Synthesis of optically active hydroxy amino acids *via* 2-*O*-benzylglyceraldehyde *N*-[(*R*)-1-phenylethyl]imine†

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***N*-Boc esters of 3-phenylisoserine D, norstatine E, statine F, 'methylsilastatine' G and homostatine H are prepared in 4 to 5 steps from 2-*O*-benzylglyceraldehyde *N*-[(*R*)-1-phenylethyl]imine 1.**

Much attention is currently focussed on practical syntheses of hydroxy amino acids, notably of those acting as peptidomimetics in protease inhibitors.[1] A related, second major target is 3-phenylisoserine, part of the essential side-chain of the anti-tumor/anti-leukemic agents taxol and taxotere.[2] These hydroxy amino acids constitute disubstituted 2-amino alcohols, see **A**, that have mostly been prepared from natural amino acids already possessing the required side-chain R. We have recently outlined a complementary strategy to assemble structures **A**, based on the finding that, depending on the conditions, Grignard reagents add to the C=N bond of *N*,*O*-dibenzylglyceraldimines **C** either in a *threo*- or an *erythro*-selective manner.[3,4] Improved selectivity was discovered later on by the use of either *N*-(R)- or -(S)-(1-phenylethyl)imines.[5] With amino diol derivatives **B**, secured from 2-*O*-benzylglyceraldehyde[6] in the form of optically pure diastereoisomers, access to the series of phenylisoserine **D**, norstatine **E**, statine **F**, 'methylsilastatine' **G** and homostatine **H** demanded different transformations of the CH_2OH group of **B**: (i) oxidation for **D** and **E**, (ii) substitution of OH by a carboxyl equivalent for **F** and **G** and (iii) substitution by an acetic acid moiety for **H**. These plans were put into practice with the amino diols **2a–c** obtained from the (*R*)-(1-phenylethyl) imine **1**,[5] as detailed below.‡

For the synthesis of 3-phenylisoserine **D**, the amino diol **2a** was converted into the *N*-Boc derivative **3a** by hydrogenation with Pearlman's catalyst in the presence of Boc_2O,[7] monitored by TLC (to avoid *O*-benzyl cleavage). The primary alcohol **3a** was oxidized to the aldehyde **4a**[8a] and further to the methyl ester **5a** with bromine–methanol,[8b] in 73% yield from **3a**. Hydrogenation of **5a** in acidic methanol[9] gave the phenylisoserine ester **6a**.[10,11] Norstatine **E** was obtained in the form of **6b**, following the same protocol.[12]

The aldehyde **4b** also served to attain the homostatine series. Horner–Emmons olefination of **4b** led to the unsaturated ester **7b**. On hydrogenation of **7b** either the hydroxyester **8b** or the lactone **9b**[13] were obtained, depending on the reaction conditions (see Scheme 1).

Entry to the statine series proved more troublesome. The conversion of the primary hydroxy function into a leaving group suitable for *inter*molecular displacement could not be achieved at first, since the *N*-alkoxycarbonyl group consistently interfered.[14] Stimulated by related uses of 5-membered sulfates[15a] and amidosulfates,[15b,c] we tried to apply these protocols to 1,3-amino alcohols which had not yet been considered in this respect.[15d] Indeed, the 6-membered amidosulfates **10b,c** were obtained in fair yield from **2b,c** by the action of thionyl chloride and then oxidation of the intermediate amidosulfites. Cyanide introduction required harsher conditions than needed for the

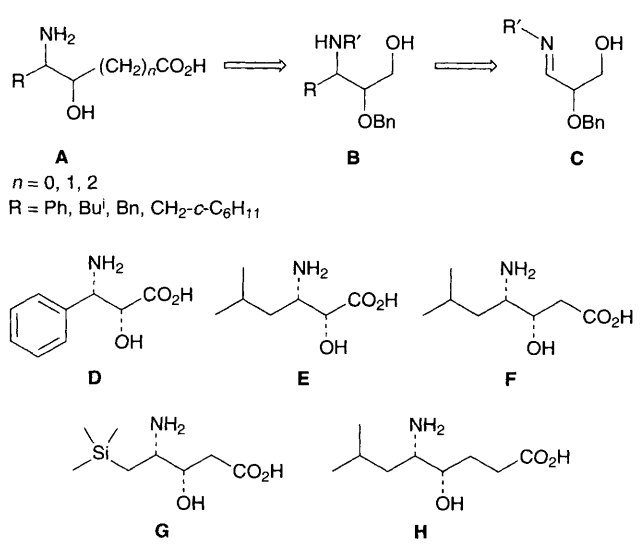
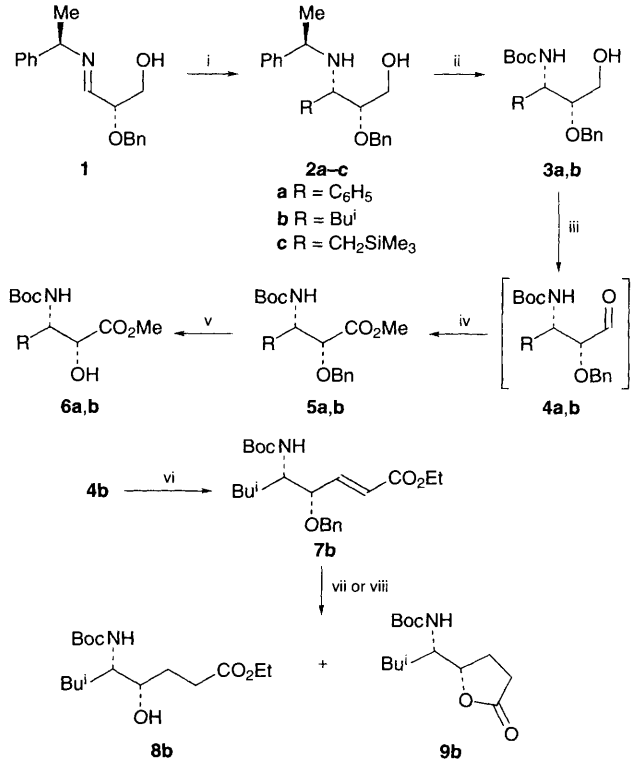
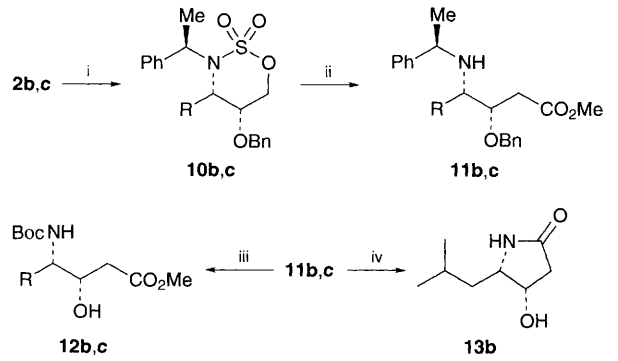


Fig. 1 Projected syntheses of hydroxy amino acids **A** from 2-*O*-benzylglyceraldehyde imines **C** *via* amino diol intermediates **B**[3] and target structures **D–H**



Scheme 1 *Reagents and conditions*: i, ref. 5; ii, Boc_2O, H_2 (4 bar), $Pd(OH)_2$–C, MeOH, 25 °C, 77% **3a** and 83% **3b**; iii, CrO_3·2 pyridine, CH_2Cl_2, 25 °C, 25 min; iv, Br_2, $NaHCO_3$, MeOH–H_2O (9 : 1), 73% **5a** from **3a** and 65% **5b** from **3b**; v, H_2 (4 bar), Pd–C, MeOH–HCl, 25 °C, 86% **6a** and 65% **6b**; vi, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 → 25 °C, 18 h, 63% **7b** from **3b**; vii, H_2, Pd–C, NaOAc, THF, 25 °C, 6 d, 74% **8b** and 22% **9b**; viii, H_2, $Pd(OH)_2$–C, MeOH, 25 °C, 19 h, 7% **8b** and 93% **9b**



Scheme 2 *Reagents and conditions*: i, $SOCl_2$, NEt_3, CH_2Cl_2, −15 → 25 °C; $NaIO_4$, $RuCl_3$ (cat.), MeCN–H_2O, 0 °C, 15 min [*cf.* ref. 15(*c*)], 72% **10b** and 71% **10c**; ii, NaCN, DMF, 130 °C, 3 h [*cf.* ref. 15(*c*)], MeOH–HCl, 5 °C, 4–6 d, H_2O, 5 °C, 24 h, $NaHCO_3$, 67% **11b** and 65% **11a**; iii, Boc_2O, H_2, Pd–C, MeOH, 87% **12b** and 100% **12c**; iv, NH_4HCO_2, Pd–C, MeOH, 60 °C, 100% **13b**

5-membered series,[15b,c] but proceeded well in DMF at 130 °C. Both *N*-desulfonation and nitrile methanolysis were effected with methanol–HCl at 5 °C to afford the *O*,*N*-diprotected methyl esters **11b,c**. On catalytic hydrogenation with Boc_2O added,[7] both intermediates were transformed into the respective *N*-Boc statine esters **12b**,[16a] **12c** in high yield. Catalytic transfer hydrogenation of **11b** with ammonium formate gave a near quantitative formation of the known[16b] γ-lactam **13b**[16c] (see Scheme 2).

The preparation of the silyl compound, 'methylsilastatine' **12c**, meets one of the original objectives,[3] namely, to provide an easy entry to unnatural statine congeners likewise. The methylsila analogue **12c** had been chosen as the first of such targets, since its side-chain volume and lipophilicity differ from those of the commonly employed *iso*-butyl or benzyl compounds.[1] **12c** was incorporated into a pseudopeptide with known excellent HIV 1-protease inhibition;§ however, only moderate activity was registered.[17]

The above syntheses present new, practical, stereoselective routes to the statine family starting from the amino diols **2**, which in each case represent one of the four diastereoisomers available as a pure enantiomer from glyceraldehyde imine addition.[3,5] The optically active ingredients used are diethyl tartrate and *N*-(1-phenylethyl)amine. The efficiency of this approach is seen by the overall yields achieved and number of steps used to attain the *N*-Boc esters of phenylisoserine **6a** (46%, 6 steps), norstatine **6b** (34%, 6 steps), homostatine **8b** (40%, 6 steps), statine **12b** (41%, 5 steps) and 'methylsilastatine' **12c** (37%, 5 steps), respectively, from 2-*O*-benzylglyceraldehyde.[6] While superior routes may be known for some of these cases, the scheme outlined here presents a unified approach to all four stereoisomers, including options for structure variations (*e.g.* intermediates **4**, **7b** and **10** relate to other structures of dipeptide mimetics[18]).

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Footnotes

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‡ Structures and configurations of the compounds given are based on spectroscopic and analytical data, as well as comparison with literature data. *Selected data* for **6a**: mp 129–130 °C (lit.,[10a] 130.5–131.5 °C), $[\alpha]_D^{20}$ −6.5 (*c* 1.33, $CHCl_3$) [lit.,[10a] −7 (*c* 1.2, $CHCl_3$)]. For **6b**: mp 85–86 °C (lit.,[12a] 84–85 °C); $[\alpha]_D^{20}$ −11.8 (*c* 1.00, MeOH) [lit.,[12a] (enantiomer) + 10.8 (*c* 1.00, MeOH)]. For **8b**: colourless oil, $[\alpha]_D^{20}$ −20.0 (*c* 1.53, $CHCl_3$). For **9b**: mp 72–73 °C, $[\alpha]_D^{20}$ −35.2 (*c* 1.52, $CHCl_3$). For **12b**: mp 56–58 °C (lit.,[16a] 57–58 °C); $[\alpha]_D^{20}$ −39.8 (*c* 1.00, $CHCl_3$) [lit.,[16a] −40 (*c* 1, $CHCl_3$)]. For **12c**: mp 98 °C, $[\alpha]_D^{20}$ −20.9 (*c* 1.00, $CHCl_3$). For **13b**: mp 74–75 °C; $[\alpha]_D^{20}$ −12.5 (*c* 1.08, CH_2Cl_2) [lit.,[16b] −12.2 (*c* 1.08, CH_2Cl_2)].

§ From **12c** a trifluoromethylpyrrolidid pseudopeptide[17] was prepared: IC_{50} on HIV 1-protease 150 [nM], no antiviral activity (IC_{50} > 17 μM) towards HIV 1 infected cell cultures (human blood lymphocytes). We thank Drs D. Häbich, J. Hansen and S. Raddatz, Bayer AG (Wuppertal), for accordingly processing **12c** and for the above tests.

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