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Stereoselective reduction of *N*-phthaloyl α-amino ketones: an expeditious synthesis of statine

Saumitra Sengupta * and Debarati Sen Sarma

Department of Chemistry, Jadavpur University, Calcutta 700 032, India

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Abstract

A highly diastereoselective synthesis of a protected statine derivative via *syn*-selective LiAlH(OBu-*t*)$_3$ reduction of a leucine derived *N*-phthaloyl α-amino ketone is described.

1. Introduction

Statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, **1**] is the key pharmacophore present in the naturally occurring renin inhibitor pepstatin.[1] Due to its unusual structure and associated biological importance, especially in the development of the dipeptide isostere theory for inhibition of aspartyl proteases,[1a] considerable effort has been directed toward its stereoselective synthesis.[2] Since statine acts as a transition-state mimic of peptide hydrolysis (hydroxyethylene dipeptide isostere), its biological activities are strongly dependent on the relative (*syn*) and absolute (3*S*,4*S*) configurations of its chiral centers. Hence, the key challenge in statine synthesis is to establish its *syn*-aminoalcohol disposition. Until now, this has been mostly attempted via diastereoselective addition reactions of acetate enolates to NH-monoprotected leucinal derivatives. These approaches, however, suffer from modest levels of *syn*-selectivity and the operational problems that are usually associated with the use of chemically sensitive and racemization-prone NH-monoprotected α-amino aldehydes. In 1989, Reetz et. al., while investigating the non-chelation controlled reductions of *N*,*N*-Bn$_2$ α-amino ketones, described a complementary strategy in which the *syn*-aminoalcohol disposition of statine was established in 88% de via a highly *syn*-selective borohydride reduction of a leucine derived *N*,*N*-Bn$_2$ γ-amino-β-keto ester.[3] Similar *syn*-selective reduction (93% de) of a leucine derived NH-trityl γ-amino-β-keto ester has also been reported by Hoffman and Tao in their recent statine synthesis.[4] This amino ketone reduction strategy is undoubtedly more attractive than addition reactions to α-amino aldehydes since it provides high levels

* Corresponding author. Fax: 91-33-4734266.

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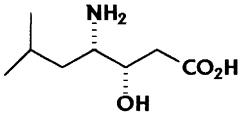
of the desired *syn*-selectivity and at the same time, avoids handling of sensitive educts like the α-amino aldehydes. The strategy, however, requires special and bulky *N*-protecting groups like the *N*,*N*-Bn_2 or NH-trityl to be present on the α-amino ketone in order to achieve the high levels of *syn*-selectivity in the reduction step. It may be noted that borohydride or K-selectride reductions of α-amino ketones having other common *N*-protecting groups such as *t*-Boc, Cbz or Fmoc usually lead to *anti*-diastereoselectivity.[3b] Hence, if applied to statine synthesis, they would lead to the wrong diastereomer (3*R*,4*S*) and would require subsequent inversion of the C-3 stereochemistry.



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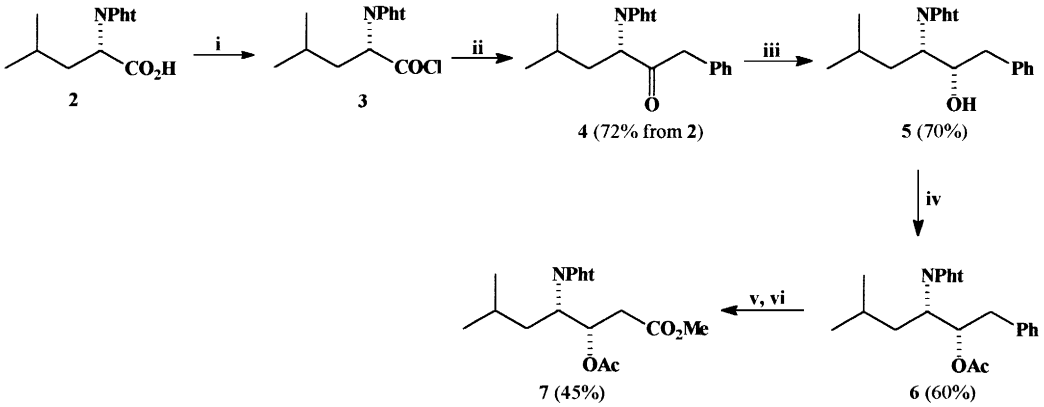
We have recently reported that *N*-phthaloyl α-amino ketones, having a conventional *N*-protecting group, can be reduced with LiAlH(OBu-*t*)$_3$ via the Felkin-mode with high *syn*-selectivity (≥90% des) and have applied this protocol towards stereoselective syntheses of *syn*-α-amino epoxides and *syn*-3-amino-1,2-diols.[5,6] As a further application of this protocol, we now present here an expeditious synthesis of statine via a highly diastereoselective *syn*-reduction of a leucine derived *N*-phthaloyl α-amino ketone.

2. Results and discussion



Scheme 1. (i) $SOCl_2$, benzene, reflux; (ii) $PhCH_2ZnBr$, 10% $PdCl_2(PPh_3)_2$, THF, rt; (iii) LiAlH(OBu-*t*)$_3$ (2 equiv.), THF, −20°C; (iv) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt; (v) cat. $RuCl_3$, $NaIO_4$, CH_3CN–CCl_4–H_2O, rt; (vi) CH_2N_2, ether, 0°C

N-Phthaloyl (NPht) L-leucine **2** was first converted to its acid chloride **3** ($SOCl_2$, benzene, reflux) and the latter coupled with $PhCH_2ZnBr$ in the presence of 10% $Pd(PPh_3)_2Cl_2$[7] (THF, rt) to give the α-amino benzyl ketone **4** in 72% yield over two steps (Scheme 1). In earlier studies,[6] we have observed that LiAlH(OBu-*t*)$_3$ reductions of *N*-phthaloyl γ-amino β-keto esters lead to complex product mixtures, perhaps due to the presence of dense functionalities in the latter. Hence, in the present approach, we decided to use the less functionalized benzyl ketone **4** as a latent γ-amino-β-keto ester. LiAlH(OBu-*t*)$_3$ reduction of **4** proceeded smoothly in THF at −20°C to give the *syn*-aminoalcohol **5**, virtually as a single diastereomer (90% de by ^{1}H NMR), in 70% yield. The highest levels of des were obtained only at −20°C; reductions carried out at 0°C gave, at best, an 85:15 ratio of the *syn*:*anti* aminoalcohols. LiAlH(OBu-*t*)$_3$, a bulky and chemoselective reducing agent,[8] was found to be absolutely essential for this reduction. $NaBH_4$ or $NaB(CN)H_3$, on the other hand, not only gave lower diastereoselectivities (ca. 40% des) but

also poor chemical yields due to extensive hydride attacks on the phthaloyl moiety of **4**. Moreover, it was found that two equivalents of LiAlH(OBu-*t*)$_3$ were necessary for complete reduction of **4**. The *syn*-stereochemistry in **5** was clearly evident from the ^{1}H NMR spectra, especially after conversion to the acetate **6** (60%), which showed a relatively large coupling constant between its aminoalcohol protons H-2 and H-3 ($J_{2,3}$=7.6 Hz). The synthesis was completed by Sharpless oxidation (cat. $RuCl_3$, $NaIO_4$, CH_3CN–CCl_4–H_2O)[9] of the phenyl ring in **6** to the carboxylic acid and subsequent esterification with diazomethane to give the protected statine ester **7** in 45% overall yield from **6**. The *syn*-stereochemistry in **7** was again evident from its ^{1}H NMR spectrum which showed a large *J*-value for the H-3 and H-4 protons ($J_{3,4}$=6.8 Hz).

In summary, a facile synthesis of a protected statine ester based on a highly diastereoselective *syn*-reduction of NPht leucinyl benzyl ketone with LiAlH(OBu-*t*)$_3$ has been achieved. Also noteworthy is the use of a Pd-catalyzed α-amino acylation reaction of an organozinc reagent for the preparation of the key α-amino benzyl ketone under mild conditions.

3. Experimental

All melting points are uncorrected. IR spectra were taken on a Perkin Elmer R-297 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS as internal standard) on Bruker DPX-200 (200 MHz) and DPX-300 (300 MHz) instruments and reported in ppm scale. Optical rotations were measured in $CHCl_3$ at 25°C on a JASCO DIP-360 digital polarimeter. Column chromatography was performed on silica gel (60–120). Pet. ether refers to the fraction boiling at 60–80°C.

*3.1. (*S*)-5-Methyl-1-phenyl-3-phthalimidohexan-2-one **4***

A solution of *N*-Pht L-leucine (**2**) (0.26 g, 1.0 mmol) and $SOCl_2$ (0.35 g, 3.0 mmol) in benzene (10 ml) was heated under reflux for 3 h. The solution was then evaporated under reduced pressure to afford the acid chloride **3** which was used as such in the subsequent reaction.

Zinc dust (0.13 g, 2.0 mmol), 1,2-dibromoethane (0.03 g, 0.01 ml, 0.2 mmol) in THF (3 ml) was heated gently until ebullition of solvent was observed. The suspension was stirred for a few minutes at rt and heated again. The process was repeated three times. It was then cooled to 0°C and benzyl bromide (0.34 g, 0.23 ml, 2.0 mmol) in THF (2 ml) was added dropwise over 15 min. It was then stirred at rt for 1 h after which the acid chloride **3** and $PdCl_2(PPh_3)_2$ (0.07 g, 0.1 mmol) were added in quick succession. After stirring overnight at rt, the reaction mixture was diluted with water (10 ml), extracted with ether (3×10 ml), dried and evaporated under reduced pressure. The crude product was then purified by silica-gel chromatography (5% EtOAc in pet. ether) to give **4** as an oil (0.23 g, 72%); $[\alpha]_D^{25}$ −3.5 (*c* 1.5, $CHCl_3$); IR (neat): 1700–1740 (br), 1770, 2860, 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (d, 3H, *J*=6 Hz), 0.91 (d, 3H, *J*=6 Hz), 1.42–1.47 (m, 1H), 1.84–1.99 (m, 1H), 2.19–2.34 (m, 1H), 3.75 (s, 2H), 4.87 (dd, 1H, *J*=4.3, 11.4 Hz), 7.07–7.12 (m, 2H), 7.18–7.26 (m, 3H), 7.69–7.74 (m, 2H), 7.80–7.86 (m, 2H). Found: C, 75.06; H, 6.25; N, 4.20; $C_{21}H_{21}NO_3$ requires C, 75.22; H, 6.26 and N, 4.17%.

*3.2. (2*S*,3*S*)-2-Acetoxy-5-methyl-1-phenyl-3-phthalimidohexane **6***

LiAlH(OBu-*t*)$_3$ (1.53 g, 6.0 mmol) was added to a solution of **4** (1.0 g, 3.0 mmol) in THF (15 ml) at −20°C. After 30 min, the reaction mixture was diluted with water (10 ml) and extracted with ether (3×10 ml). The organic layer was dried, evaporated under reduced pressure and the residue purified by

silica-gel chromatography (10% EtOAc in pet. ether) to give **5** (0.70 g, 70%); mp 95–96°C (EtOAc–pet. ether). To a solution of **5** (0.67 g, 2.0 mmol) in CH_2Cl_2 (10 ml) was added acetic anhydride (0.4 g, 4.0 mmol), Et_3N (0.24, 2.4 mmol) and DMAP (0.002 g) and the mixture was stirred at rt for 12 h. It was then washed with water, dried and evaporated under reduced pressure. The residue was purified by silica-gel chromatography (7–8% EtOAc in pet. ether) to give **6** (0.45 g, 60%); mp 84–85°C; $[\alpha]_D^{25}$ –5.1 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 1700–1740 (br), 1765, 2950 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.86 (d, 3H, *J*=5.8 Hz), 0.90 (d, 3H, *J*=6 Hz), 1.35–1.44 (m, 2H), 1.73 (s, 3H), 2.40–2.48 (m, 1H), 2.76 (dd, 1H, *J*=9.4, 14.1 Hz), 3.10 (dd, 1H, *J*=3.6, 14.1 Hz), 4.46 (ddd, 1H, *J*=3.8, 7.6, 11.7 Hz), 5.62 (ddd, 1H, *J*=3.6, 7.6, 9.4 Hz), 7.17–7.29 (m, 5H), 7.70–7.72 (m, 2H), 7.81–7.84 (m, 2H). Found: C, 72.65; H, 6.70; N, 3.71; $C_{23}H_{25}NO_4$ requires C, 72.82; H, 6.59 and N, 3.69%.

*3.3. (3S,4S)-Methyl (3-acetoxy-6-methyl-4-phthalimido)heptanoate **7***

To a biphasic mixture of **6** (0.38 g, 1.0 mmol) in CH_3CN (4 ml), CCl_4 (4 ml) and H_2O (8 ml) was added $NaIO_4$ (3.85 g, 18.0 mmol) and $RuCl_3 \cdot H_2O$ (0.004 g, 0.022 mmol) and the mixture stirred vigorously at rt for 48 h. It was then filtered, CH_2Cl_2 (15 ml) added to the filtrate and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 ml) and the combined organic layer dried and concentrated under reduced pressure to a volume of 5 ml. It was then added dropwise to a freshly prepared solution of CH_2N_2 [prepared from nitrosomethyl urea (0.41 g, 4.0 mmol) and KOH (0.5 g)] in ether (10 ml) at 0°C. After reaching rt, the solution was washed with satd. $NaHCO_3$ soln., dried and evaporated under reduced pressure. The residue was purified by silica-gel chromatography (15% EtOAc in pet. ether) to give **7** as an oil (0.16 g, 45%); $[\alpha]_D^{25}$ −4.2 (*c* 0.09, $CHCl_3$); IR (neat): 1700–1740 (br), 1770, 2950 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, 3H, *J*=5.8 Hz), 0.90 (d, 3H, *J*=5.8 Hz), 1.33–1.47 (m, 2H), 1.93 (s, 3H), 2.35–2.42 (m, 1H), 2.59 (dd, 1H, *J*=8.0, 15.8 Hz), 2.75 (dd, 1H, *J*=4.4, 15.8 Hz), 3.69 (s, 3H), 4.52 (ddd, 1H, *J*=4.1, 6.8, 11.5 Hz), 5.70 (ddd, 1H, *J*=4.4, 6.8, 8.0 Hz), 7.71–7.75 (m, 2H), 7.81–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 21.1, 23.3, 25.0, 36.4, 36.9, 51.9, 52.3, 70.5, 123.3, 131.5, 134.0, 168.4, 170.0, 170.1. Found: C, 63.30; H, 6.12; N, 3.90; $C_{19}H_{23}NO_6$ requires C, 63.15; H, 6.37 and N, 3.87%.

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