Concise enantiospecific syntheses of α-hydroxy-β-amino acids and indolizidines of natural origin

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Abstract. A new procedure has been developed for synthesizing enantiomerically pure β-amino acids, α-hydroxy-β-amino acids and certain alkaloids from aspartic acid. By protection, anhydride formation and regioselective reduction, L-aspartic 10 is converted to the N-tosylamino lactone 12. Hydroxylation of 12 by an oxaziridine gives the trans-2-hydroxy-3-N-tosylamino derivative 20. Opening of 12 and 20 by trimethylsilyl iodide and ethanol affords the iodo-homoserine esters 13 and 21 respectively. Submission of 13 and 21 to Gilman reagents followed by saponification and deprotection gives 4-substituted 3-amino and 3-aminoo-2-hydroxybutyric acids (15 and 23), exemplified by the syntheses of cyclohexynonorstatine (25), and the components of bestatin (23, R=Ph) and microginin (14). Certain β-amino acids are transformed into solenopsin A (33) and indolizidine 209D (41).

In the last few years, interest has focused on β-amino acids and α-hydroxy-β-amino acids. The reasons are not hard to find. Many of them are the vital components of biologically active molecules. Others are intermediates for preparing β-lactams. Typical examples are S-β-lysine (1) and R-β-tyrosine (2), components of streptothricin F and jasplakinolide respectively (1). More striking are taxol (3), an anti-tumor reagent, bestatin (4), a dipeptide endowed with immuno-regulatory properties, microginin (5), an ACE inhibitor, and KRI 1314 (6) which inhibits renin (2). Consequently, numerous methods have been developed for synthesizing enantiomerically pure β-amino acids and their α-hydroxy derivatives.
We now describe a new synthetic approach which is based on the strategy required for assembling the crucial diastereomeric C2,C3 entity. As all the aforementioned α-hydroxy-β-amino acids have the syn configuration, typified by acid 7, a logical first disconnection would be the diastereospecific electrophilic hydroxylation of a suitable β-amino acid 8. The attachment of the required substituents (R) would entail the alkylation of an appropriate organometallic reagent by the butyryl cationic synthon 9. Finally, the electrophilic terminus of 9 would be generated by selective transformation of the α-carboxylic group of L-aspartic acid (10). In practice, all these desiderata were fulfilled by a judicious choice of a few simple manipulations of either L- or D-aspartic acid.

N-Tosylaspartic anhydride (11), obtained from 10, was reduced with sodium borohydride to give exclusively the lactone 12. Opening of 12 with trimethylsilyl iodide in the presence of ethanol gave the key intermediate, the iodo-homoserine ester 13. Treatment of 13 with lithium dialkyl- and diphenylcuprates (Gilman reagents) in THF at -30°C afforded the 4-alkylbutyric esters 14 which were saponified and deprotected by standard methods to give the desired β-amino acids 15 in high yields (3). The methyl, n-butyl, n-pentyl, benzyl and phenyl groups were all successfully introduced in high yield (74-96%).

The sequence worked equally well with D-aspartic acid (16). As a test, the ethyl derivative 17 was prepared from 16 and compared with its enantiomer obtained from L-aspartic acid (10). Treatment of both acids, 17 and 15 (R=Et) with (-)-camphanoyl chloride and diazomethane gave a pair of diastereomeric methyl camphanates (18 and 19), each of which turned out to be enantiomerically pure as attested by their 1H-NMR spectra.

Having prepared the β-amino acids, the next step was α-hydroxylation. A convenient means of ensuring diastereoselection is to take advantage of the stereoelectronic properties of the γ-lactone 12. These should be the same as those of β-alkylated butyrolactones which are known to undergo stereospecific hydroxylation (4). Submission of 12 to sodium hexamethyldisilazide (NaHMDS) and trans-2-phenylsulfonyl-3-phenyloxaziridine delivered the desired trans-hydroxy-N-tosylaminobutyrolactone 20 in 64% yield as a single product. Opening of 20 with trimethylsilyl iodide and ethanol gave the hydroxy-iodo intermediate 21 of the required syn configuration in 88% yield. Nucleophilic substitution on 21 with the usual Gilman reagents permitted the introduction of the methyl, ethyl, n-butyl, benzyl and phenyl groups, so giving the corresponding 2-hydroxy-3-(N-tosylamino) ethyl esters (22) in high yield. Saponification
and deprotection furnished the 2S,3R-4-substituted-3-amino-2-hydroxybutyric acid 23 in yields of 21-25% from L-aspartic acid (5). The acid 23 bearing a phenyl substituent is the non-leucine part of bestatin.

The foregoing sequence, but starting from D-aspartic acid (16) and employing lithium dihexyl- and dicyclohexyl cuprates, provided (2R,3S)-3-amino-2-hydroxydecanoic acid (24) and cyclohexylnorstatine (25), the terminal components of microginin (5) and KR1 1314 (6) respectively (6).

β-Amino acids also have potential for the economical synthesis of assorted pyroles, piperidines, pyrrolizidines and indolizidines. By way of illustration, solenopsin A (33) and indolizidine 209D (41) were synthesized. Despite its simple structure, the creation of the trans-configuration of the 2,6-dialkyl substituents in 33 is ticklish. Our approach starts by the alkylation of lithium didecylcuprate with the homoserine iodo ester 13. Systematic extension of the chain of the resulting ester 26 was accomplished by reduction to the aldehyde 27, Wittig reaction to the α,β-unsaturated ketone 28 and hydrogenation. The ketone 29, so obtained, was cyclized with acid to the enamine 30. Reduction with sodium cyanoborohydride was largely subject to stereocontrol giving a mixture of the trans and cis-tosylated solenopsins 31 and 32 in yields of 76 and 22%. Deprotection released solenopsin A (33) in 72% yield, fortunately separable from its epimer 34 (17% yield) (7).

The last example is an extension of our 3-step procedure for preparing enantiomerically pure indolizidines from chiral α-amino acids (8). Initially, the acid was converted to its N-pyrrole derivative which on homologation and subsequent intramolecular cyclization created a bicyclic pyrrole entity. Lastly, hydrogenation of the pyrrole ring to the indolizidine product was controlled by the chiral center of the original acid. Clearly, homologation can be avoided by using β- and γ- amino acids at the outset (9). Once again, the same intermediate 13 served as the starting point. Alkylation to the nonanoate ester 35, hydrolysis and deprotection to the β-amino acid 36, enabled the pyrrole derivative 38 to be prepared from 2,5-dimethoxymethylenehydrofuran (37). Thereafter, the diazoketone 39, obtained from 38, was, by rhodium acetate catalysis, cyclized to the bicyclic ketone 40. Finally, substituent-directed catalytic hydrogenation afforded indolizidine 209D (41) in high yield (10).
Conclusions

These examples demonstrate that L- and D-aspartic acids can be efficiently transformed into β-amino and α-hydroxy-β-amino acids with retention of the implanted chirality. They also show that homochiral β-amino acids are valuable as intermediates for preparing 2,6-alkylpiperidines and 5-substituted indolizidines of natural origin.

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References