A Simple Synthetic Route to Statine and Statine Analogues

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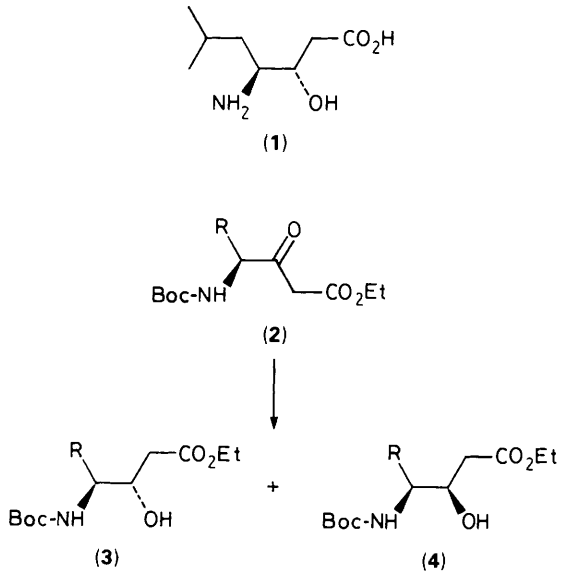
The biologically important amino acid statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, as well as optically active statine analogues, are readily accessible in the ester form by simple reduction of the corresponding *N*,*N*-dibenzyl β-keto esters using $NaBH_4$ followed by deprotection.

Chiral β-amino alcohols are biologically and pharmacologically interesting compounds.[1] An example is statine (**1**), a constituent of the naturally occurring small peptide pepstatin which is a strong inhibitor of such aspartic proteinases as pepsin, renin, and cathepsin.[2] Since renin inhibitors are currently of great interest in the treatment of hypertension and congestive heart failure, considerable efforts have gone into the synthesis of statine and statine analogues.[3]

Since the (3*S*,4*S*)-configuration is an essential requirement for biological activity, stereoselective routes are required. The most efficient approach to date involves the conversion of t-butoxycarbonyl (Boc) protected L-amino acids into the corresponding β-keto esters (**2**) followed by reduction to (**3**). Unfortunately, common achiral reducing agents such as $NaBH_4$ or $NaCNBH_3$ lead to mixtures of diastereoisomers (**3**)/(**4**) or to the wrong (3*R*,4*S*)-diastereoisomer (**4**), and bulky reagents such as $K(Bu^s)_3BH$ afford <25% of (**3**).[3—5] Therefore, *chiral* reducing agents had to be applied, *e.g.*, enzymes[5] or optically active Wilkinson catalysts.[6]

We now report an unusually simple synthesis of (**1**) and analogues which *relies solely on the influence of the chiral centre already present in the precursor* (Scheme 1).

Naturally occurring L-amino acids (**5**) were first protected at nitrogen to provide the *N*,*N*-dibenzylated acid derivatives (**6**), which were then converted into the imidazolides. Without isolation the latter were allowed to react with the magnesium enolate of malonic acid monoethyl ester[7] at 0 → 40 °C, affording after acidic work-up the keto esters (**7**). These are also accessible by the reaction of the lithium enolate of ethyl acetate with the imidazolides at −78 °C (70—78% yield) or with the benzyl esters[9] of (**6**) (40%). The decisive reduction of (**7**) using $NaBH_4$ in methanol at −20 °C occurred stereoselectively with non-chelation control[8] to form the desired (*S*,*S*)-products (**8**) preferentially (Scheme 1). Non-chelation control is also observed in Grignard and aldol additions to the analogous *N*,*N*-dibenzylamino aldehydes and is in line with the Felkin–Anh model.[9] Control experiments show that compounds (**9**) are enantiomerically pure [enantiomeric



excess (e.e.) 99% for (**9a**) and (**9b**); 97% for (**9c**)],[10] proving that essentially no racemization occurs at any stage of the sequence. This was accomplished by acylating the pure diastereoisomers (**8**) using (*R*)(+)-2-methoxy-α-trifluoromethylphenylacetyl chloride[10] and investigating the products by ^{13}C and ^{19}F n.m.r. spectroscopy as well as h.p.l.c. Essentially only one diastereoisomer was detected, in contrast to the results obtained when working in the racemic series using (±)-amino acids as starting materials. The products are readily deprotected using Pd-black/HCO_2H/MeOH;[9] *e.g.* (**9a**) gives the corresponding free amine in 85% yield.

Since the above four-step sequence can be performed on a multigram scale, it constitutes a simple synthesis of statine-like compounds using cheap reagents and reaction partners. It can also be used to prepare the (*R*,*R*)-enantiomers starting from D-amino acids. The present method is stereochemically complementary to the previously described non-chelation-controlled aldol additions of lithium enolates to *N*,*N*-dibenzyl α-amino aldehydes which provide 95% of the (*S*,*R*)- or (*R*,*S*)-diastereoisomers.[9] Both methods demonstrate the power of 'protective group tuning,' Boc and 9-phenylfluoren-9-yl protective groups generally leading to mixtures of diastereoisomers.[1,3—5,7,11]

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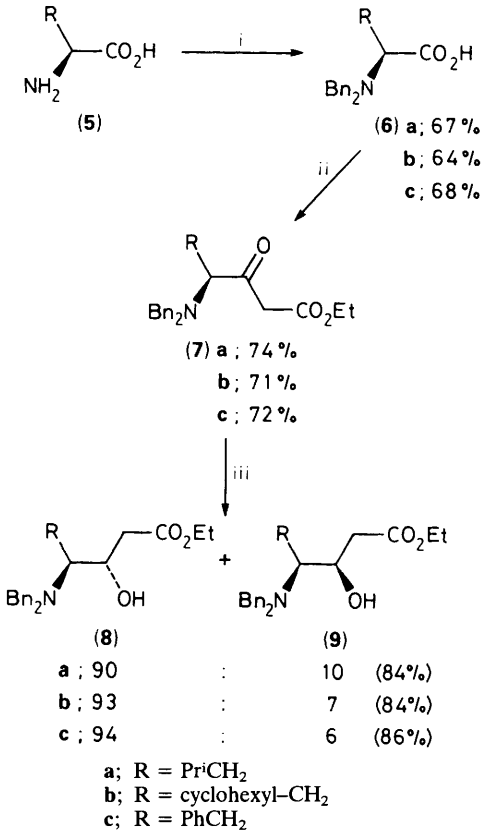

Scheme 1. *Reagents and conditions*: i, K_2CO_3/BnBr (Bn = $PhCH_2$),[9] then KOH/H_2O/dioxane; ii, *N*,*N*-carbonyldi-imidazole, then $Pr^iMgCl/CH_2(CO_2Et)CO_2H$;[7] iii, $NaBH_4$/MeOH, −20 °C.

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