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

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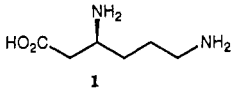
Abstract. A new procedure has been developed for synthesizing enantiomerically pure β-amino acids, α-hydroxy-β-amino acids and certain alkaloids from aspartic acid. By protection, anhydride formation and regioselective reduction, L-aspartic **10** is converted to the N-tosylamino lactone **12**. Hydroxylation 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-amino-2-hydroxybutyric acids (**15** and **23**), exemplified by the syntheses of cyclohexylnorstatine (**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 jasplaskinolide 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.



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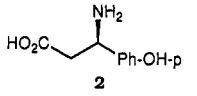

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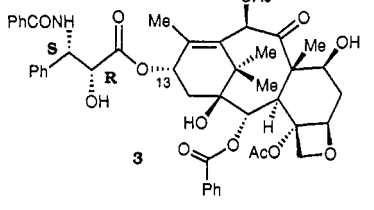

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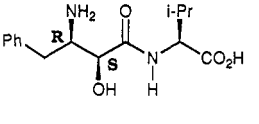

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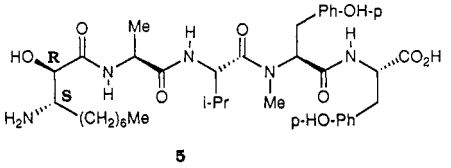

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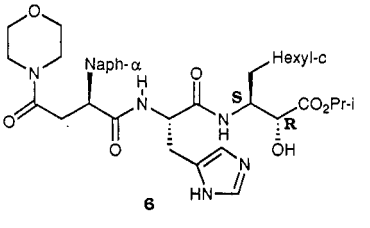

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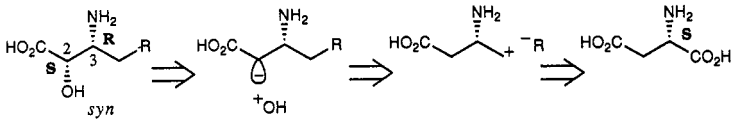
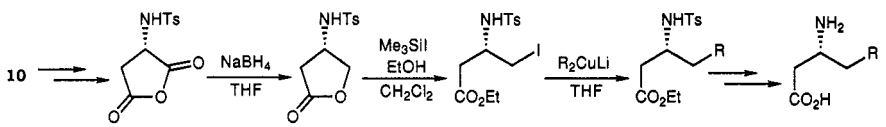
We now describe a new synthetic approach which is based on the strategy required for assembling the crucial diastereomeric C2,C3 entity. As all the aforementioned α-hydroxy-β-amino acids have the *syn* configuration, typified by acid **7**, a logical first disconnection would be the diastereospecific 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.



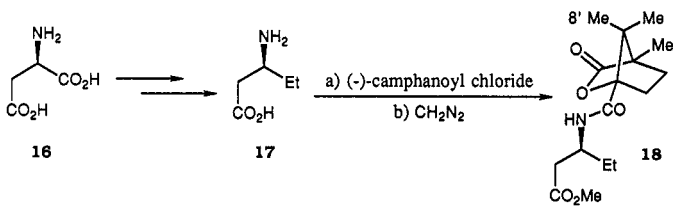
7 **8** **9** **10**



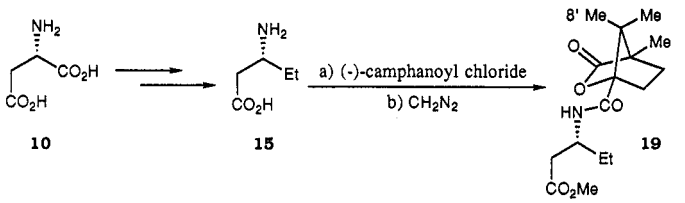
11 **12** **13** **14** **15**

R = Me, n-Bu, t-Bu, n-C_5H_{11}, CH_2Ph, Ph

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%).



16 **17** **18**

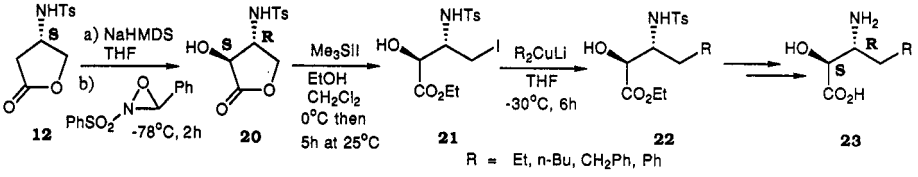


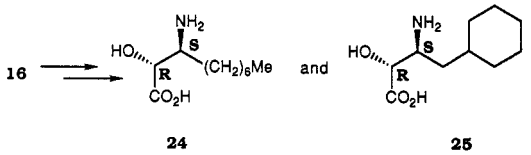
10 **15** **19**

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 ^{1}H-NMR spectra.

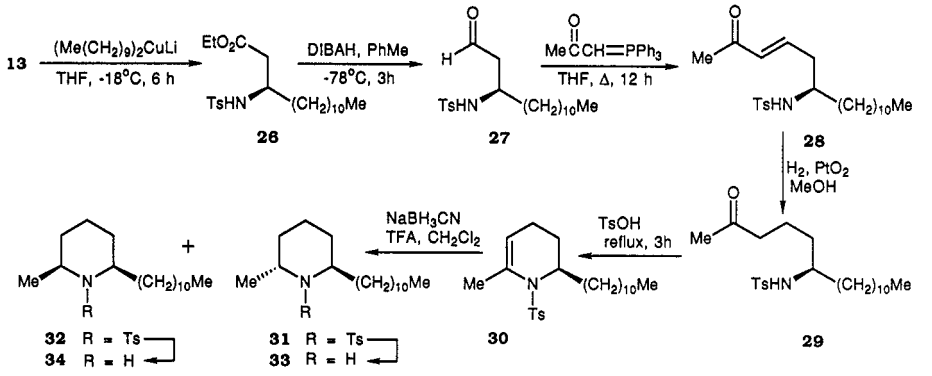
Having prepared the β-amino acids, the next step was α-hydroxylation. A convenient means of ensuring diastereoselection is to take advantage of the stereoelectronic properties of the γ-lactone **12**. These should be the same as those of β-alkylated butyrolactones which are known to undergo stereospecific 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.



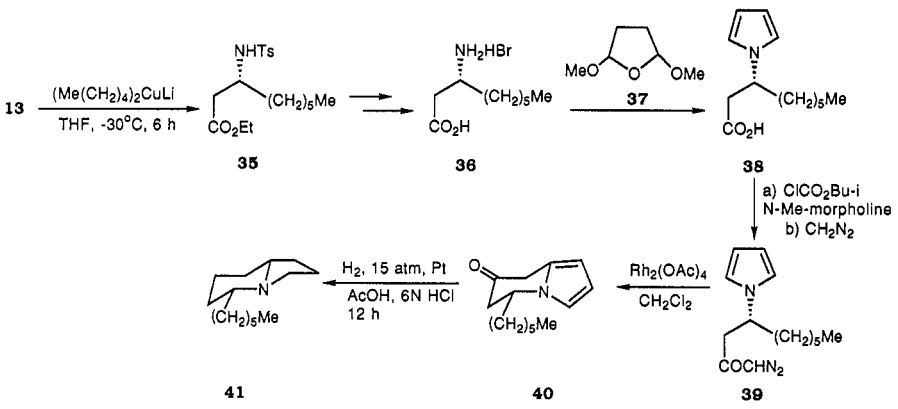


The foregoing sequence, but starting from D-aspartic acid (**16**) and employing lithium dihexyl- and dicyclohexyl cuprates, provided (2R,3S)-3-amino-2-hydroxydecanoic acid (**24**) and cyclohexylnorstatine (**25**), the terminal components of microginin (**5**) and KRI 1314 (**6**) respectively (6).



β-Amino acids also have potential for the economical synthesis of assorted pyrroles, 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-dimethoxytetrahydrofuran (**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

1. T.K. Thiruvengadam, S.J. Gould, D.J. Aberhart and H.J. Lin, *J. Am. Chem. Soc.* **105**, 5470 (1983); P.A. Grieco, Y.S. Hon and A. Perez-Medrano, *J. Am. Chem. Soc.* **110**, 1630 (1988).
2. D. Guénard, F. Guéritte-Voegelein and P. Potier, *Acc. Chem. Res.* **26**, 160 (1993); H. Umezawa (Ed.), "Small Molecular Immunomodifiers of Microbial Origin. Fundamental & Clinical Studies of Bestatin", Pergamon Press, Oxford (1981); H. Suda, T. Takita, T. Aoyagi and H. Umezawa, *J. Antibiotics* **26**, 100 (1976)
3. C.W. Jefford and J. Wang, *Tetrahedron Lett.* **34**, 1111 (1993).
4. S. Hanessian and D.J. Murray, *J. Org. Chem.* **52**, 1170 (1987).
5. C.W. Jefford, J.B. Wang and Z.H. Lu, *Tetrahedron Lett.* **34**, 7557 (1993).
6. T. Okino, H. Matsuda, M. Murakami and K. Yamaguchi, *Tetrahedron Lett.* **34**, 501 (1993); T. Matsumoto, Y. Kobayashi, Y. Takemoto, Y. Ito, T. Kamigo, H. Harada and S. Terashima, *Tetrahedron Lett.* **31**, 4175 (1990).
7. C.W. Jefford and J.B. Wang, *Tetrahedron Lett.* **34**, 2911 (1993).
8. C.W. Jefford, Q. Tang and A. Zaslona, *J. Am. Chem. Soc.* **113**, 3513 (1991).
9. C.W. Jefford, S. Thornton and K. Sienkiewicz, article in preparation.
10. C.W. Jefford and J.B. Wang, *Tetrahedron Lett.* **34**, 3119 (1993).