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Stereocontrolled Conversion of L-Serine into a Series of Valuable Unnatural α-Amino Acids

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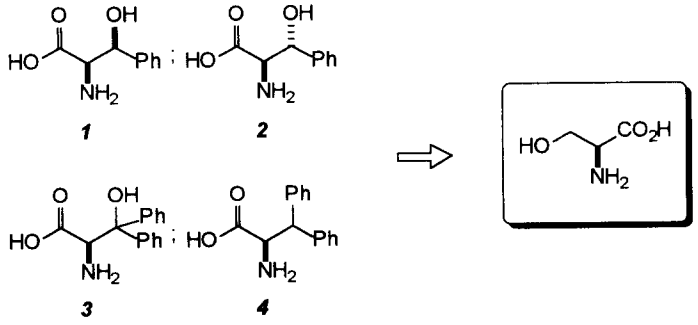
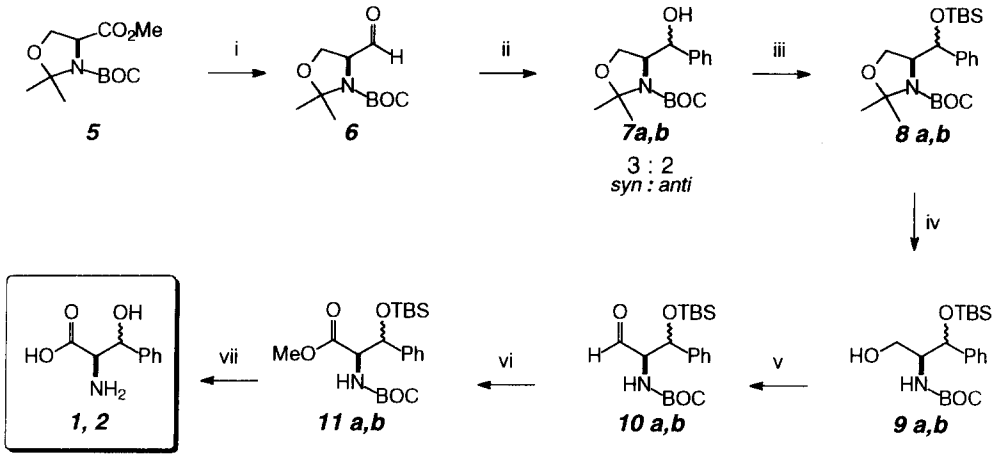
Abstract: Stereocontrolled synthesis of (2R,3S)- and (2R,3R)-phenylserine, (R)-3,3-diphenylserine and (R)-3,3-diphenylalanine are described.

Synthetically prepared nonproteinaceous α-amino acids are well established in pharmaceutical applications as well as chiral starting materials and auxiliaries. Several synthetic methods, most of which include stereoselective introduction of substituents at the α-carbon atom, have been developed to obtain feasible accesses into these compounds.[1] Both enantiomers of the natural twenty amino acids are often available in high enantiomeric purity and can thus be utilised in the preparation of more complex amino acids and their derivatives. We have employed the latter approach to gain access to some interesting serine and alanine derivatives **1-4** starting from L-serine.

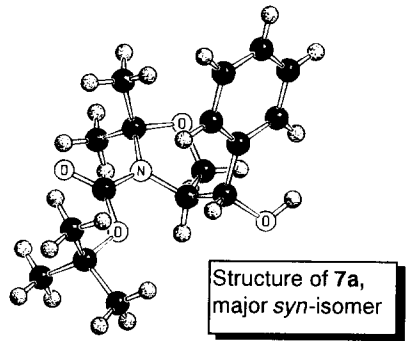


Scheme 1.



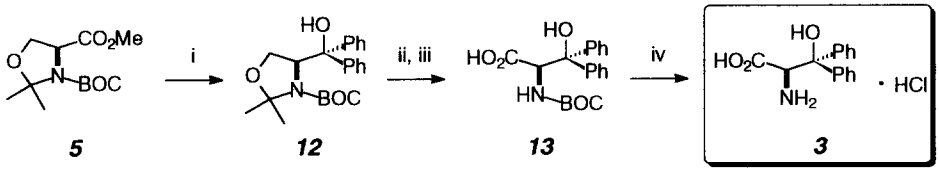
Scheme 2. i) 170 mol% DIBAL, toluene, -78 °C, 45 min, 84 %; ii) 200 mol% PhMgBr, Et_2O, 0 °C, 1 h, quant.; iii) 105 mol% TBSOTf, 110 mol% DIPEA, 10 mol% DMAP, CH_2Cl_2, 25 °C, 30 min, 96 %; iv) 80 % aq. AcOH, 25 °C, 2.5 h, 60 % **9a**, 24% **9b**; v) 200 mol% PDC, CH_2Cl_2, 4Å MS, 25 °C, 4h; vi) 600 mol% PDC, 600 mol% MeOH, DMF, 25 °C, 36 h, 50 %; vii) 110 mol% LiOH, THF/H_2O 9:1, 25 °C, 18 h; then TFA/DCM 1:1, 25 °C, 24 h; then H_2O, 25 °C, 14 days, 95 %.

The synthesis of phenylserines **1** and **2** was started from the fully protected L-serine derivative **5**, which was reduced to the α-aminoaldehyde **6** using literature methodology.[2] Alkylation with phenylmagnesiumbromide yielded a 3:2 mixture of two diastereomeric aminodiols **7**, which could be separated by fractional crystallisation from hexane. The major *syn*-diastereomer **7a** was typically obtained in > 99 %de after two recrystallisations. The relative stereochemistry of this major product was determined by X-ray crystallography.[3] The corresponding *anti*-diastereomer **7b** was obtained in > 98 %de only after six subsequent crystallisations of the material obtained from the mother liquor of the first separation.


Structure of **7a**, major *syn*-isomer

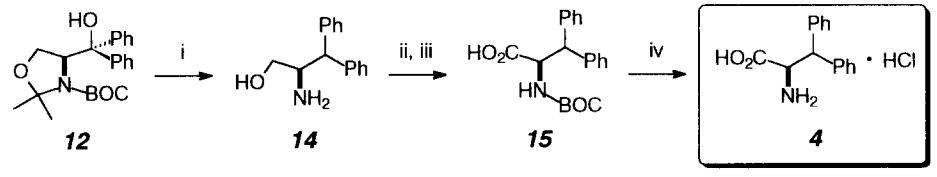
Deketalisation and selective oxidation of the primary hydroxyl group[4] of **7a/b** gave modest results with problems encountered especially in the isolation of the products. Thus, protection of the secondary hydroxyl group as *tert*-butyl dimethylsilyl (TBS) ether followed by deketalisation (80 % AcOH at r.t.)[5] gave the diols **9a/b**. Direct oxidation to the corresponding carboxylic acids[6] proved

in this case to be unsuccessful and therefore a two-step sequence *via* the corresponding aldehyde to the methyl ester was utilised.[7] Alkaline hydrolysis of the ester and cleavage of the protecting groups yielded the target compounds **1** and **2** after purification by ion exchange.[8] Optical rotations of the final products were found to be in good accordance with literature values.[9,10]



Scheme 3. **i)** 400 mol% PhMgBr, Et_2O, 0 °C, 84 %; **ii)** 80 % aq AcOH, 25 °C, 1 h, 95 %; **iii)** 250 mol% CrO_3, H_2SO_4, acetone, 0 °C, 3 h, 51%; **iv)** 500 mol% HCl, EtOAc, 3 days.

Diphenylserine **3** was prepared from the protected L-serine derivative **5** by first performing a double Grignard addition on the ester function to give the protected diphenylserinol **12**. Deketalisation with 80% aqueous acetic acid[5] followed by standard Jones oxidation[11] yielded the BOC-protected D-(*R*)-3,3-diphenylserine **13** in moderate yield. Clearly a whole range of methods can be applied in this step since only one of the hydroxyl groups can be readily oxidised. Extreme reaction conditions, however, can provoke various side reactions due to the instability of the tertiary, doubly benzylic hydroxyl group. Finally in this reaction sequence the cleavage of the BOC-group was achieved by treatment of **13** with a solution of dry HCl in ethyl acetate.[12,13]



Scheme 4. **i)** 5 bar H_2, $Pd(OH)_2/C$, HCO_2H, 60 °C, 5 h; then 10 eq. NaOH, MeOH/H_2O; reflux, 12 h, 82 %; **ii)** 110 mol% BOC_2O, 5 mol% *n*-Bu_4NHSO_4, EtOAc, 1M aq. NaOH, 2 h, 83 %; **iii)** 250 mol% CrO_3, H_2SO_4, acetone, 0 °C, 4 h, 80%; **iv)** 500 mol% HCl, EtOAc, 3 days, 90 %.

For the needs of our studies on asymmetric cyclopropanation[14] we wanted a short access to the sterically bulky amino alcohol diphenylalaninol **14**. This sequence started from the amino diol **12**, which after catalytic dehydroxylation gave the desired amino alcohol **14**. To further

demonstrate the usefulness of this method we decided to carry out the oxidation of the amino alcohol to corresponding amino acid **4**. Although direct Jones oxidation of the free amino alcohol was possible it proved to be capricious in scale up. Therefore, BOC-protection was introduced under phase-transfer conditions to facilitate extractive work up after the oxidation. Removal of the BOC-protection finally yielded (*R*)-3,3-diphenylalanine hydrochloride **4**.[15]

In conclusion, new routes for preparation of some synthetically useful rare amino acids in stereocontrolled manner were developed. Synthetic steps can be scaled up and in some cases several synthetic methods are available to perform the desired transformation. This allows the main strategies to be modified according to technical resources available in each laboratory.

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8. All compounds gave satisfactory spectral (^{1}H NMR, ^{13}C NMR, MS) and analytical data.
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