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Enantiospecific Synthesis of (3*S*, 4*S*)-Statine and Its Analogue from D-Glucosamine as a Chiral Pool

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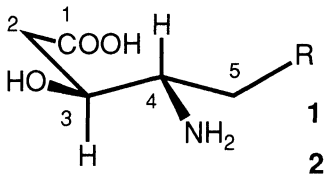
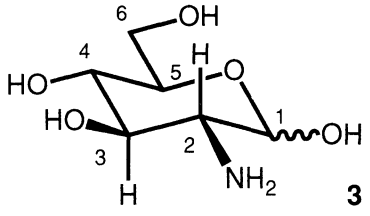
The C(6)-carbon degradation and elimination of C(4)-hydroxy group of D-glucosamine were achieved in 8-steps and 30% overall yield to furnish (4*R*, 5*S*)-5-vinyl-2-oxazolidin-one-4-carbaldehyde dimethyl acetal, which was utilized as a key intermediate for enantiospecific synthesis of biologically important threo β-hydroxy-γ-amino acids, natural (3*S*, 4*S*)-statine and (3*S*, 4*S*)-AHPPA

Novel β-hydroxy-γ-amino acids, statine ((3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid) (**1**)[1] and AHPPA ((3*S*, 4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid) (**2**)[2] are the key components of natural peptides pepstatin and ahpatinin, respectively, which are potent inhibitors of aspartic proteases pepsin and renin.[3] Recently, analogues of AHPPA (**2**) involved in oligopeptides have been found to play important roles in the inhibitory activities against the aspartic protease of human immunodeficiency virus type-1 (HIV-1).[4] In view of development for new antihypertensive drugs inhibiting the renin-angiotensin-aldosterone pressor system[5] and for the therapeutic agents of acquired immunodeficiency syndrome (AIDS),[6] efficient synthesis of natural statine (**1**) and AHPPA (**2**) and their analogues has been one of the most attractive decoys for synthetic chemists.

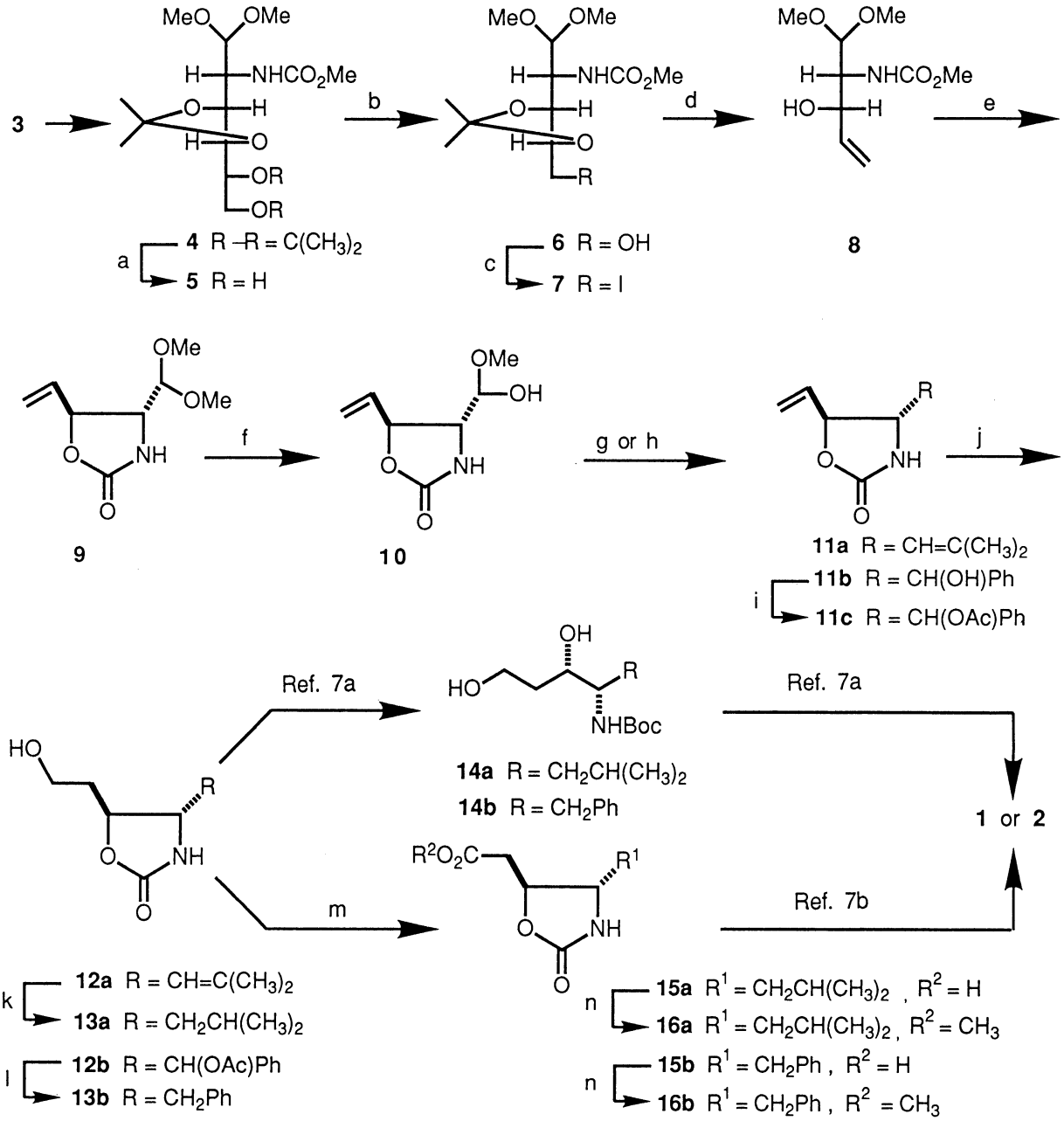
All synthetic methods for these compounds reported to date have been concerned with construction of the one or two chiral centers involved in **1** and **2** by asymmetric induction mainly starting from α-amino acids, (*S*)-leucine[7] and (*S*)-phenylalanine,[7b,8] and in a few cases from malic acid[9] and sugar derivatives[10] and by asymmetric synthesis using (-)-3-ketopinyl-2-oxazolone[11a] and applying the Sharpless oxidation.[11b] We envisaged that inexpensive and readily available D-glucosamine (**3**) serves as a facile starting material for natural statine and its analogues if eliminations of the C(6)-carbon and C(4)-hydroxy group and introduction of alkyl or aryl group with deoxygenation at the C(1)-position of **3** are achieved. Now we wish to report realization of the strategy including the enantiospecific synthesis of natural (3*S*, 4*S*)-statine (**1**) and (3*S*, 4*S*)-AHPPA (**2**) starting from D-glucosamine (**3**) through effective utilization of the inherent chiral threo-2,3-aminoalcohol system of **3**.



1 R = $CH(CH_3)_2$
2 R = Ph



3



a) AcOH - H_2O (4 : 1), 40 °C, 2 h, 84%; b) i. $NaIO_4$, acetone - H_2O (1 : 1), 0 °C–rt, 1 h; ii. $NaBH_4$, CH_2Cl_2 - MeOH (1 : 1), 0 °C–rt, 2 h, 85% for **6** from **5**; c) I_2, Ph_3P, imidazole, toluene, 90 °C, 0.5 h, 87%; d) Zn, i-PrOH - H_2O (9 : 1), reflux, 1 h; e) NaOMe, MeOH, rt, 97% for **9** from **7**; f) conc. HCl - dioxane (1 : 1), rt, 1.5 h, and then chromatography on silica gel ($CHCl_3$ - MeOH (7 : 1)); g) $Ph_3P{=}C(CH_3)_2$, THF, 0 °C–rt, 5 h, 76% for **11a** from **9**; h) PhMgBr (4 equiv.), THF, - 80–0 °C, 2 h, 66% for **11b** from **9**; i) Ac_2O, pyridine, CH_2Cl_2, 2 h, 83%; j) 9-BBN, THF, rt, 5 h, and then 3 mol dm^{-3} NaOH, 30% H_2O_2, EtOH, 0–50 °C, 77% for **12a** from **11a** or 9-BBN, THF, rt, 3 h, and then $NaHCO_3$, 30% H_2O_2, EtOH - H_2O, rt, 1.5 h, 73% for **12b** from **11c**; k) H_2, 5%Pd/C, MeOH, quant.; l) H_2, 20%$Pd(OH)_2$/C, EtOH, 44 h, 78%; m) Jones reagent, acetone, 0 °C, 0.5 h, 98% for **15a** from **13a** or 71% for **15b** from **13b**; n) CH_2N_2, ether, quant.

D-glucosamine (**3**) was transformed through protection of the amino group by methoxycarbonylation and acetalization according to the known method[12] to the urethane derivative (**4**). Selective removal of 5,6-O-isopropylidene group with aqueous acetic acid gave the diol (**5**). Degradation of the C(6)-carbon was carried out by oxidation of **5** with $NaIO_4$ to provide the unstable aldehyde, which was immediately reduced to alcohol (**6**). The next C(4)-deoxygenation to lead to the key intermediate (4*R*, 5*S*)-5-vinyl-2-oxazolidinone-4-carbaldehyde dimethyl acetal (**9**) in high overall yield (84%) was achieved by a consecutive 3-steps procedure including iodination of **6** with iodine in the presence of Ph_3P and imidazole[13] affording the iodide (**7**), reductive β-elimination on treatment of **7** with activated zinc producing the terminal olefin (**8**), followed by C(3)-OH protection in the formation of 2-oxazolidinone ring by treatment of **8** with NaOMe in MeOH. Thus, a versatile protected chiral threo aminoalcohol (**9**)[14] bearing a vinyl and a protected aldehyde functionalities was prepared from D-glucosamine (**3**) in 8-steps and 30% overall yield.

The 2-oxazolidinone (**9**) served as the key intermediate for synthesis of statine (**1**) and AHPPA (**2**). Thus, acidic hydrolysis of **9** followed by treatment of the product with MeOH on silica gel column gave the methyl hemiacetal (**10**).[15] The Wittig reaction of **10** with (2-propylidene)triphenylphosphorane in THF afforded the crystalline diene (**11a**) in 76% overall yield from **9**. Site-selective hydroboration-oxidation of the diene (**11a**) was attained by using 9-borabicyclo[3.3.1]nonane (9-BBN) to give the primary alcohol (**12a**). Hydrogenation of the unsaturated alcohol (**12a**) gave the saturated alcohol (**13a**), which had been used as a synthetic precursor for (3*S*, 4*S*)-statine (**1**)[7a] and was characterized by derivation to the known N-*tert*-butoxycarbonyl aminodiol derivative (**14a**) followed by spectral comparison with the authentic sample.[7a] The alcohol (**13a**) was also converted into the known carboxylic acid (**15a**)[8] and the methyl ester (**16a**).[7b]

For derivation of **9** to (3*S*, 4*S*)-AHPPA (**2**), a quite similar route as for statine (**1**) was adopted to start with addition of phenyl Grignard reagent to the hemiacetal (**10**). The resulted alcohol (**11b**) was protected to its acetate (**11c**), which on hydroboration-oxidation using 9-BBN afforded the terminal alcohol (**12b**). The acetoxy group of **12b** was hydrogenolized to lead to the saturated alcohol (**13b**), which is also an intermediate for synthesis of (3*S*, 4*S*)-AHPPA (**2**)[7a] and was verified structurally by conversion into the known N-*tert*-butoxycarbonyl aminodiol (**14b**).[7a] The carboxylic acid (**15b**) and its ester (**16b**) were derived analogously from the alcohol (**13b**) and were comparable to the known compounds [8,7b] in the respects of the reported spectral data.

The synthesis of the alcohols (**13a, b**) and carboxylic acids (**15a, b**) described here implies not only the synthesis of natural statine (**1**) and AHPPA (**2**) starting from an easily available threo aminoalcohol chiral pool, but also versatility of the chiral oxazolidinone (**9**) as a synthon[7c] for synthesis of biologically important threo aminoalcohols and their analogues.

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14) Selected data for **9**: oil; $[\alpha]_D$ -67.4° (c 1.38, $CHCl_3$); IR (neat) cm^{-1} 3060, 1750; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.40 (*s*, 3H), 3.46 (*s*, 3H), 3.59 (*dd*, 1H, J=6.8, 4.4), 4.32 (*d*, 1H, J=6.8), 4.80-4.87 (*m*, 1H), 5.31 (*dd*, 1H, J=9.3, 1.0), 5.45 (*dd*, 1H, J=17.1, 1.0), 5.53 (*bs*, 1H), 5.91 (*ddd*, 1H, J=17.1, 9.3, 6.4).

15) Attempts for obtaining the corresponding free aldehyde were in vain because the aldehyde was found to be susceptible to hydration through the usual workup and chromatography.

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