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The Stereocontrolled Synthesis of Orthogonally Protected (R)-α-Methyltryptophan

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Abstract: An expedient and highly stereocontrolled route to (R)-α-methyltryptophan and its orthogonally protected analogs has been developed via a four-step conversion from L-alanine in good overall yields. The stereochemistry of the products is confirmed by X-ray diffraction analysis, NMR spectroscopy and optical rotations.

Peptidomimetic building blocks based on α-substituted α-amino acids have recently emerged as important synthetic targets. They are used in the design of highly potent and non-proteinogenic enzyme inhibitors and conformationally biased peptide ligands.[1,2] As a major part of our current research program directed to the synthesis of biologically interesting peptidomimetics, we are developing general and highly efficient synthetic routes for preparation of conformationally contrained α-amino acids.[3] In connection with these studies, we wish to report herein a short and efficient route for the stereocontrolled synthesis of (R)-α-methyltryptophan and its orthogonally protected analogs which can be readily used in solid phase and combinatorial synthesis. [4]

The biological relevance of α-methyltrytophan was previously demonstrated in the literature.[5] For example, a series of potent and highly selective antagonists for the central cholecystokinin-B (CCK-B) receptor was discovered through the incorporation of (R) or /and (S)-α-methyltryptophan into dipeptide structures. Several approaches to asymmetric synthesis of optically pure α-methyltryptophan were reported in the literature.[6] The early approach to this target molecule was undertaken via asymmetric alkylation of a chiral oxazolidinone obtained from a natural α-amino acid through Seebach's chiral self-reproduction concept. However, this synthesis yields only free α-methyltrytophan because of the harsh conditions required to cleave the auxiliary result in complete remove of all protecting groups. Therefore, additional manipulations are necessary in order to achieve an appropriately protected α-methyltrytophan through the selective reprotection of the amino group at the α-postion and the indole ring. Thus, there remains a need for a more practical route to the the desired protected products with efficient stereocontrol. We have developed a synthetic route to both protected and free (R)-α-methyltryptophan in a straightforward and highly efficient manner as shown in **Scheme 1**.

The synthetic strategy for the construction of the chiral quarternary α-carbon builds on the stereoselective alkylation of salicylaldehyde-derived oxazolidinones recently developed by Zydowsky and coworkers.[7] The method was claimed to be particularly useful for the preparation of α-amino acids containing acid-labile side chains since the alkylated intermediates can be removed under basic conditions. Thus, we reasoned that the

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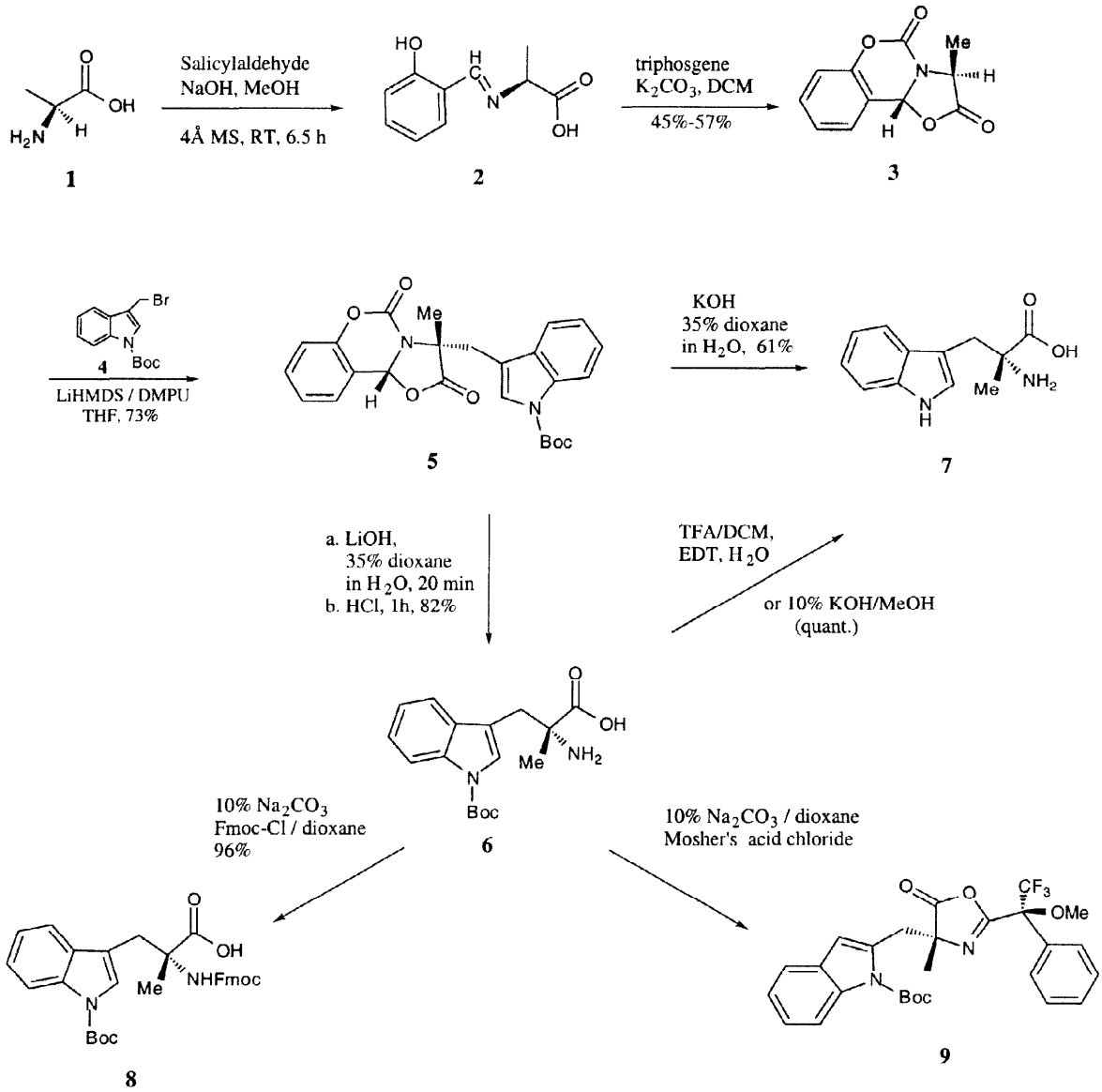
alkylation of an alanine derived oxazolidinone using an appropriately N-protected 3-bromomethyl indole as an electrophile should also generate an intermediate which could be readily hydrolyzed to the product under very mild conditions without cleaving the N-protecting group.

Scheme 1



The literature procedure[7,8] was repeated for the preparation of the oxazolidinone **3** through the Schiff base intermediate **2** which was obained by the coupling of L-alanine with salicylaldehyde in the presence of NaOEt in EtOH. However, racemization occurred to some extent during the preparation of the Schiff base, which was confirmed by acidic hydrolysis of **3** to alanine and comparison of optical rotations of the product amino acid. A complete racemization was observed if NaOMe was used in this reaction. Fortunately, we found that this problem could be avoided by using NaOH as the base. As shown in **Scheme 1**, the condensation of alanine and

salicylaldehyde preceeded in the presence of NaOH in MeOH followed by cyclization using triphosgene which gave the desired oxazolidinone **3** as a single isomer with no measurable loss of enantiomeric purity.[9] Subsequently, alkylation of **3** was carried out by treatment with lithium bis(trimethylsilyl)amide and DMPU in THF at -78°C to give the lithium enolate which was then trapped with 1-(*tert*-butoxycarbonyl)-3-(bromomethyl)indole **4**[10] at -78°C. The crude alkylated product was obtained with a >10:1 diastereomeric ratio. Chromatographic purification on neutral alumina column gave a single diastereomer **5** in 73% yield.[9] The expected R configuration at the newly formed quaternary α-carbon was confirmed by NOE studies which suggested the methyl group and the proton in the oxazolidinone ring had a syn relationship. It was further supported by X-ray diffraction analysis of the Mosher derivative **9** (**Scheme 1**) and the optical rotation value of the final α-methyltrytophan. The observed stereochemistry was opposite to the Seebach's method which provides S-enantiomer from L-amino acids.

The alkylated compound **5** was hydrolyzed under mild conditions (LiOH, 35% aquous dioxane, 20 min; then acidified with 6N HCl). As expected, indole t-Boc protected α-methyltryptophan was obtained in good yield. The high enatiomeric purity of **6** was verified by NMR analysis of its Mosher derivative **9**.[11] The final protection of **6** was accomplished by reaction with FmocCl under standard conditions to give the desired fully protected α-methyltrytophan **8** in high yield. In addition, the treatment of **5** with potassium hydroxide in aqueous dioxane gave the completely deprotected amino acid **7** ($[\alpha]_D$ = +15.3°, C 0.7 in MeOH, Lit.[6e] $[\alpha]_D$ = +15.5°, C 1.0 in MeOH).[12] Boc (Indole) α-methyltryptophan could be easily further deprotected to generate the free amino acid **7** under either acidic or basic conditions in very high yield.

In conclusion, we have developed an expedient and highly stereocontrolled route to the orthoganally protected (R)-α-methyltryptophan of which the stereochemistry was unambiguously characterized by X-ray crystallography. This four-step conversion from an amino acid includes formation of an oxazolidinone, asymmetric alkylation, hydrolysis and the final protection or deprotection in good overall yields. The building block **8** can be readily incorporated into specific biologically important peptides by solid phase synthesis and combinatorial chemistry, and the results will be reported elsewhere.

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9. **Preparation of 3.** To a solution of L-alanine (10 g, 112.2 mmol) and NaOH (4.49 g, 112.2 mmol) in MeOH (200 ml) was added salicylaldehyde (13.7 g, 112.2 mmol) followed by powdered 4 Å molecular sieves (45 g). The resulting mixture was stirred ar room temperature for 6.5 h. The mixture was then filtered, the filtrate was concentrated to give the desired imine which was dried in vacuo at 50°C for 3 h. The above obtained material was dissolved in 250 ml of anhydrous CH_2Cl_2, K_2CO_3 (110 g, 0.8 mol) was then added. To this suspension was added triphosgene (12.3 g, 41.5 mmol) in portions over an hour. The resulting mixture was continued stirring for another 3 h, then filtered over celite. Concentration of the filtrate gave the crude product which was then recrystallized in EtOAc to yield the pure product as a white solid (12.7 g, 57%). mp. 166-167°C. $[\alpha]_D$ = +145.6° (c 1.1, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.61 (d, J = 8.4 Hz, 3H, Me), 4.68 (q, J = 8.4 Hz, 1H, α-H), 6.59 (s, 1H, CH), 7.06-7.45 (m, 4H, aromatic-H).
Preparation of 5: A pre-cooled solution of **3** (1.08 g, 4.94 mmol) in 40 ml of dry THF was transferred to a round flask placed with 1 M LiHMDS in THF (4.82 ml) cooled at -78°C via a cannula under nitrogen atmosphere. To this mixture was then added DMPU (1.26 g, 9.87 mmol). After stirring for 15 min, a solution of bromide (3.04 g, 9.86 mmol) in 10 ml of THF was added dropwise over 15 min. The mixture was continued stirring at -78°C for 1 h, it was warmed to -55°C with stirring for 3 h, then at -30°C for another 2 h. The reaction was quenched with 0.55 ml of acetic acid. After warming to the ambient temperature, the mixture was concentrated and partitioned between EtOAc and saturated aqueous citric acid. The organic layer was washed water, brine, then dried over Na_2SO_4 to yield the crude alkylated product with a 10:1 diastereomeric ratio, determined by ^{1}H-NMR analysis.. The residue was purified by flash chromatography on neutral alumina (hexane / EtOAc, 4 : 1) to give the desired product **5** (1.6 g, 73%). $[\alpha]_D$ = +21.5° (c 0.4, EtOAc). ^{1}HNMR ($CDCl_3$): δ 1.74 (s, 9H, t-Bu), 2.07 (s, 3H, Me), 3.40 and 3.90 (dd, 2H, J = 12 Hz, CH_2), 6.42 (s, 1H, CH), 6.91-7.90 (m, 9H, aromatic-H). MS (FAB+): m/z 449 ($M+H^+$).
10. The bromide **4** was prepared from the corresponding alcohol by using a known procedure. Venkatachalam, T. K., Mzengeza, S, Diksic, M. *Org. Prep. Proc. Int.* **1993**, *25*, 249-251.
11. The high enantiomeric purity of **6** was determined by the NMR studies of both diastereomeric Mosher esters from R-(-) and S-(+) Mosher's acid chloride.
12. Strongly acidic conditions (6N HCl, reflux) were also examined, but only a trace amount of the free amino acid was obtained with the formation of another major by-product.