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Asymmetric Synthesis of Unusual Amino Acids: Synthesis of Optically Pure Isomers of N-Indole-(2-mesitylenesulfonyl)-β-methyltryptophan

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Abstract : We have developed methods for the synthesis of the four optically pure isomers of β-methyltryptophan with the 2-mesitylenesulfonyl indole protecting group for peptide synthesis. Starting from 3-indoleacrylic acid, the β-methyl function was generated by a chiral auxiliary-directed asymmetric conjugate 1,4-addition. Asymmetric bromination was achieved via a tandem addition of N-bromosuccinimide to the enolate formed by the conjugate addition. Displacement of the bromide by azide, hydrolysis of the chiral auxiliary and then reduction, led to the two *erythro* isomers. Chiral imide enolate azidation of the conjugate adduct, hydrolysis of the chiral auxiliary and reduction yielded the two *threo* isomers in high optical purity.

INTRODUCTION

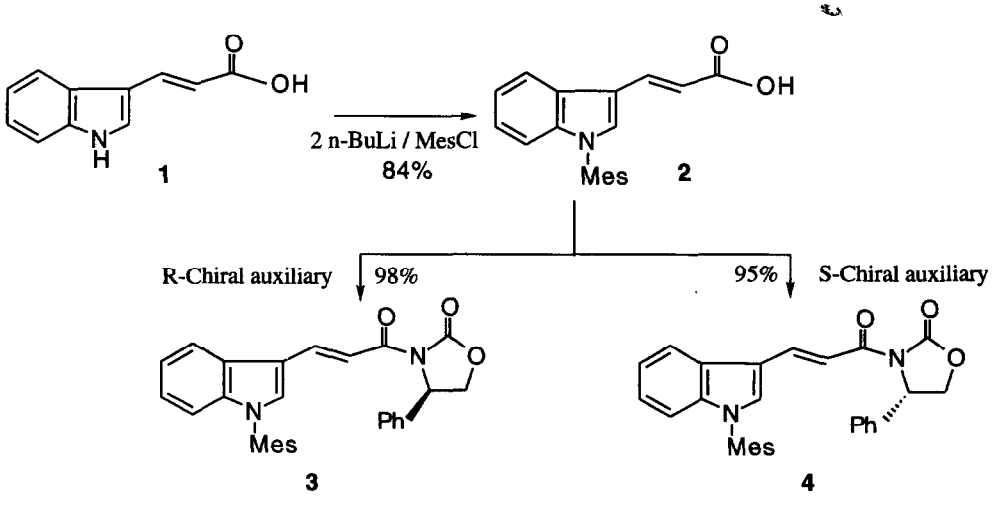
The rational design of highly potent and specific ligands as biological receptor probes is a central goal in present day peptide and protein research.[1] Over the past two decades, a vast and diverse array of peptides and peptidomimetics have been prepared and tested for this purpose. However, almost all of these studies have focussed on the investigation of the conformational properties of the peptide backbone. Recently, we have described a novel approach for the rational design of peptidic ligands by focussing on the topography, which is defined as 'the relative, cooperative three dimensional arrangement of the side chain groups in a polypeptide[2]. This concept involves the design of amino acids capable of restricting conformational freedom around the side chain χ_1 and χ_2 torsional angles (chi space). Replacement of either the pro-R or pro-S β–hydrogens by a methyl group causes one of the gauche ((-) or (+)) conformations to be significantly more stable than the other due to steric interactions.[3,4] Recent work in our laboratory has shown that incorporation of isomers of such amino acids such as β-methylphenylalanine[4] and β-methyltyrosine[5] into bioactive peptides causes large differences in receptor binding and selectivity,[6] suggesting that this is a powerful approach in peptide ligand design. In this context, we have achieved the asymmetric synthesis of the four optically pure isomers of β-methyltryptophan, with suitable indole protection for further incorporation into peptides. Early attempts to synthesize isomers of this unusual amino acid by others[7] only led to the isolation of two diastereoisomeric,

inseparable *dl*-pairs. Although recent literature indicates diastereoselective approaches to substitution at the β-position of L-tryptophan,[8] so far there has not been any description of the synthesis of the four individual optically pure isomers of β-methyltryptophan. The availability of these optically pure isomers should further facilitate structure-activity studies of important natural products such as telomycin,[9a] and streptonigrin[9b] and also should facilitate the synthesis of optically pure substituted β-carbolines.[7b]

RESULTS AND DISCUSSION

In a previous preliminary report, we have outlined an approach for the asymmetric synthesis of the four individual isomers of β-methyltryptophan.[10] Since tryptophan is an important amino acid in many biologically relevant peptides, it is essential to have practical large scale synthesis of the four isomers of β-methyltryptophan. During scale up, it was found that significant modifications of the reaction conditions were necessary in some steps of the synthetic route in order to obtain conditions necessary for good stereoselectivity and optimal yields. In this paper, we provide experimental details for efficient large scale syntheses of these amino acids.

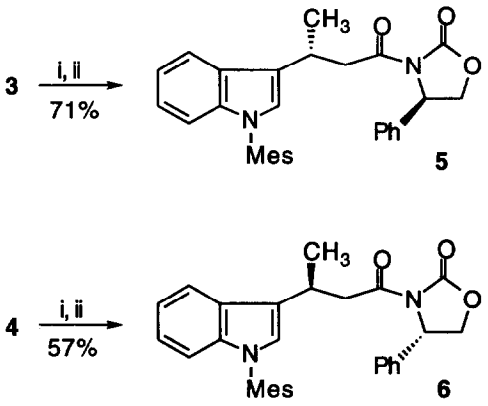
The synthesis of the β-methyltryptophan isomers consisted of generating two asymmetric centers starting from 3-indoleacrylic acid, **1**. For reasons that will be discussed later, the 2-mesitylenesulfonyl (Mes) group[11] was chosen as the protection for the indole nitrogen. The Mes group also serves as an indole protecting group during incorporation of the amino acids into peptides. Incorporation of the Mes group was achieved via generation of the dianionic species of **1** with n-BuLi, followed by sulfonylation with 2-mesitylenesulfonyl chloride to yield **2** (Scheme 1).



Scheme 1

R- and S-4-phenyl-2-oxazolidinone were used as the chiral auxiliaries for the asymmetric functionalization of the α and β positions of **2**. These chiral auxiliaries were coupled to **2** via the formation of

mixed anhydrides[12] to yield **3** and **4** respectively. The addition of the β-methyl group was performed via an asymmetric conjugate addition reaction for which optimal conditions have been developed in our laboratory.[13] Asymmetric conjugate additions to α,β unsaturated enones has attracted considerable attention in the past decade.[14] Efficient chirality transfer of alkylorganometallic reagents to α,β unsaturated enones via covalently bound chiral auxiliary groups have been described in recent literature.[15] We have further developed these strategies for the addition of methylorganometallic reagents to the enones **3** and **4**. Although alkylmagnesium halides have been used for stereospecific addition to α,β unsaturated enones,[15c] methylmagnesium bromide alone as the methylating reagent did not fare well in our hands, giving poor stereoselectivity and low yields of the desired methylated products. We have thus used copperorganometallic reagents that perform better in stereospecific methyl (and aryl) transfer[15b] for this asymmetric Michael addition. Thus, the methylcopper reagent generated by the reaction of methylmagnesium bromide and CuBr - dimethyl sulfide complex[16] was added to the acyloxazolidinones **3** and **4** to give the methylated products **5** (ratio of isomers (3R) : (3S) = 90 : 10) and **6** (ratio of isomers (3S) : (3R) = 85 : 15) respectively (Scheme 2). The predominant isomer could easily be obtained in diastereomerically pure form by flash chromatography.

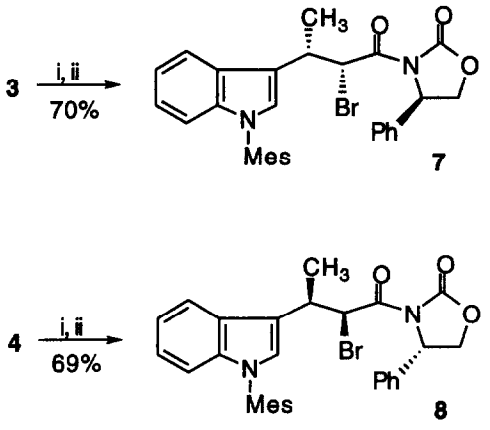


(i) MeMgBr, CuBr-Me_2S, 0 °C (ii) NH_4Cl

Scheme 2

The stereochemistry at 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. The addition of the higher order methylcuprate to the enone-imides **3** and **4** was expected to generate a metal enolate intermediate that chelated the chiral auxiliary carbonyl oxygen thereby fixing the chiral auxiliary in a specific spatial conformation. Such an intermediate is analogous to the base-generated enolate-chelates described by Evans and co-workers,[17] in which the spatial conformation of the chiral auxiliary is fixed by chelation with Lewis acids such as boron. Chelated enolates formed from the Evans chiral auxiliary have been quenched with electrophiles approaching from a preferred face (Re or Si) to yield asymmetric additions.[18] We have utilized the metal-chelated enolate formed from the conjugate addition of the methylcopper reagent to generate the second

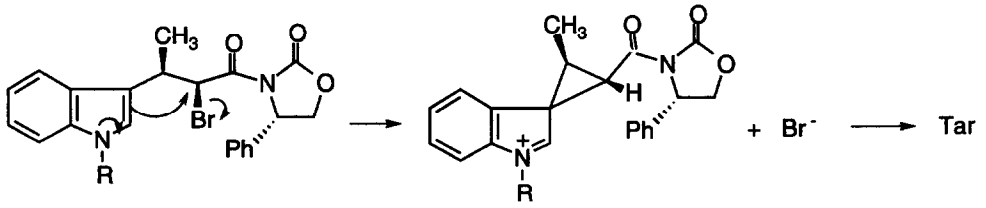
asymmetric center of the prospective amino acid by a stereoselective halogenation reaction.[10, 19] This reaction is analogous to chiral auxiliary based enolate halogenations that have been previously described.[20] Thus, the addition of an excess of N-bromosuccinimide (NBS) which serves as the bromine electrophile at -78 °C to the metal-chelated enolates formed by **3** and **4**, gave the bromides **7** (ratio of isomer (3S, 2R) : total other isomers = 86 :14) and **8** (ratio of isomer (3R, 2S) : total other isomers = 91 : 9) respectively.



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

Scheme 3

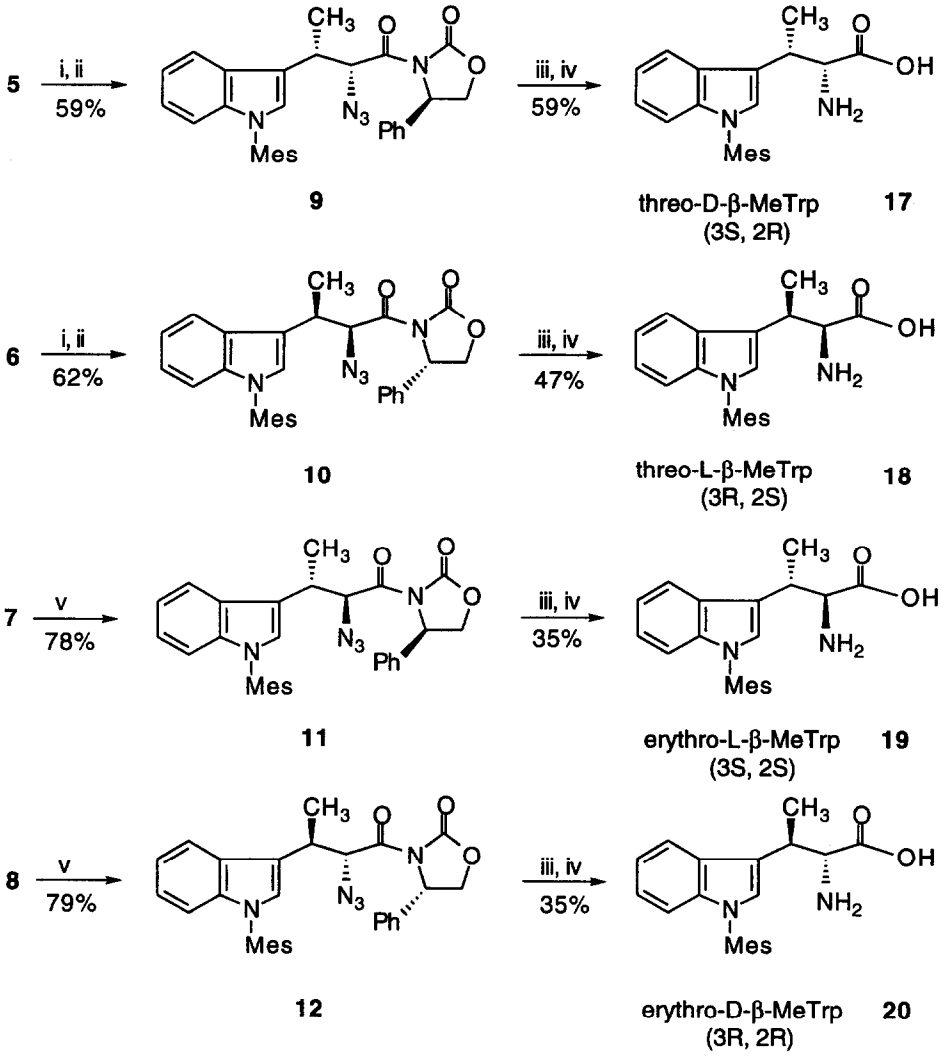
An important fact regarding the stability of the bromides **7** and **8** emerged from initial studies. Electron rich indole nitrogen protecting groups such as the methoxymethyl group and even electron 'neutral' protecting groups such as the benzyl group led to compounds that were unstable at room temperature. The product(s) from these reactions consisted mainly of dark (tarry) products. In previous reports, we have described the synthesis of analogous bromides which contain a phenyl[4a] or methoxyphenyl[5] group instead of the indole ring in **7** or **8**, which are very stable. Thus, it is likely that the electron rich nature of the indole group is contributing to the instability of these bromides. A possible scheme of bromide elimination leading to tarry byproducts is depicted in Scheme 4.



Scheme 4

Electron-withdrawing indole protecting groups such as sulfonamides (toluenesulfonyl and mesitylenesulfonyl) were able to effectively overcome this undesired elimination reaction, preventing the formation of tars

completely. The Mes group was chosen because it could be extended as an indole protecting group during peptide synthesis.[11] Thus, the bromides **7** and **8**, with electron-withdrawing Mes groups, can be purified in diastereomerically pure form by flash chromatography.



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

Scheme 5

The β-methyltryptophan analogues were synthesized from their β-methyl, α-azido precursors (Scheme 5). The bromides **7** and **8** were subjected to an S_N2 azide displacement with tetramethylguanidium azide

(TMGA).[21] These reactions required several days at room temperature and underwent completion with < 2% epimerization. (CAUTION: The use of dichloromethane as the solvent[17a] for this reaction can result in formation of the shock-sensitive liquid diazidomethane[21] which can cause serious explosions. DO NOT USE THIS OR OTHER HALOGENATED SOLVENTS. The use of acetonitrile as the solvent is recommended). The other two azides, **9** and **10** were synthesized from the optically pure Michael adducts **5** and **6** by the potassium imide-enolate azidation procedure described by Evans and co-workers[17a] (Scheme 5). 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.

The non-destructive removal of the phenyloxazolidinone chiral auxiliary from the optically pure compounds **9** - **12** was achieved according to published procedures[17a] (Scheme 5). 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**. Due to the high lipophillic nature of the N-indole-(2-mesitylenesulfonyl)-β-methyltryptophan products, silica gel chromatography with high polar eluents proved to be more efficient than the ion-exchange chromatography[4a] used in the purification of the amino acids. The diasteroisomeric purity of the β-methyltryptophan isomers (> 95%) was determined by NMR spectroscopy and also by thin-layer chromatography on reverse-phase chiral silica gel plates.[22] The incorporation of these topographically constrained amino acids into bioactive peptides such as Cholecystokinin, α-Melanotropin and Somatostatin analogs has been achieved and results will be published elsewhere.

EXPERIMENTAL

General. All reactions were performed under a dry nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium / benzophenone ketyl prior to use. Triethylamine was distilled from CaH_2. Trimethylacetyl chloride, n-butyllithium (1.6 M in hexanes), 2-mesitylenesulfonyl chloride, methylmagnesium bromide (3 M in ether), N-bromosuccinimide was purchased from Aldrich Chemical Co, Milwaukee, WI, USA. N-Bromosuccinimide was recrystallized from water and dried over P_2O_5 in vacuo prior to use. Tetramethylguanidinium azide was prepared as previously described.[23] Triisopropylsulfonyl azide was synthesized as described in literature.[24] Flash chromatography was performed on silica gel (230 - 400 mesh), and gravity chromatography was performed on silica gel (70 - 230 mesh). Analytical thin-layer chromatography was performed on Analtech silica gel 60F-254 plates and the spots were visualized with UV light. Chiral thin-layer chromatography was performed on Chiralplate® reversed phase silica gel plates, impregnated with a chiral selector and Cu^{2+} ions (Machery-Nagel Co., FRG). Melting points were measured on a Thomas Hoover capillary melting point apparatus, and are uncorrected. NMR spectra were obtained from a Bruker spectrometer at 250 MHz for ^1H spectra and at 63 MHz for ^{13}C spectra. Chemical ionization mass spectrometry (CIMS) was performed at the University of Arizona, Department of Chemistry, and the high resolution chemical ionization (HR CIMS) was performed at the University of Arizona, College of Pharmacy. High resolution fast atom bombardment mass spectra (HR FAB) were obtained at the Department of Chemistry, University of Minnesota, Minneapolis, MN. Elemental Analysis was performed by Desert Analytics, Tucson, AZ.

(2-Mesitylenesulfonyl)indole-3-acrylic acid (2).

To a - 78 °C solution of indole-3-acrylic acid (**1**) (14.27 g, 76.2 mmol) in THF (450 mL), was added n-butyllithium (1.6M in hexanes, 100 mL, 160 mmol), in a slow, dropwise manner. Stirring was continued at - 78 °C for 15 min and at 0 °C for 40 min. After recooling to - 78 °C, the emulsion was treated with the dropwise addition of mesitylenesulfonyl chloride (25.0 g, 114.3 mmol) in THF (200 mL). The white suspension was stirred at 0 °C for 1 h and at room temperature for 2 h. Water (400 mL) and ethyl ether (200 mL) were added and the layers separated. The organic layer was extracted with water (100 mL). The combined aqueous phases were washed with ether (2 x 50 mL) and acidified at 0 °C to pH 2.0 with 6N HCl. The precipitate was filtered, washed with water (3 x 100 mL) and dried in vacuo over P_2O_5 to yield 23.5 g (84%): mp 210-211 °C dec.; IR (KBr): 2950, 1625, 1320, 1171cm^{-1}; ^{1}H NMR (DMSO-*d6*) δ 8.46 (s, 1H), 8.1 (m, 2H), 7.82 (d, 1H, J = 16.3 Hz), 7.3-7.1 (4H, aromatic), 6.61 (d, 1H, J = 16.3 Hz), 2.46 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.7, 144.7, 139.6, 135.4, 132.4, 130.2, 126.9, 125.1, 123.8, 120.9, 118.5, 115.4, 112.1, 21.8, 20.4; CIMS (methane) 370 $(M + H)^+$; Anal. calcd for $C_{20}H_{19}NO_4S$: C, 65.02%; H 5.19%; N 3.79%. Found C, 65.21%; H 5.03%, N 3.72%.

(3(2E), 4R)-3-[3-(N-(2-Mesitylenesulfonyl)-3-indolyl)-1-oxopropenyl]-4-phenyl-2-oxazolidinone (3) and **(3(2E), 4S)-3-[3-(N-(2-Mesitylenesulfonyl)-3-indolyl)-1-oxopropenyl]-4-phenyl-2-oxazolidinone (4)**

To a - 78 °C solution of **2** (23g, 62.3 mmol) in dry THF (350 mL) was added triethylamine (9.11 mL, 65.37 mmol) and trimethylacetyl chloride (8.4 mL, 68.49 mmol) via syringe. The reaction mixture was stirred at 0 °C for 1 h and recooled to - 78 °C. Meanwhile, the chiral auxiliary (R or S) (10.16g, 62.26 mmol) in THF (300 mL) at -78 °C was treated with the dropwise addition of nBuLi (1.6M in hexanes, 38.9 mL, 62.26 mmol). This reaction was stirred at - 78 °C for 25 min. The preformed mixed anhydride was cannulated into the lithiated chiral auxiliary solution at - 78 °C and stirred in an ice bath afterward, allowing the reaction mixture to achieve room temperature overnight. Water (400 mL) and diethyl ether (200 mL) were added and the organic phase was separated, washed with water (2 x 200 mL) and saturated aqueous NaCl (2 x 150 mL) and dried ($MgSO_4$). Evaporation led to the product, **3**, 32g (99%). The product can be purified by flash chromatography with 20% ethyl acetate in hexanes as the eluent: mp 136 - 137 °C; $[\alpha]^{25}_D$ +20.2 ° (c 0.5, $CHCl_3$); IR (KBr) :1752 (s), 1693 (s), 1613 (b), 1342 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 15.8 Hz, 1H), 7.2 - 8.0 (10H aromatic, and 1H olefinic), 6.95 (s, 2H aromatic), 5.55 (dd, J = 3.8, 8.8 Hz, 1H), 4.74 (t, 1H), 4.32 (dd, J = 3.8, 8.8 Hz, 1H), 2.52 (s, 6H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.8, 154.1, 144.7, 140.29, 139.3, 137.9, 135.5, 132.6, 132.1, 130.7, 129.2, 128.6, 127.4, 125.9, 125.2, 124.1, 121.3, 116.4, 112.6, 70.0, 57.8, 22.6, 21.1; CIMS: 515 $(M + H)^+$; Anal. calcd for $C_{29}H_{26}N_2O_5S$: C, 67.68%, H, 5.09%, N 5.45%. Found C, 67.93%, H, 4.97%, N, 5.34%.

Similarly, compound **4** was prepared in 95% yield: mp 140 - 141 °C; $[\alpha]^{25}_D$ = -23.2 ° (c 0.5, $CHCl_3$); IR (KBr) :1751 (s), 1691 (s), 1613 (b), 1341 (s); ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 15.8 Hz, 1H), 7.99 - 7.24 (aromatic 10H , and olefinic, 1H), 6.95 (s, 2H aromatic), 5.57 (dd, J = 4.8, 8.8 Hz, 1H), 4.74 (t, 1H), 4.32 (dd, J = 3.8, 8.8 Hz, 1H), 2.51 (s, 6H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.0, 154.1, 144.7, 140.29, 139.1, 137.9,

135.5, 132.6, 132.2, 130.5, 129.2, 128.6, 128.7, 125.9, 125.2, 124.1, 121.2, 116.1, 112.6, 69.9, 57.8, 22.6, 21.0; CIMS: 515 $(M + H)^+$; Anal. Calcd for $C_{29}H_{26}N_2O_5S$: C, 67.68%; H, 5.09%; N 5.45%. Found C, 67.60%; H, 5.02%; N, 5.31%.

(3(3R), 4R)-3-[3-(N-(2-Mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (5) and **(3(3S), 4S)-3-[3-(N-(2-Mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (6)**

A solution of CuBr - dimethylsulfide complex (9.29g, 45.18 mmol) in methyl sulfide (45 mL) and THF (150 mL) at 0 °C, was treated with methylmagnesium bromide (3M in ether, 15.06 mL, 45.18 mmol), via syringe. The green-yellow slurry was stirred for 30 min at 0 °C and the substrate, **3** (15.5g, 30.12 mmol), in THF (100 mL) was added dropwise over 15 min. The green solution was stirred at 0 °C for 2 h and 0.5 h at room temperature. TLC (3:7 ethyl acetate: hexanes) indicated the absence of starting material. The reaction was carefully quenched with the dropwise addition of saturated aqueous NH_4Cl (200 mL) and stirring for 0.5 h. The organic layer was separated and washed with saturated aqueous NH_4Cl (4 x 50 mL), saturated aqueous NaCl (2 x 50 mL) and dried ($MgSO_4$). Evaporation led to the product which was purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes as the eluent), to yield a colorless foam 11.3g, (71%) : $[\alpha]^{24}_D$ = - 63.7 ° (c 0.19, $CHCl_3$); IR (CH_2Cl_2): 1782 (s), 1709 (s), 1605 (s), 1354 (s), 1167 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.15 - 7.62 (aromatic, 10H), 6.91 (s, aromatic, 2H), 5.35 (dd, J = 3.6, 8.6 Hz, 1H), 4.61 (t, 1H), 4.22 (dd, J = 3.6, 8.6 Hz, 1H), 3.63 (m, 1H), 3.47 (dd, J = 3.7, 8.8 Hz, 1H), 3.27 (dd, J = 3.7, 8.8 Hz, 1H), 2.47 (s, 6H), 2.28 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H); ^{13}C NMR $CDCl_3$): δ 171.1, 153.8, 143.9, 139.0, 132.4, 129.1, 128.7, 125.7, 124.2, 124.1, 122.7, 122.5, 119.4, 112.4, 69.9, 57.6, 42.1, 26.9, 22.6, 21.0; HR CIMS (methane), m/z 530.1876; Anal. Calcd for $C_{30}H_{30}N_2O_5S$: C, 67.90%; H, 5.70; N, 5.28%. Found: C, 67.59%; H, 5.62%; N, 5.34%.

With a similar procedure, the Michael adduct **6** was obtained from **4** as a colorless foam in 57% yield after purification to optical purity: $[\alpha]^{24}_D$ = + 53.4 ° (c 0.61, $CHCl_3$); IR (CH_2Cl_2): 1783 (s), 1709 (s), 1605 (s), 1354 (s), 1167 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.16 - 7.42 (aromatic, 10H), 6.92 (s, aromatic, 2H), 5.35 (dd, J = 3.6, 8.6 Hz, 1H), 4.62 (t, 1H), 4.23 (dd, J = 3.7, 8.9 Hz, 1H), 3.62 (m, 1H), 3.45 (dd, J = 3.9, 9.2 Hz, 1H), 3.25 (dd, J = 3.9, 9.0 Hz, 1H), 2.47 (s, 6H), 2.28 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.1, 153.8, 143.8, 138.9, 132.4, 129.1, 128.7, 125.7, 124.2, 124.1, 122.7, 122.4, 119.8, 112.4, 69.9, 57.6, 42.1, 26.9, 22.6, 21.0; CIMS (methane), m/z 531$(M + H)^+$; Anal. Calcd for $C_{30}H_{30}N_2O_5S$: C, 67.90%; H, 5.70; N, 5.28%. Found: C, 67.60%; H, 5.74%; N, 5.08%.

(3(2R, 3S), 4R)-3-[2-Bromo-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (7) and **(3(2S, 3R), 4S)-3-[2-Bromo-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (8)**.

A solution of CuBr - dimethylsulfide complex (9.29g, 45.18 mmol) in methyl sulfide (45 mL) and THF (150 mL) at 0 °C, was treated with methylmagnesium bromide (3M in ether, 15.06 mL, 45.18 mmol), via syringe. The green-yellow slurry was stirred for 30 min at 0 °C and the substrate, **3** (15.5g, 30.12 mmol), in THF (100 mL) was added dropwise over 15 min. The green solution was stirred at 0 °C for 2 h and 0.5 h at room temperature. TLC (3:7 ethyl acetate: hexanes) indicated the absence of starting material. The reaction

mixture was recooled to -78°C and cannulated into a -78 °C solution of N-bromosuccinimide (10.7g, 60.24 mmol) in THF (200 mL). The slurry was stirred at -78 °C for 2 h and at 0 °C for 0.5 h. The reaction was quenched with 0.5N $NaHSO_4$: brine (1 : 1, 200 mL). The dark brown organic layer was separated and washed with 0.5N $Na_2S_2O_3$ (2 x 100 mL). The organic extract which became clear was separated and washed with saturated aqueous NH_4Cl (4 x 50 mL), saturated aqueous NaCl (2 x 50 mL) and dried ($MgSO_4$). Evaporation led to the product which was purified by flash chromatography (silica gel, 15 - 20% ethyl acetate in hexanes as the eluent), to yield a white foam 12.6g, (70%) : $[\alpha]^{24}_D$ = - 64.9 ° (c 0.99, $CHCl_3$); IR (KBr): 1775 (s), 1715 (s), 1601 (s), 1341 (s), 1162 (s), 672 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.17 - 7.64 (aromatic, 10H), 6.95 (s, aromatic, 2H), 6.13 (d, J = 10.7 Hz, 1H), 5.11 (dd, J = 4.1, 8.9 Hz, 1H), 4.48 (t, 1H), 4.16 (dd, J = 4.1, 8.9 Hz, 1H), 3.70 (m, 1H), 2.51 (s, 6H), 2.29 (s, 3H), 1.57 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.3, 144.5, 140.2, 135.2, 132.5, 129.1, 128.8, 125.7, 124.6, 123.6, 122.7, 121.1, 120.2, 112.4, 69.8, 57.6, 48.2, 33.3, 22.6, 21.0, 20.1; HR CIMS (methane), m/z 608.0998.

With a similar procedure, the bromide **8** was obtained from **4** as a white foam in 69% yield: $[\alpha]^{24}_D$ = + 69.9 ° (c 0.6, $CHCl_3$); IR (CH_2Cl_2): 1781 (s), 1713 (s), 1605 (s), 1356 (s), 1169 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.18 - 7.64 (aromatic, 10H), 6.96 (s, aromatic, 2H), 6.13 (d, J = 10.6 Hz, 1H), 5.13 (dd, J = 4.3, 8.9 Hz, 1H), 4.49 (t, 1H), 4.16 (dd, J = 4.4, 8.9 Hz, 1H), 3.72 (m, 1H), 2.51 (s, 6H), 2.30 (s, 3H), 1.57 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.8, 144.6, 140.2, 137.3, 132.5, 129.2, 128.9, 125.8, 124.6, 123.7, 122.8, 120.2, 112.4, 69.9, 57.6, 48.3, 33.3, 22.6, 21.1, 20.1; CIMS (methane), m/z 610 $(M + H)^+$; Anal. Calcd for $C_{30}H_{29}N_2O_5SBr$: C, 59.20%; H, 4.81%, N, 4.61%. Found: C, 59.53%; H, 5.04%; N, 4.56%.

(3(2R, 3S), 4R)-3-[2-Azido-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (9) and **(3(2S, 3R), 4S)-3-[2-Azido-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (10)**.

A solution of **5** (8.75g, 16.49 mmol) in THF (70 mL) at -78°C was cannulated into a precooled (-78°C) solution of potassium bis(trimethylsilyl)amide (0.5M solution in toluene, 36.28 mL, 18.14 mmol) in THF (50 mL). After 30 min at -78°C, the reaction mixture was cannulated into a precooled (-78°C) solution of triisopropylsulfonyl azide (6.13g, 19.79 mmol) in THF (60 mL). The reaction was allowed to proceed for 5 min and was quenched with glacial acetic acid (4.4 mL). After quenching, the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with ether (50 mL) and dilute aqueous NaCl solution (50 mL). The aqueous phase was re-extracted with ether : THF (1 : 1, 3 x 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (2 x 50 mL), saturated aqueous NaCl (2 x 50 mL) and dried ($MgSO_4$). Evaporation of the solvents led to a crude oil which was purified by flash chromatography using 15% ethyl acetate in hexanes as the eluent to yield the azide **9**, as a pale yellow oil, 5.52g (59%): $[\alpha]^{24}_D$ = - 99.8 ° (c 0.48, $CHCl_3$); IR (KBr): 2100 (s), 1778 (s), 1704 (s), 1352 (s), 1167 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.17 - 7.69 (aromatic, 10H), 6.97 (s, aromatic, 2H), 5.39 (d, J = 9.1 Hz, 1H), 4.86 (dd, J = 4.3, 6.4 Hz, 1H), 4.10 (m, 2H), 3.63 (m, 1H), 2.55 (s, 6H), 2.29 (s, 3H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.1, 153.2, 143.8, 140.2, 138.9, 134.9, 133.1, 132.3, 129.2, 128.6, 125.7, 124.2, 122.4, 119.8, 112.4, 69.9, 63.5, 57.6, 42.1, 27.0, 22.6, 20.9, 17.5; HR CIMS (methane), m/z 571.1916.

With a similar procedure, the azide **10** was obtained from **6** as an oil in 62% yield: $[\alpha]^{24}_D$ = + 110.8 ° (c 0.56, $CHCl_3$); IR ($CHCl_3$): 2107 (s), 1782 (s), 1710 (s), 1358 (s), 1166 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.18 - 7.50 (aromatic, 10H), 6.97 (s, aromatic, 2H), 5.41 (d, J = 8.9 Hz, 1H), 4.88 (dd, J = 3.1, 7.0 Hz, 1H), 4.10 (m, 2H), 3.65 (m, 1H), 2.55 (s, 6H), 2.29 (s, 3H), 1.53 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 169.2, 153.1, 144.3, 140.3, 138.1, 134.7, 132.5, 129.2, 128.8, 125.7, 124.7, 124.4, 123.7, 122.8, 120.1, 119.9, 112.5, 70.3, 63.5, 57.9, 32.9, 22.6, 21.1, 17.5; HR FAB 571.1898 (M^+).

(3(2S, 3S), 4R)-3-[2-Azido-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (11) and **(3(2R, 3R), 4S)-3-[2-Azido-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (12).**

A solution of **7** (23.0g, 38 mmol) in acetonitrile (250 mL) was stirred with tetramethylguanidinium azide (23g, 151 mmol) at room temperature. The reaction was monitored by NMR spectroscopy. After 5 days, the mixture was carefully concentrated under reduced pressure at room temperature to a volume of approximately 25 mL. This mixture was loaded onto a silica gel column equilibrated with hexanes and was eluted with 15 - 20% ethyl acetate in hexanes to give the azide **11**, 19g, (78%): $[\alpha]^{24}_D$ = -92.9 ° (c 0.93, $CHCl_3$); IR ($CHCl_3$): 2100 (s), 1776 (s), 1715 (s), 1600 (w), 1352 (s), 1164 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.18 - 7.62 (aromatic, 10H), 6.89 (s, aromatic, 2H), 5.53 (d, J = 8.2 Hz, 1H), 5.48 (dd, 1H, these peaks overlap with the peak at 5.53), 4.77 (t, 1H), 4.35 (dd, J = 4.4, 8.8 Hz, 1H), 3.61 (m, 1H), 2.42 (s, 6H), 2.27 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 169.6, 153.5, 143.9, 140.2, 137.9, 134.7, 132.4, 129.1, 129.0, 126.1, 125.9, 124.6, 124.2, 122.7, 119.7, 119.1, 112.4, 70.3, 63.2, 57.9, 33.9, 22.6, 21.1, 18.3; CIMS (methane), m/z 572 (M + H)$^+$; Anal. Calcd for $C_{30}H_{29}N_5O_5S$: C, 63.03%; H, 5.12%, N, 12.26%. Found: C, 63.01%; H, 5.26%; N, 11.86%.

With a similar procedure, the azide **12** was prepared from **8** in 79% yield: $[\alpha]^{24}_D$ = + 106.4 ° (c 0.5, $CHCl_3$); IR ($CHCl_3$): 2110 (s), 1781 (s), 1672 (s), 1598 (w), 1385 (s), 1168 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.16 - 7.58 (aromatic, 10H), 6.89 (s, aromatic, 2H), 5.53 (d, J = 8.3 Hz, 1H), 5.50 (dd, J = 4.1, 9.0 Hz, 1H, these peaks overlap with the peak at 5.53), 4.77 (t, 1H), 4.34 (dd, J = 4.1, 9.0 Hz, 1H), 3.62 (m, 1H), 2.42 (s, 6H), 2.27 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 169.6, 153.5, 143.9, 132.3, 129.1, 126.1, 124.6, 122.7, 119.7, 119.1, 112.4, 70.3, 63.1, 57.9, 33.9, 22.5, 21.0, 18.3; HR FAB 571.1887.

General Procedure for the Removal of Chiral Auxiliaries from Compounds 9 - 12.

(2R, 3S)-2-Azido-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid (13).

The lithium peroxide-mediated hydrolysis of the chiral auxiliaries is illustrated by the following procedure: (3(2R, 3S), 4R)-3-[2-Azido-3-(N-(2-mesitylenesulfonyl)-3-indolyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone, **9**, (7.8g, 13.65 mmol) in THF (150 mL) and water (150 mL) at 0°C, were treated with the dopwise addition of hydrogen peroxide (30% aq. solution, 8.48 mL) and $LiOH.H_2O$ (1.14g, 27 mmol). After 2 h at 0°C, sodium bisulfite (8.5g) in water (10 mL) and saturated aqueous $NaHCO_3$ was added. After stirring for 30 min at room temperature, ether (100 mL) was added and the layers were separated. The organic phase was re-extracted with saturated aqueous $NaHCO_3$ (3 x 25 mL) and the combined aqueous phases were acidified to pH 2 with 1N HCl. The emulsion was extracted with ethyl acetate (4 x 100 mL). The combined

organic extracts were washed with water (2 x 50 mL), sat. aq. NaCl (2 x 50 mL) and dried ($MgSO_4$). Evaporation led to the product, a colorless oil, 4.2g, (72%): $[\alpha]^{24}_D$ = + 19.5 ° (c 0.79, $CHCl_3$); IR ($CHCl_3$): 2114 (s), 1719 (s), 1604 (s), 1450 (w), 1356 (s), 1169 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.19 - 7.61 (aromatic, 6H), 6.95 (s, aromatic, 2H), 4.32 (d, J = 4.7 Hz, 1H), 3.71 (m, 1H), 2.53 (s, 6H), 2.28 (s, 3H), 1.42 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.7, 144.1, 140.1, 134.7, 132.8, 132.5, 128.8, 126.0, 124.6, 122.7, 119.9, 119.1, 112.6, 66.1, 32.8, 22.6, 21.1, 15.0; HR CIMS (methane) 426.1373.

(2S, 3R)- 2-Azido-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid (14).

This compound was obtained from **10** in a similar manner as described above, in 97% yield: $[\alpha]^{24}_D$ = - 21.4 ° (c 0.5, $CHCl_3$); IR ($CHCl_3$): 2978 (b), 2109 (s), 1722 (s), 1603 (s), 1449 (w), 1354 (s), 1165 (s), 1133 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.18 - 7.60 (aromatic, 6H), 6.95 (s, aromatic, 2H), 4.33 (d, J = 4.7 Hz, 1H), 3.72 (m, 1H), 2.53 (s, 6H), 2.28 (s, 3H), 1.42 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.7, 144.2, 140.2, 132.8, 128.9, 124.6, 122.8, 120.1, 119.2, 112.6, 66.1, 32.8, 22.6, 21.0, 15.1; HR FAB 426.1347 (M^+).

(2S, 3S)- 2-Azido-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid (15).

This compound was obtained from **11** in a similar manner described above, in 72% yield: $[\alpha]^{24}_D$ = - 26.7 ° (c 0.45, $CHCl_3$); IR ($CHCl_3$): 2982 (b), 2110 (s), 1723 (s), 1604 (s), 1450 (w), 1356 (s), 1169 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.14 - 7.63 (aromatic, 6H), 6.92 (s, aromatic, 2H), 4.27 (d, J = 5.9 Hz, 1H), 3.66 (m, 1H), 2.49 (s, 6H), 2.26 (s, 3H), 1.47 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.9, 140.2, 132.3, 124.7, 122.6, 119.6, 118.8, 112.4, 66.5, 33.1, 22.5, 21.0, 18.4; HR FAB 426.1369 (M^+).

(2R, 3R)- 2-Azido-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid (16).

This compound was obtained from **12** in a similar manner described above, in 72% yield: $[\alpha]^{24}_D$ = + 23.6 ° (c 0.5, $CHCl_3$); IR ($CHCl_3$): 2980 (b), 2114 (s), 1734 (s), 1356 (s), 1166 (s), 1132 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.14 - 7.63 (aromatic, 6H), 6.92 (s, aromatic, 2H), 4.26 (d, J = 5.6 Hz, 1H), 3.65 (m, 1H), 2.49 (s, 6H), 2.26 (s, 3H), 1.47 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 175.4, 140.2, 134.5, 132.3, 124.4, 122.6, 119.6, 118.8, 112.4, 66.5, 33.1, 22.5, 21.0, 18.4; HR FAB 426.1372 (M^+).

General Procedure for the Reduction of Azido Acids 13 - 16.

(2R, 3S)-2-Amino-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid; threo - D - β - Methyltryptophan (17) (acetic acid salt).

The reduction of the azido acids is illustrated by the following procedure: (2R, 3S)-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid, **13**, (2.8g, 6.6 mmol) in methanol (25 mL) and glacial acetic acid (2 mL), was hydrogenated at 35 psi with palladium on carbon (10%, 2g), for 6 h. The mixture was filtered through a sintered glass funnel and the residue was washed with methanol (5 x 25 mL). The combined organic washings were concentrated under reduced pressure at room temperature. The residual oil was dissolved in ethyl acetate : methanol (7 : 3, 10 mL) and loaded onto a silica gel (70 - 230 mesh, 80g) column equilibrated with ethyl acetate : methanol (7 : 3). Elution with ethyl acetate : methanol : acetic acid (50 : 50 : 1) separated the low-polar byproducts. Then, elution with methanol : ethyl acetate : acetic acid (70 : 30 : 5), followed by

evaporation of the solvents at reduced pressure at room temperature gave an oil which was dissolved in glacial acetic acid (100 mL) and lyophillized to give the acetate salt of **17** as a white powder, 2.5g (82%): $[\alpha]^{24}_D$ = - 5.2 ° (c 1.0, MeOH); TLC (Chiral silica gel plates), eluent acetonitrile : methanol : water (4 : 1 : 1), *Rf* = 0.48; IR (KBr): 2978 (b), 1706 (s), 1561 (s), 1356 (s), 1167 (s) cm^{-1}; ^1H NMR (CD_3OD, 250 MHz): δ 7.08 - 7.74 (aromatic, 5H), 6.97 (s, aromatic, 2H), 3.85 (m, 1H), 3.83 (m, 1H) 2.40 (s, 6H), 2.19 (s, 3H), 1.81 (s, 3H, CH_3COO), 1.31 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CD_3OD): δ 179.8, 173.5, 146.0, 141.4, 136.5, 134.1, 133.5, 130.3, 121.4, 59.2, 32.7, 23.3, 22.8, 21.0, 13.5; HR FAB 401.1532 $(M + H)^+$.

(2S, 3R)-2-Amino-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid; threo - L - β - Methyltryptophan (18) (acetic acid salt).

Compound **18** was prepared from the azido acid **14** as its acetate salt as described above, in 49% yield: $[\alpha]^{24}_D$ = + 7.0 ° (c 1.0, MeOH); TLC (Chiral silica gel plates), eluent acetonitrile : methanol : water (4 : 1 : 1), *Rf* = 0.55; IR (KBr): 2977 (b), 1706 (s), 1560 (s), 1355 (s), 1167 (s) cm^{-1}; ^1H NMR (CD_3OD, 250 MHz): δ 7.05 - 7.74 (aromatic, 5H), 6.96 (s, aromatic, 2H), 3.86 (m, 1H), 3.82 (m, 1H) 2.39 (s, 6H), 2.19 (s, 3H), 1.82 (s, 3H, CH_3COO), 1.30 (d, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD): δ 179.2, 173.2, 141.6, 136.6, 134.2, 130.4, 121.4, 59.3, 32.7, 22.9, 22.7, 21.2, 13.6; HR FAB 401.1508 $(M + H)^+$.

(2S, 3S)-2-Amino-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid; erythro - L - β - Methyltryptophan (19) (acetic acid salt).

Compound **19** was prepared from the azido acid **15** as its acetate salt as described above, in 48% yield: $[\alpha]^{24}_D$ = - 2.5 ° (c 1.0, MeOH); TLC (Chiral silica gel plates), eluent acetonitrile : methanol : water (4 : 1 : 1), *Rf* = 0.60; IR (KBr): 2978 (b), 1705 (s), 1560 (s), 1355 (s), 1166 (s) cm^{-1}; ^1H NMR (CD_3OD, 250 MHz): δ 7.00 - 7.64 (aromatic, 5H), 6.92 (s, aromatic, 2H), 3.67 (m, 1H), 3.44 (m, 1H) 2.36 (s, 6H), 2.15 (s, 3H), 1.80 (s, 3H, CH_3COO), 1.38 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD): δ 179.6, 173.2, 141.4, 136.3, 130.2, 120.8 60.3, 34.2, 22.8, 22.6, 21.0, 18.6; HR FAB 401.1536 $(M + H)^+$.

(2R, 3R)-2-Amino-3-[N-(2-mesitylenesulfonyl)-3-indolyl]butanoic acid; erythro - D - β - Methyltryptophan (20) (acetic acid salt).

Compound **20** was prepared from the azido acid **16** as its acetate salt as described above, in 48% yield: $[\alpha]^{24}_D$ = + 4.7 ° (c 1.0, MeOH); TLC (Chiral silica gel plates), eluent acetonitrile : methanol : water (4 : 1 : 1), *Rf* = 0.35; IR (KBr): 2977 (b), 1560 (s), 1449 (s), 1355 (s), 1166 (s) cm^{-1}; ^1H NMR (CD_3OD, 250 MHz): δ 7.04 - 7.66 (aromatic, 5H), 6.95 (s, aromatic, 2H), 3.71 (d, J = 6.3 Hz, 1H), 3.48 (m, 1H) 2.39 (s, 6H), 2.18 (s, 3H), 1.80 (s, 3H, CH_3COO), 1.40 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD): δ 178.8, 173.8, 141.4, 136.3, 133.5, 130.5, 120.9, 60.2, 34.1, 22.8, 22.6, 21.0, 18.5; HR FAB 401.1530 $(M + H)^+$.

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