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Asymmetric Synthesis of Unusual Amino Acids: Synthesis of the Optically Pure Isomers of Indole-Protected β-Methyltryptophan Suitable for Peptide Synthesis.

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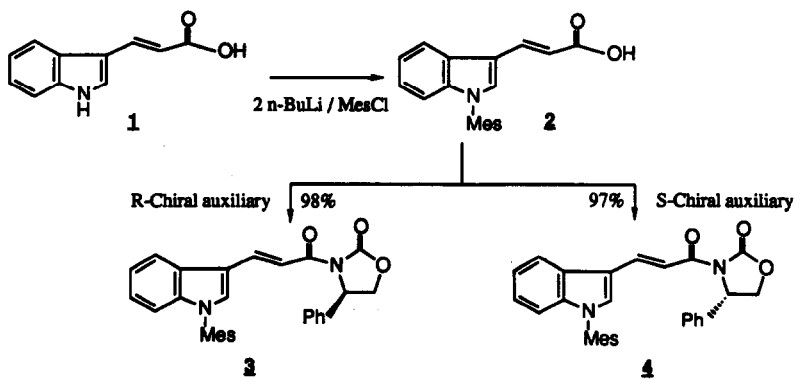
Abstract: The four isomers of N-indole-(2-mesitylenesulfonyl)-β-methyltryptophan have been synthesized in high optical purity using in part, asymmetric conjugate 1, 4-additions followed by chiral imide enolate azidation and reduction.

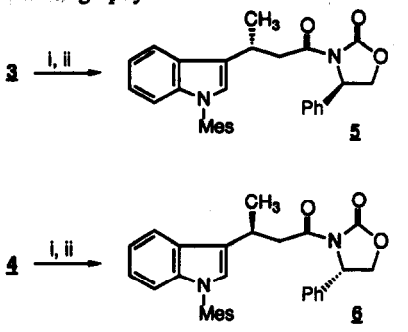
The use of β-substituted amino acids such as β-methylphenylalanine[1] and β-methyltyrosine[2] as topographical constraints in peptides is emerging as a powerful tool in the design of ligands for receptors.[3] We have now developed methods for the synthesis of the four isomers of β-methyltryptophan (β-MeTrp) in high optical purity with 2-mesitylenesulfonylindole protection for peptide synthesis. Attempted syntheses of this amino acid thus far have only yielded two diastereomeric, inseparable DL-pairs.[4] The availability of pure isomers of β-MeTrp should further facilitate the synthesis of optically pure β-carbolines[4b] and natural products like Telomycin.[5]

The synthesis of the β-methyltryptophan isomers was accomplished by generating two asymmetric centers starting from 3-indoleacrylic acid, **1**. Preliminary experiments revealed that electron withdrawing indole-nitrogen protecting groups were essential to stabilize some of the intermediates formed during the synthetic route. Thus, the 2-mesitylenesulfonyl[6] (Mes) group, which also is used as a tryptophan protecting group in peptide synthesis, was chosen for indole protection (Scheme 1). The chiral auxiliaries, R- and S-4-phenyl-2-oxazolidinone[7] were coupled to **2** via the formation of mixed anhydrides[8] to yield **3** and **4** respectively.



Scheme 1

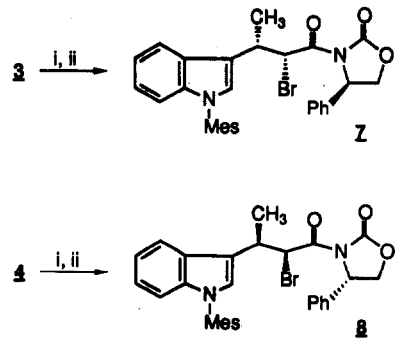
The stereospecific addition of a β-methyl group was performed via an asymmetric 1,4-conjugate addition reaction.[9] Chirality transfer from organoalkyl reagents to α,β unsaturated enones via covalently bound chiral auxiliaries is well documented.[10] Thus, solutions of the α,β-unsaturated acyloxazolidinones 3 and 4 were added dropwise, at 0 °C, to a cuprate obtained by reaction of MeMgBr and CuBr-dimethylsulfide complex,[11] and quenched with NH_4Cl to give the methylated products 5 (ratio of isomers (3R) : (3S) = 90 : 10; yield of the R-isomer after purification, 71%) and 6 (ratio of isomers (3S) : (3R) = 85 : 15; yield of the S-isomer after purification, 65%), respectively (Scheme 2). The predominant isomer could easily be obtained in optically pure form by silica gel chromatography.



(i) MeMgBr, CuBr-Me_2S, 0 °C (ii) NH_4Cl

Scheme 2

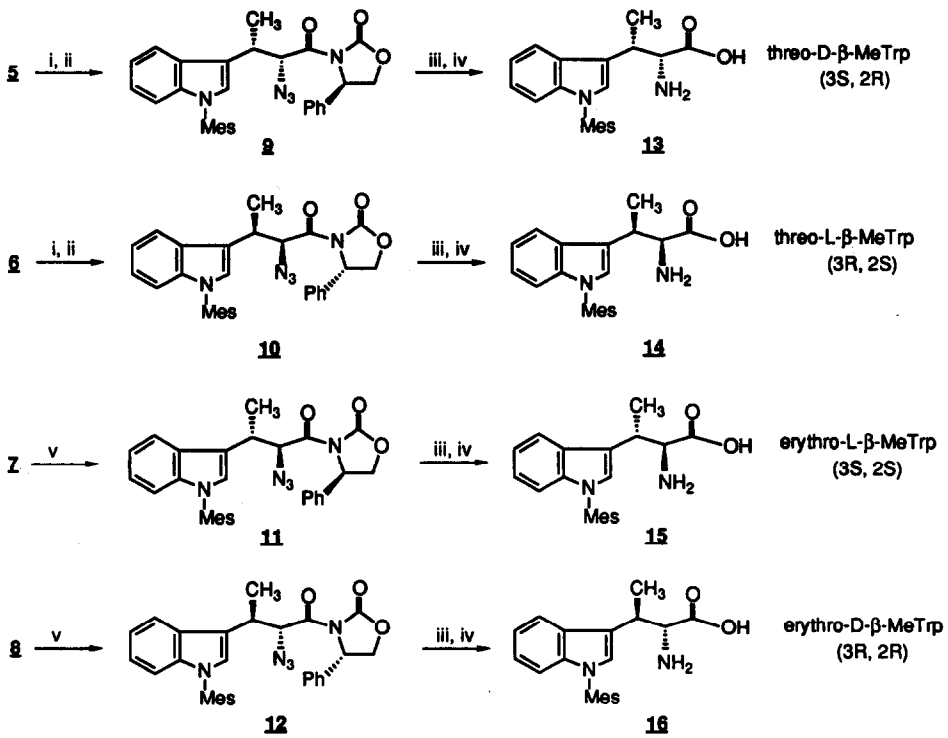
The stereochemistry of the α-carbon in two of the amino acid precursors 7 and 8 (Scheme 3) was simultaneously set along with the homologation of the β-carbon. This was achieved by stereoselective halogenation of the metal-chelated enolate formed by the addition of the higher order methylcuprate to the α,β-unsaturated acyloxazolidinones.[12] Thus, after the reaction of 3 and 4 with the methylcuprate was complete (0 °C, 2 h), the respective metal-chelated enolates were reacted, at -78 °C, with an excess (2.5 fold) of N-bromosuccinimide (NBS) to yield the bromides 7 (ratio of isomer (3S, 2R) : total other isomers = 86 : 14; yield of the 3S, 2R isomer after purification, 70%) and 8 (ratio of isomer (3R, 2S) : total other isomers = 91 : 9; yield of the 3R, 2S isomer after purification, 69%) respectively.



(i) MeMgBr, CuBr-Me_2S, 0 °C (ii) NBS, -78 °C

Scheme 3

The β-methyltryptophan analogues were synthesized from their β-methyl, α-azido precursors (Scheme 4). The bromides **7** and **8** were subjected to azide displacement with tetramethylguanidium azide (TMGA).[12] These reactions require several days at room temperature, with < 2% epimerization. (CAUTION: The use of dichloromethane as the solvent[13] for this reaction can result in formation of the shock-sensitive liquid diazidomethane[14] which can cause serious explosions. The use of chloroform or acetonitrile as the solvent is recommended). The other two azides, **9** and **10** were synthesized by the potassium imide-enolate azidation procedure described by Evans and co-workers[13] (Scheme 3). Compound **9** was obtained as a mixture of isomers (3S, 2R) : (3S, 2S) in the ratio of 94 : 6, and compound **10** was obtained in the ratio of (3R, 2S) : (3R, 2R) = 96 : 4.



(i) KHMDS / Trisyl azide, -78 °C (ii) HOAc (iii) LiOH / H_2O_2, 0 °C (iv) H_2, Pd/C, MeOH (v) TMGA

Scheme 4

The non-destructive removal of the phenyloxazolidinone chiral auxiliary of the optically pure compounds **9** - **12** was achieved according to published procedures[13] (Scheme 4). Less than 1% epimerization at the α-carbon was observed in all cases. The resulting azido acids were reduced to yield the corresponding amino acids **13** - **16**. The diasteroisomeric purity of the β-methyltryptophan isomers (> 96%) was determined by NMR spectroscopy and also by thin-layer chromatography on reverse-phase chiral silica gel plates.[15] Large scale syntheses of these amino acids and their incorporation into biologically relevant peptides are being performed and results will be reported elsewhere.

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9. CuBr-dimethylsulfide complex (1.5 eq) in THF : dimethylsulfide (3 : 1) at 0 °C is reacted with MeMgBr (1.5 eq) for 0.5 h. The acyloxazolidinone (1 eq) in THF is then added dropwise. After completion of the reaction (2 h at 0 °C), the reaction is quenched with aqueous NH_4Cl. Optimum conditions for various substrates have been developed: Nicolas, E; Russell, K. C.; Hruby, V. J. *J. Org. Chem.*, submitted.
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15. Chiralplate® reverse phase silica gel, impregnated with a chiral selector and copper (II) ions. (Machery-Nagel Co. FRG). The separation of optical isomers is based on ligand exchange. Eluent acetonitrile : methanol : water (4 : 1 : 1). The isomers **13**, **14**, **15** and **16** revealed single spots upon ninhydrin visualization with *Rf* values of 0.27, 0.18, 0.44 and 0.33 respectively.

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