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Heterocyclic templates for assembling α-hydroxy-β-amino acids, sphingosines and indolizidines

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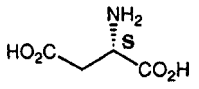
Abstract: L-Aspartic acid is converted into (3S)-3-(tosylamino)butano-4-lactone (**7**). Electrophilic hydroxylation and methylation of **7** give, after opening with ethanolic trimethylsilyl iodide, the *syn*-disposed 2-hydroxy- and 2-methyl-3-tosylamino-4-iodobutyric ethyl esters (**9** and **13**). Nucleophilic phenylation of **9** with subsequent saponification and deprotection gives a component of bestatin. Similarly, methylation of **13** gives (2S,3R)-3-amino-2-methylpentanoic acid. The enantiomer of **9** on reaction with morpholine affords an ester which by reduction to the aldehyde and Wittig olefination gives the 1-(N-morpholine) derivative of D-*threo*-Z-sphingosine. Condensation of diethyl L-glutamate hydrochloride and 2,5-dimethoxytetrahydrofuran gives the pyrrole derivative **31**, which is cyclized to(5S)-5,6-dihydro-5-ethoxycarbonyl-8(7H)-indolizinone (**32**). Hydrogenation of **32**, depending on the catalyst (Pd/C or Rh/Al_2O_3), gives predominantly (5S,9R)-5-ethoxycarbonylindolizidine (**33**) or the corresponding (8S)-8-hydroxy derivative (**34**) respectively. By functional group conversions, **33** is transformed into piclavine A and indolizidine 209D. Indolizidine 209B is similarly obtained from **34**, whereas **31** after butyrylation at C2 provides for the synthesis of (-)-monomorine through an analogous sequence.

Enantioselective syntheses that are conducted in the laboratory inevitably require the intervention of pre-existing optically pure molecules. Such primal entities, conveniently provided by Nature, can be deployed as catalysts, auxiliaries or reagents. We now report that L-aspartic (**1**) and L-glutamic acids (**2**) can be used as internal reagents for constructing all-purpose intermediates which enable a variety of target molecules to be readily synthesized in an enantiomerically pure state. Not only are the innate chirality and carbon framework of **1** and **2** conserved and transmitted to the final product, but by selecting appropriate heteroatoms as substituents, the reactivity of the relevant transformations can also be modulated.



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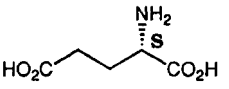

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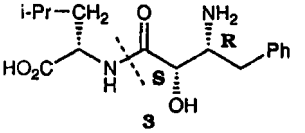

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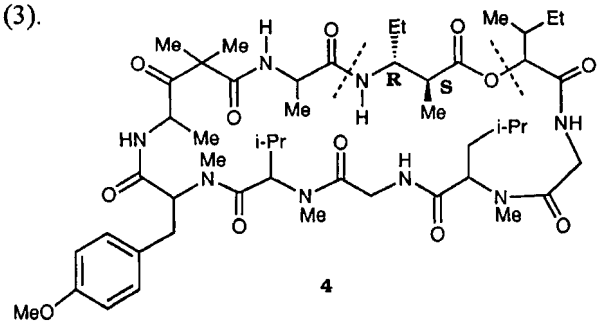
As a first illustration, the syntheses of the non-leucine part of bestatin (**3**), the β-amino acid component of dolastatin 11 (**4**) and a morpholine-substituted analogue of glucosylceramide (**5**) are described. These structures are of great current interest because of their immunoregulatory (1) and antineoplastic properties (2) (3).



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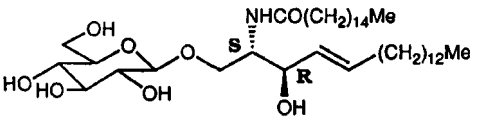

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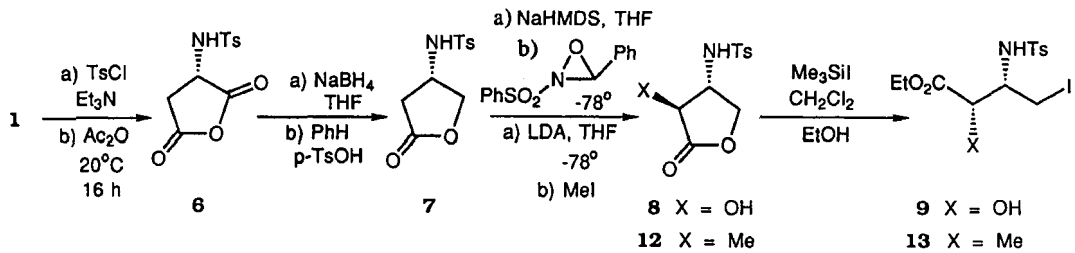
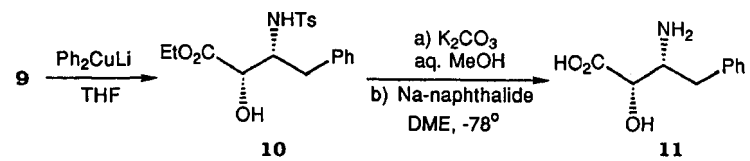
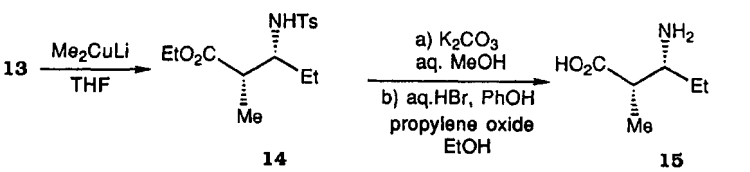
L-Aspartic acid (**1**) initially protected as the N-tosyl derivative was converted into the crucial γ-lactone **7** from the anhydride **6** by regioselective reduction. The 3S configuration of **7** and its purity were confirmed by comparing its ^{1}H-NMR spectrum in the presence of chiral shift reagent with that of the 3R enantiomer, similarly prepared from D-aspartic acid. Hydroxylation of **7** with sodium hexamethyldisilazide (NaHMDS) and *trans*-2-phenylsulfonyl-3-phenyloxaziridine was completely controlled by the bulk of the tosylamino substituent since only the *trans* derivative **8** was obtained in 64% yield as a single product. Treatment of **8** with trimethylsilyl iodide in ethanol gave the hydroxy-iodo ethyl ester **9** in 88% yield. Although not isolated, the corresponding silyl ester was formed first, but in the presence of excess ethanol, transesterification supervened almost instantaneously. Submission of **9** to a two-fold excess of lithium diphenylcuprate, first at -78° and later at room temperature, gave the phenylbutyric ester **10**, which on hydrolysis with methanolic potassium carbonate and reduction with sodium naphthalide in dimethoxyethane (DME) furnished the acid component **11** of bestatin (**3**) (4).





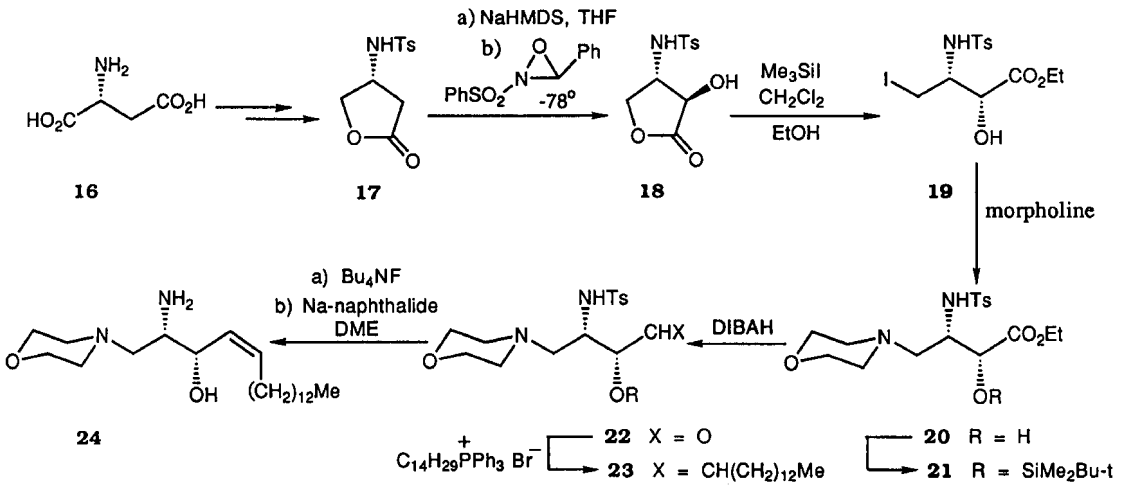


Alkylation of **7** was similarly subject to steric hindrance by the toslyamino group. The anion of **7**, produced by the action of lithium di-isopropylamide (LDA), chiefly underwent monomethylation with methyl iodide. The *trans* methyllactone **12** was obtained together with a little of the *gem*-dimethyllactone (2.5%), which was not much of a nuisance since it could be simply removed by chromatography. Opening of the lactone ring with ethanolic trimethylsilyl iodide proceeded as expected to produce the iodo-butyric ester **13**. Nucleophilic methylation of **13** led to the pentanoic ester **14**, which by saponification and deprotection as before afforded 3-amino-2-methylpentanoic acid (**15**) of the desired 2S,3R configuration (5). This method is the most practical since it yields **15** in 34% and in seven steps from **1**.

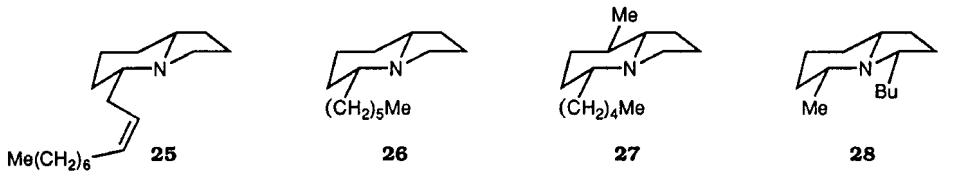
The preceding results owe their success to the choice of tosyl for protecting the amino group. Unlike the *tert*-butyloxycarbonyl protecting group, tosylamino survives exposure to trimethylsilyl iodide and equally importantly, confers high diastereoselectivity in electrophilic reactions (*v. supra*). By way of comparison, the closely related 3-[(benzyloxycarbonyl)amino]butano-4-lactone gives both the *cis* and *trans* isomers on monomethylation (6).

With minor modifications of the preceding scheme, access to valuable derivatives of sphingosine is possible. As an example, the synthesis of the morpholine derivative **24** was accomplished from D-aspartic acid (**16**). Conversion to the lactone **17**, hydrolysis to **18** and opening with ethanolic trimethylsilyl iodide furnished the iodo ester **19** having the *syn* configuration. Nucleophilic displacement with morpholine was easy and gave the corresponding ester **20**. Protection of the hydroxyl group

permitted the ester function of **21** to be reduced to aldehyde **22**, which turned out to be sufficiently stable for immediate Wittig olefination. The Z-olefin **23** was formed exclusively. Deprotection with tetrabutylammonium fluoride to the alcohol followed by reductive removal of the tosyl group with sodium naphthalide delivered the *syn*-configured sphingosine **24** in good yield and in very few steps (7). This route is particularly appealing because any number of nucleophiles, such as aminosugars and carbocyclic analogues, for example, could be attached to the end of the sphingosine chain thereby offering a wide range of potential glucosylceramide inhibitors from **16** at little cost.



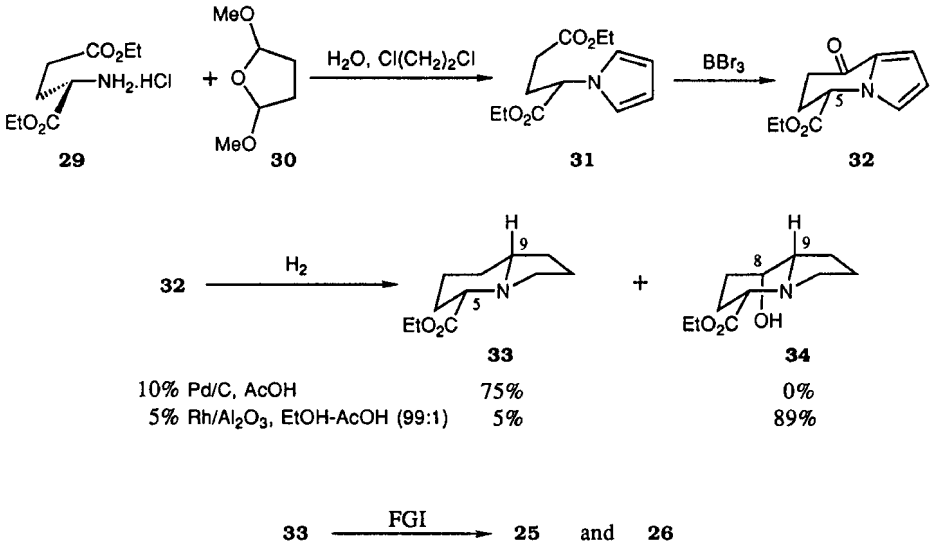
The second illustration relies on L-glutamic acid (2) as the chiral keystone. The syntheses of piclavine A (**25**), the indolizidines 209D (**26**) and 209B (**27**), and (-)-monomorine (**28**) are presented. These molecules have attracted attention because of their biological properties, exotic provenance and scarcity. The piclavines, possessing antimicrobial activity, are the first examples of indolizidines isolated from a marine source and have yet to be synthesized (8). The indolizidines **26** and **27** are found in infinitesimally small amounts in the skin of neotropical tree-frogs and are notorious for their toxicity (9), while **28** is the trail-laying pheromone of the Pharaoh ant (10). Despite the apparent simplictiy of these bicyclic structures, a surprisingly large number of enantioselective syntheses of different complexity have been devised (11) (12) (13).



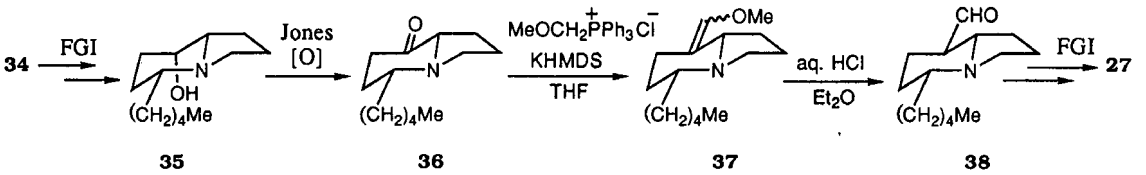
By means of a non-racemizing protocol, **2**, or rather its diethyl ester hydrochloride (**29**), was converted into its N-pyrrole derivative **31** by treatment with 2,5-dimethoxytetrahydrofuran (**30**) by vigorous stirring in a mixture of warm water and 1,2-dichloroethane. Condensation, an acid-catalysed process, was rapid and furnished **31** of undiminished configurational purity thanks to its immediate solution in the organic phase. Although unprecedented, since esters normally do not undergo Friedel-Crafts acylation, ring-closure of **31** was cleanly effected by treatment with at least an equivalent of boron tribromide for about 15 minutes. The bicyclic pyrrole template **32** was obtained in high yield and in an optically pure state as attested by chromatography over a chiral column.

Catalytic hydrogenation of **32** was entirely directed by the C5 substituent and, depending on the conditions (Pd/C or Rh/Al_2O_3), could be altered to favor the fully reduced indolizidine **33** or its 8-hydroxy derivative **34**. Both of these templates were judged to be optically pure from their ^{1}H-NMR spectra in the presence of chiral shift reagent and by chromatography over a chiral column. Consequently they possess all the chirality that is needed in the target molecules, namely the 5S,9R and 5S,8S,9S configurations respectively. Moreover they are perfectly suited for functional group interchange (FGI) reactions and with little manipulation can be fashioned into 5-alkyl, 5,8- and 3,5-dialkylindolizidines.

Reduction of the ester group of **33** to the corresponding aldehyde was accomplished with an excess of diisobutylaluminum hydride (DIBAH). Wittig olefination to the methoxymethylidene derivative and hydrolysis afforded the homologous aldehyde. Both aldehydes were configurationally stable and by further conventional chain extensions were transformed into piclavine A (**25**) and indolizidine 209D (**26**) in overall yields of 17 and 33% and in 7 and 6 steps respectively from **29** (14). This route to **36** is the shortest so far and gives product of the highest optical rotation, which is probably indicative of partial racemization in the previous procedures (11).

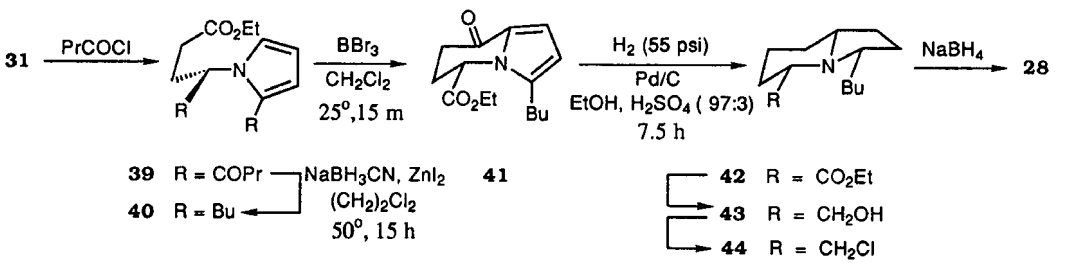


The synthesis of indolizidine 209B (**27**) from **34** entailed some unavoidable extra steps in order to change the 8-hydroxy into a methyl substituent with inversion of configuration. First, the ester group was tackled. By reduction to aldehyde, followed by Wittig butenylation and hydrogenation of the resulting 5-pentenyl substituent, 5-pentyl-8-hydroxy indolizidine (**35**) was obtained without any isomerization at the C5 or C8 positions. Jones' oxidation to the ketone **36**, olefination to the methoxymethylidene derivative **37** and hydrolysis afforded the equatorial 8-formyl derivative **38**. Reduction with sodium borohydride gave the relay, the known hydroxymethyl derivative. As the latter has already been converted to 5-pentyl-8-methylindolizidine (or indolizidine 209B) (**27**) by derivatization to the mesylate followed by reduction, the synthesis may be regarded as complete. In this way, **27** of the correct configuration was obtained in 12 steps and in an overall yield of 9% from **29** (14). This shortcut compares favorably with the previous multi-step scheme which also started from L-glutamic acid (15).



Lastly, the synthesis of (-)-monomorine (**28**), a classic example of a 3,5-disubstituted indolizidine, is outlined. The starting point is the N-pyrrole derivative **31**. By lengthy heating with an excess of butyryl chloride in toluene, acylation occurred exclusively at the 2-position of the pyrrole ring. Deoxygenation of **39** to the 2-butylpyrrole **40** was straightforward. The boron tribromide-promoted cyclization of **40** took place smoothly to give bicyclic pyrrole **41**, containing the latent directing substituent at C5. Catalytic hydrogenation over Pd/C in slightly acidified ethanol proceeded stereospecifically and with hydrogenolysis giving the 3,5-disubstituted indolizidine **42** of the correct final stereochemistry. The finishing touches, namely reduction to the alcohol **43**, conversion to the chloride **44** and reductive dechlorination with sodium borohydride, were trouble-free and efficiently provided (-)-monomorine (**28**).

This sequence requires only 8 steps from diethyl L-glutamate hydrochloride (**29**) and gives **28** in 33% yield as a single product(16). Clearly, repetition of this sequence, but starting from the enantiomer of **31**, obtainable from D-glutamic ester, would enable the naturally-occurring (+)-monomorine to be synthesized.



Conclusion.

The present examples amply demonstrate the versatility and stereocontrol offered by the chiral heterocyclic templates which themselves are readily derived from commercially available aspartic and glutamic acids of either the L- or D-configuration. The operations are simple to perform, few in number and involve mainly accretion of material with a minimal amount of protection-deprotection steps. The basic stereochemical cores of the target molecules are secured at an early stage thereby enabling standard functional group changes to be effected later without compromising the implanted chirality. Further applications of 3-(tosylamino)butano-4-lactone and 5,6-dihydro-5-ethoxycarbonyl-8(7H)-indolizinone of the desired configurations to the practical synthesis of enantiomerically pure pyrroles, β-amino acids, β-lactams, sphingosines, indolizidines and related structures are clearly possible and the results will be reported in due course.

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