.2–7.4 (m, 10H, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 11.1 (2-C-*C*H$_3$); 14.1 (5-*C*); 43.2 (2-*C*); 51.9 (O-*C*H3); 55.3 (*C*H$_2$-N); 57.7 (3-*C*-OH); 76.1 (4-*C*-N); 126.5, 127.6, 128.7 and 136.6 (4×*C* Ar.); 175.8 (1-*C*=O).