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Efficient asymmetric synthesis of important tryptophan analogs for biological research via the Schöllkopf chiral auxiliary

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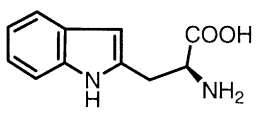
Abstract

An efficient method has been developed via the Schöllkopf chiral auxiliary for the asymmetric synthesis of the important tryptophan analogs: L-isotryptophan, L-benzo[*f*]tryptophan and L-homotryptophan.

Keywords: tryptophan analogs; Schöllkopf chiral auxiliary; isotryptophan; benzo[*f*]tryptophan; homotryptophan.

Indoleamine 2,3-dioxygenase (IDO) is an interferon-ɣ-induced protein that is the first enzyme in the pathway involved in degradation of tryptophan in macrophages and other cells. Many inflammatory diseases and neurodegenerative diseases have been linked to aberrant L-tryptophan metabolism effected by the elevation of IDO activity.[1] One class of competitive IDO inhibitors are tryptophan analogs. For example, the compounds with structures generated by replacement of the N–H function of the indole ring of tryptophan with O or S exhibited moderate inhibitory activity towards rabbit intestine IDO.[2] It was further demonstrated that the L-isomer of N_a-methyl tryptophan was the most competitive inhibitor of IDO reported to date and bound in preference to the D-isomer.[2,3] In the continued effort to search for potent inhibitors of IDO, it was of interest to evaluate IDO activity of the three structurally distinct and optically active tryptophan analogs: L-isotryptophan **1**, L-benzo[*f*]tryptophan **2** and L-homotryptophan **3.** Multistep syntheses of the racemic form of these three tryptophan analogs have been previously reported.[4] However, none of them have been prepared enantioselectively. In this communication, we wish to report an efficient preparation of these three tryptophan analogs in optically active form (D or L) via the Schöllkopf chiral auxiliary.



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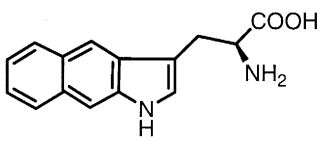

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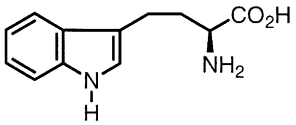

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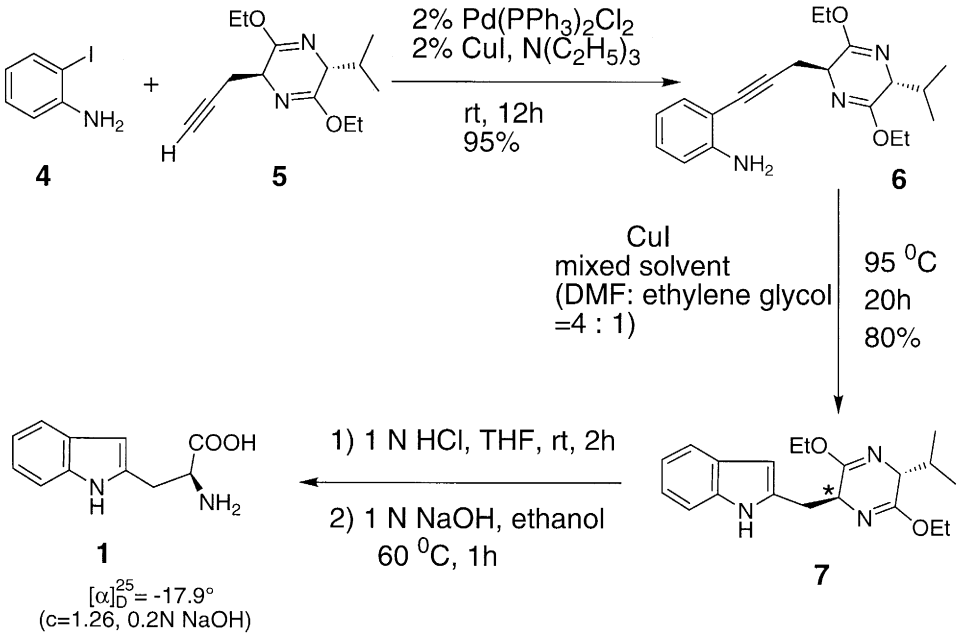
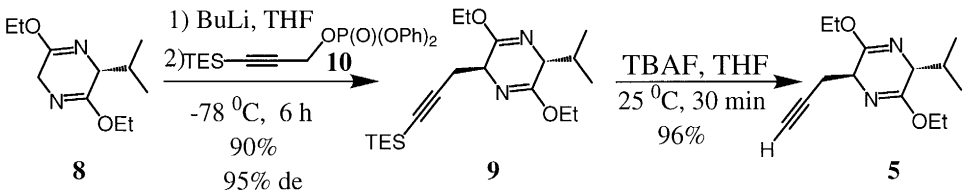


Scheme 1.

Racemic isotryptophan was first synthesized by Kornfeld and was reported to exhibit some bacteriostatic activity.[4a] The stereoselective synthesis of isotryptophan **1** developed here is depicted in Scheme 1. Schöllkopf et al. reported the preparation of alkyne **5** in 60% de by alkylation of the Schöllkopf chiral auxiliary **8** with propargyl bromide.[5] Previous studies in our laboratory have indicated that alkylation of **8** would take place with high diastereoselectivity when diphenylphosphate was employed as the leaving group.[6] However, a considerable amount of allene was obtained when propargyl diphenylphosphate was stirred with the anion of **8**. Importantly, alkyne **5** could be obtained by alkylation of **8** with triethylsilyl-substituted propargyl diphenylphosphate **10** to furnish **9** in high yield and diastereoselectivity,[6] followed by desilylation to generate **5** (Scheme 2). Palladium-catalyzed coupling of *ortho*-iodoaniline **4** with alkyne **5** provided the aminoaryl alkyne **6** in high yield. Intramolecular cyclization of **6** was successfully promoted by CuI while $PdCl_2$ and $NaAuCl_4$ both failed to effect the cyclization. Initially, the CuI promoted reaction was carried out in pure DMF. Unfortunately, these conditions resulted in significant epimerization of the chiral center (⋆) in **7**. One possible pathway for the epimerization is shown in Fig. 1; however, additional experiments are required to determine if this is reasonable. This problem was alleviated by addition of ethylene glycol to the medium as a proton source to suppress epimerization. In this fashion, indole **7** was obtained in 80% yield accompanied by only 6% of the epimerized (⋆) compound which was removed by flash chromatography. The desired L-isotryptophan **1** was obtained in 72% yield by acidic hydrolysis of **7**, followed by subsequent saponification.



Scheme 2.

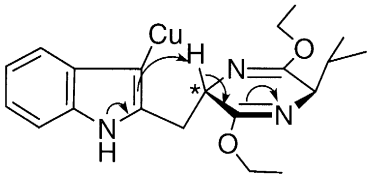
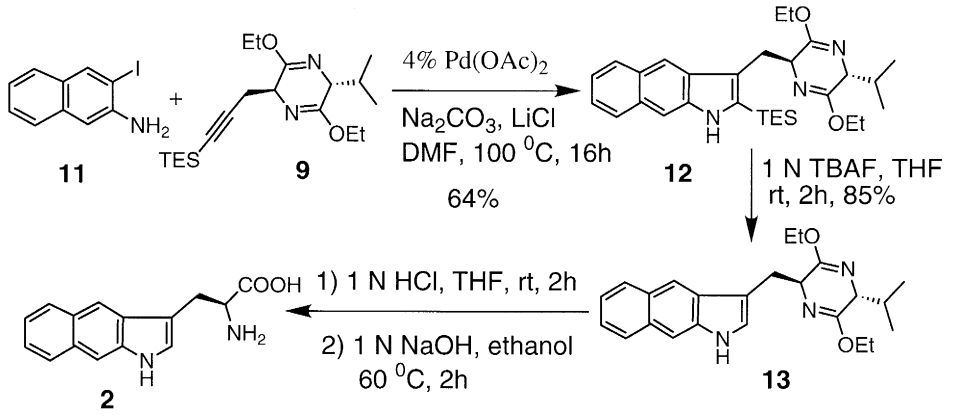
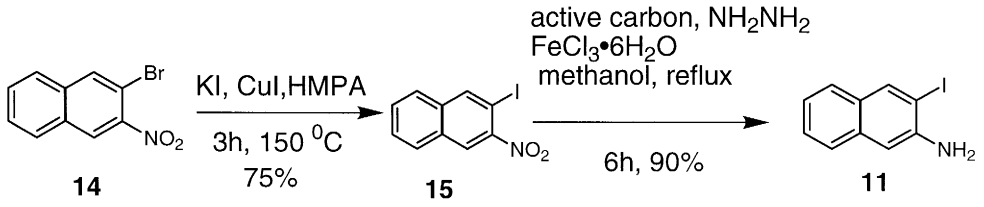


Fig. 1.

The linear benzo[*f*]tryptophan was suggested as a potential fluorescent amino acid probe because of its red-shift from the natural amino acid.[4b] In 1997, McLaughlin et al. first reported the synthesis of N_b-Boc-benzo[*f*]tryptophan in racemic form.[4b] In the course of the search for active ligands at IDO, an efficient synthesis of ring-A-substituted optically active tryptophans was developed.[7] This approach was extended to L-benzo[*f*]tryptophan **2**, as shown in Scheme 3. The 3-iodo-2-aminonaphthalene **11** was prepared via halogen exchange with 3-bromo-2-nitronaphthalene **14**,[8] which was followed by reduction of the nitro group (Scheme 4). Heteroannulation of **11** and the internal alkyne **9** generated the key benzofused indole **12** accompanied by 15% of the 2,3-substituted regioisomer which was easily removed by flash chromatography. Desilylation of **12** was achieved with TBAF in THF to provide intermediate **13**. Treatment of **12** with 1N aqueous HCl failed to effect the desilylation. L-Benzo[*f*]tryptophan **2** was obtained in 75% yield by acidic hydrolysis of **13**, followed by saponification. As expected, spectroscopy indicated the UV absorption of L-benzo[*f*]tryptophan **2** was red-shifted ~60 nm from the absorption of natural L-tryptophan. This analog **2** may provide an efficient probe to study biological processes (as well as peptides) which involve tryptophan (IDO, TDO, etc).



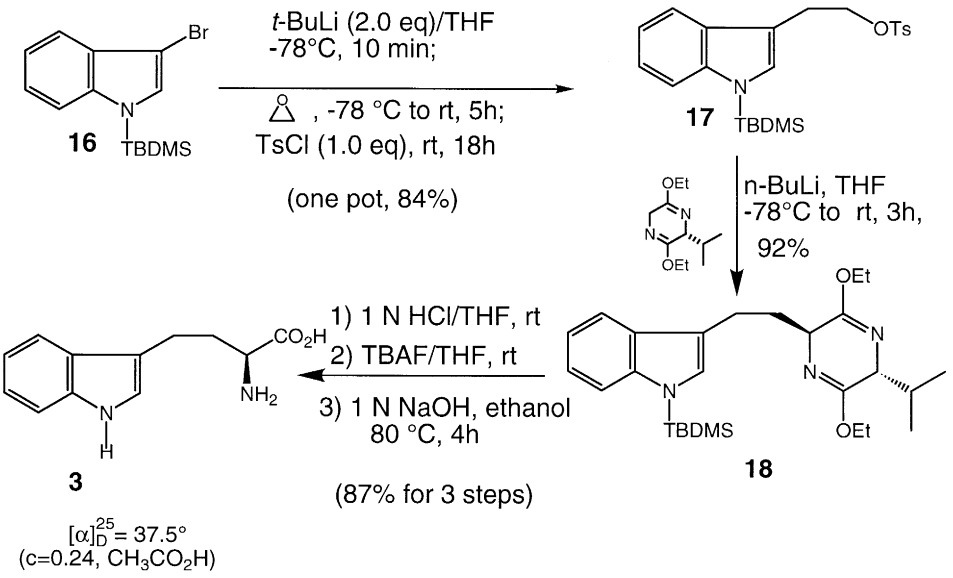
Scheme 3.



Scheme 4.

Homotryptophan was prepared earlier by Snyder and Pilgrim as a racemate.[4c] To date, no enantioselective synthesis has been reported to our knowledge. The strategy for the asymmetric synthesis of L-homotryptophan **3** was to effect a two-carbon homologation of an indole moiety to be followed by alkylation of the Schöllkopf chiral auxiliary, as depicted in Scheme 5. Initially, *N*-sulfonyl-

3-bromoindole was chosen as the starting material to effect the lithium halogen exchange (*t*-BuLi) to generate a carbanion at position 3 as previously reported by Gribble and Saulnier.[9] However, in our hands, this carbanion at C(3) was readily converted into the thermodynamically more stable carbanion at position 2 at −78°C due to the stabilizing effect of the *N*-sulfonyl group adjacent to the carbanion. Consequently, the *N*-TBDMS-substituted 3-bromoindole **16**[10] was used as the starting indole. Lithium halogen exchange of **16** with *t*-butyllithium was followed by nucleophilic attack on the oxirane, the anion of which was trapped with *p*-toluenesulfonyl chloride to generate the tosylate **17** in one pot. Alkylation of the anion of the Schöllkopf chiral auxiliary **8** with **17** furnished the intermediate **18** in high yield and stereoselective fashion. Hydrolysis of **18** and subsequent desilylation, followed by saponification provided L-homotryptophan **3** in high yield.



Scheme 5.

In summary, the efficient stereoselective synthesis of three tryptophan analogs with potential activity at IDO have been completed. These syntheses make available any of these tryptophans as D- or L-isomers in optically active form for the study of biological processes (IDO, TDO, etc).

Acknowledgements

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