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Synthesis of (2*S*,3*S*)-β-methyltryptophan†

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Abstract—N^{α}-Fmoc-protected (2*S*,3*S*)-β-methyltryptophan has been synthesized by asymmetric synthesis through the aid of an oxazolidinone auxiliary. Coupling of the mixed anhydride of N^{in}-Boc-protected indoleacrylic acid to the oxazolidinone auxiliary was achieved by lithium bromide and *N*,*N*-dimethylpyridine (DMAP). This reaction is milder and more convenient to run than the traditional conditions using butyl lithium. © 2001 Elsevier Science Ltd. All rights reserved.

Incorporation of χ-constrained amino acids into bioactive compounds has great potential for understanding ligand–receptor interactions. Since such amino acids limit the number of low energy conformations available to a bioactive compound, use of the appropriate constrained amino acids can improve receptor selectivities, potencies and stabilities.[1] In the past, many peptides with high potency and high receptor selectivities have been designed and synthesized using highly constrained amino acids in our laboratory. One example is *c*[*D*Pen^2, *D*Pen^5]enkephalin (DPDPE, Fig. 1), a δ-opioid receptor selective and potent opioid analogue.[2,3] This five-residue peptide contains two constrained *D*-penicillamine residues—β,β-dimethyl substituted Cys. Another example is SHU-9119,[4] Ac-Nle^4-*c*[Asp^5, *D*Nal(2′)^7, Lys^{10}]α-MSH(4–10)-NH_2 (Fig. 1), an α-MSH analogue with some receptor selectivity among the melanocortin receptors, with high potency and stability. This seven-residue peptide has a side-chain lactam bridge between Asp and Lys, and contains a bulky naphthyl group in the side-chain of position 7. Though this lead compound showed some receptor selectivity, it is intriguing to consider whether modification of constraints at other positions in α-MSH analogues would provide constrained analogues with better receptor selectivities and/or higher potency. One way to accomplish this goal is by modifying Trp^9, a position which has not been studied in detail in the past. As a first step, Trp^9 was constrained with β-methyl substitution. The resulting four α-MSH analogues showed both increased and decreased potency,[5] and most interestingly variable prolonged biological activity. This has prompted us to look for better ways to synthesize β-methyltryptophans in large quantities since our previous syntheses[6] suffered from a long synthetic pathway, an overall low yield, and a final product that only was useful for N^{α}-Boc chemistry.

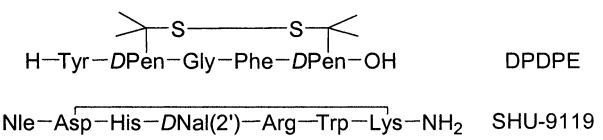

Figure 1. The annotated structures of two constrained peptides (see text for discussion).

A more efficient synthetic strategy has now been carried out in our laboratory. We hereby report this revised synthetic route to achieve one of the four β-methyltryptophan isomers using fewer synthetic steps, with moderate to high yields in most steps, and a protecting group for the nitrogen in the indole ring which is easy to incorporate and deprotect.

The synthesis (Scheme 1) started with indole-3-*trans*-acrylic acid **1** that is protected by Boc at the indole nitrogen to make it compatible with Fmoc chemistry. N^{in}-Boc is inert to basic reaction conditions, and yet can be easily removed. It is very important that the indole nitrogen is properly protected since an unprotected indole nitrogen will otherwise give side reactions in later steps in the synthesis.[6]

Keywords: constrained amino acids; auxiliary assisted asymmetric synthesis; β-methyltryptophan; lithium bromide (LiBr); *N*,*N*-dimethylaminopyridine (DMAP).

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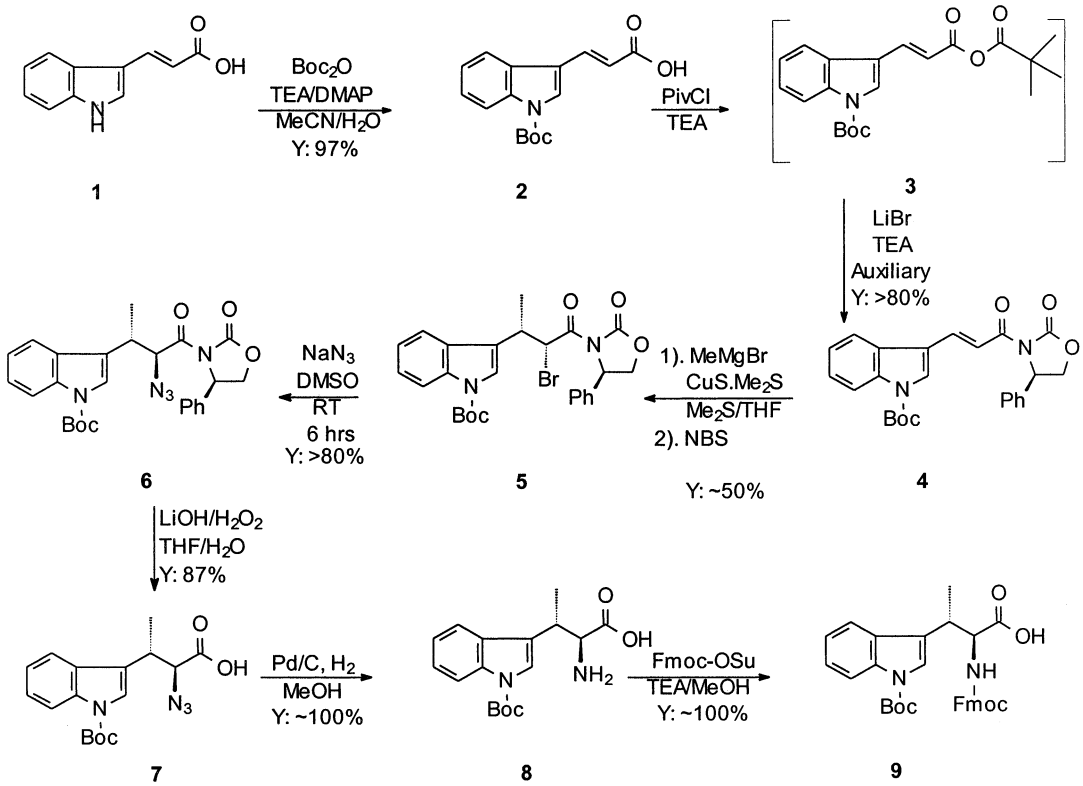

Scheme 1. Synthesis of (2*S*,3*S*)-β-methyltryptophan.

In our initial efforts to prepare the indole nitrogen-protected Boc intermediate **2** (Scheme 1) using standard conditions, we obtained numerous byproducts depending on the conditions applied. Traditional methods[7] to protect the indole ring of **1** with Boc in acetonitrile as solvent was examined first. However, no reaction was detected because the amine salt of indole-3-*trans*-acrylic acid does not dissolve in acetonitrile. Replacing acetonitrile with other common organic solvents did not help. Finally, by adding a few drops of water, the reaction went smoothly with less than 3% byproducts that could be easily washed away (Scheme 1), and N^{in}-Boc-indole-3-*trans*-acrylic acid **2** could be used directly in the next step without further purification. Coupling the chiral oxazolidinone to **2** can be troublesome. After making the mixed anhydride **3** of **2** with pivaloyl chloride (PivCl), we tried many conditions, and many common Lewis bases, acids and other promoters, to couple **3** with the chiral auxiliary. The lithium salt[8,9] was found best for this coupling reaction, which proceeded under mild conditions with excellent yields. The compound **4** obtained was used directly without further purification.

Next, Michael addition of **4** with methyl magnesium bromide and CuBr–Me_2S in methyl sulfide was carried out using reported optimized conditions. The *trans* Michael addition product was the almost exclusive product (as monitored by RP-HPLC), and then NBS was added directly into the reaction mixture. However, the yield was lower than expected in this step, though only one diastereomer **5** was detected by HPLC. The other product was the *trans* added Michael addition product **10** (Fig. 2) which was obtained in almost equal amounts, even when more than 2 equiv. of NBS was used with extended reaction time at room temperature. Nonetheless, the desired product **5** was easily isolated by flash chromatography (**10** was isolated and recycled).

Azide formation of **5** was simpler than expected. Using sodium azide in DMSO, the azide **6** was obtained after flash chromatography (in order to reduce the possible danger of explosion, the reaction was run under argon atmosphere). The S_N2 substitution occurred rapidly (6 h) and no starting material was detected by either TLC or HPLC. [Azide formation by using tetramethylguanidine azide (TMGA) requires a much longer time (about 5 days).]

Hydrolysis of the chiral auxiliary azide **6** by LiOH with H_2O_2 in an ice water bath was complete after 1 h (monitored by TLC and confirmed by HPLC). High yields of the α-azide acid **7** were achieved, and separation was rather simple using organic aqueous extraction after acidification. No purification was necessary and product **7** was used directly for hydrogenation. Unlike

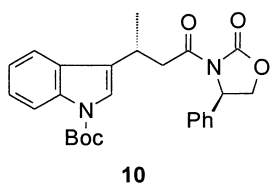

Figure 2. *trans* Michael addition adduct **10**.

when the N^{im}-Mes (1,3,5-trimethylsulfonyl) protecting group was used,[6] hydrogenation of the N^{im}-Boc-protected azide acid (**7**) was short and clean. Extension of the hydrogenation introduces some byproducts, probably over-hydrogenated compounds (not analyzed). However, by monitoring the hydrogenation reaction, product **8** can be obtained in nearly quantitative yield. Finally, protection of the α-amino group was performed in MeOH with 1 equiv. triethylamine (TEA) as base and Fmoc-OSu as the Fmoc source to give **9**[10] in almost quantitative yield.

A revised synthesis of (2*S*,3*S*)-β-methyltryptophan has been achieved. This revised route is a significant improvement over that reported previously,[6] including higher efficiency—high yields in most steps, easier protection and deprotection, more simple reaction conditions, and easier separation of products. The other three isomers of β-methyltryptophan can readily be prepared by similar methods via either changing the chiral center of the oxazolidinone and/or the azidation path.

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10. Spectra of new compound **9**. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.05–8.03 (1H, d), 7.74–7.71 (2H, t), 7.67–7.65 (1H, d), 7.52–7.50 (1H, d), 7.47 (1H, s), 7.37–7.18 (7H, m), 7.11–7.08 (1H, t), 4.59–4.58 (1H, d), 4.42–4.39 (1H, q), 4.15–4.12 (1H, t), 4.08–4.04 (1H, q), 3.59–3.54 (1H, m), 1.53 (9H, s), 1.38–1.36 (3H, d); ^{13}C NMR (500 MHz, DMSO-d_6): δ 173.1, 157.0, 149.6, 143.7, 141.1, 135.5, 129.8, 127.3, 126.7, 124.9, 124.7, 123.9, 122.5, 122.1, 121.6, 119.5, 119.1, 114.8, 83.3, 66.6, 58.1, 33.4, 26.9, 17.0; FAB-MS calculated for $C_{32}H_{32}N_2O_6$: 540.6. Found: *m*/*e* 541.7 [M+H$^+$]. A small amount of fully deprotected (2*S*,3*S*)-β-methyltryptophan hydrogen chloride was obtained by stirring **8** in HCl (6N); $[\alpha]_D = +33°$ (*c* 1, MeOH); FAB-MS: calculated for $C_{12}H_{14}N_2O_2 \cdot HCl$: 219.3 [M–Cl$^-$]. Found: *m*/*e* 219.2. Lit: $[\alpha]_D = +36°$ (*c* 1.55, MeOH).[11]
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