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Concise Synthesis of Optically Active Ring-A Substituted Tryptophans

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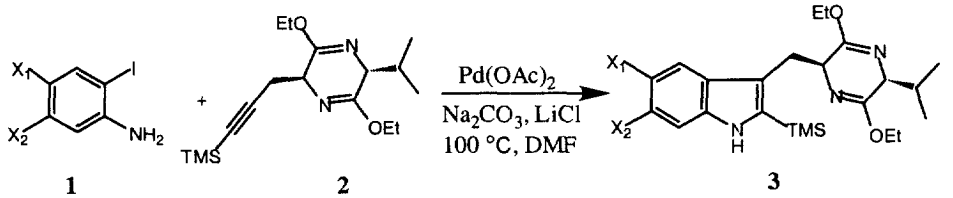
Summary: *A concise synthesis of optically active tryptophan derivatives was developed via diastereoselective alkylation of the Schöllkopf chiral auxiliary* ***4*** *to provide alkyne* ***2*** *which underwent palladium-catalyzed heteroannulation with iodoanilines* ***1*** *to furnish protected tryptophans* ***3****. Hydrolysis and subsequent saponification of* ***3*** *provided the desired tryptophans* ***12*** *in good yields.* © 1999 Elsevier Science Ltd. All rights reserved.

Indoleamine 2,3-dioxygenase (IDO) is a monomeric heme-containing enzyme. One of the functions of IDO in cells is the oxidation of L-tryptophan to kynurenine, a principal metabolic pathway for L-tryptophan. Many diseases including HIV- and AIDS-associated dementia and wasting as well as acute/chronic immunological and inflammatory diseases have been found to be associated with the elevation of IDO activity.[1] In the course of the search for potent inhibitors of IDO,[2] a facile synthesis of ring-A substituted tryptophans was required.

A few of the current methods to synthesize optically active tryptophan derivatives include synthesis and subsequent resolution of the racemic compound,[3] transformation of a readily available optically active amino acid into tryptophan derivatives,[4] or synthesis of the indole precursor followed by reaction with the Schöllkopf chiral auxiliary.[5] We wish to report an efficient method for the preparation of ring-A substituted tryptophans via a palladium-catalyzed coupling reaction between iodoaniline **1** and alkyne **2** (eq 1).



1 **2** **3** (1)

Recently, Larock et al[6] reported an excellent method for the preparation of indoles involving palladium-catalyzed heteroannulation of internal alkynes using *ortho*-iodoaniline or its derivatives. Applications of this method have been extended to the syntheses of indenones[7a], benzofurans,[7b] racemic tryptophans,[7c] and the 5-HT_{1D} receptor agonist MK-0462.[7d] However, an efficient palladium-catalyzed coupling process for the synthesis of optically active tryptophans has not been reported previously.

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Our approach to the synthesis of chiral tryptophans began with the diasteroselective preparation of propargyl substituted bislactim ethyl ether **2** (eq. 2). Schöllkopf had earlier devised a method to prepare a variety of amino acids based on the metallation and subsequent alkylation of bis-lactim ethers (Schöllkopf chiral auxiliary).[8] The popular Schöllkopf chiral auxiliary, bis-lactim ether **4**, derived from L-valine and glycine, is readily available.[9] Metallation of the bis-lactim ether **4** with n-butyllithium in THF at low temperature followed by alkylation with a variety of electrophiles usually proceeds with a high degree of stereoselectivity to furnish the trans diastereomer. Initial attempts to prepare **2** rested on reaction of Schöllkopf chiral auxiliary **4** with 3-bromo-1-(trimethylsilyl)-1-propyne. Unfortunately, the alkylation furnished **2** with low diastereoselectivity (entry 1, Table 1). Presumably, the selectivity was low because the rod-like propargyl system of the electrophile was not bulky enough to provide high diastereoselectivity at the site of reaction. Bis-lactim ethers **7** and **8** have been reported to provide exceptionally high asymmetric induction[10], but the relative cost and availability of **7** and **8** excluded them from this approach. It was decided to vary the alkylation conditions and modify the leaving group on **6** to provide substituted bis-lactim **2** with high diastereoselectivity. The electrophiles represented by **6** (Table 1) were prepared by treatment of 3-trimethylsilyl-2-propyn-ol with the corresponding sulphonyl chloride or chlorophosphate at 0 ℃ in the presence of KOH in diethyl ether.[11] As illustrated in Table 1, when the process was carried out at very low temperature, the selectivity was not improved (entry 2). Variation of the solvent (see entry 4, Table 1) also did not improve the diastereoselectivity. However, the leaving group does play an important role in formation of the desired trans diastereomer in preference to its cis counterpart. When the leaving group was bulkier and poorer, the diastereoselectivity increased (entries 6-8, Table 1). Alkylation of the Schöllkopf chiral auxiliary **4** with diphenyl (trimethylsilyl)propargyl phosphate provided the best trans selectivity (entry 8, trans : cis = 46 : 1). Only a trace of the undesired cis isomer was observed and was removed by chromatography.

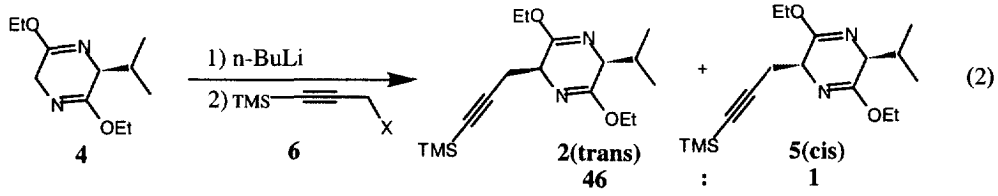
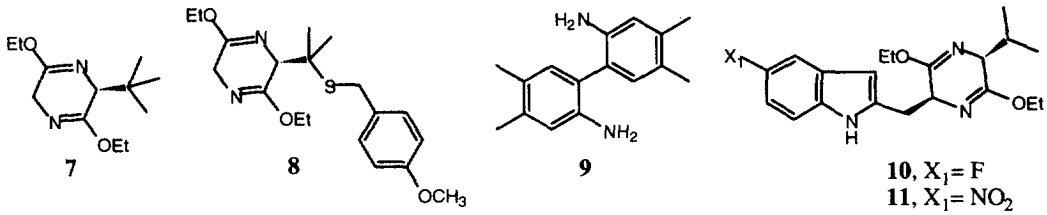


Table 1. Diastereoselective Synthesis of Internal Alkyne **2**

entry	X	solvent	temperature (°C)	isolated yield (%)	**2** (trans) : **5** (cis)
1	-Br	THF	-78	80	2.5 : 1
2	-Br	THF	-100	78	1.6 :1
3	-OTs	THF	-78	75	11 : 1
4	-OTs	DME	-58	74	5 : 1
5	$-OSO_2CH_3$	THF	-78	72	5 : 1
6	$-OSO_2(p\text{-}CH_3OPh)$	THF	-78	72	12 : 1
7	$-OPO(OEt)_2$	THF	-78	70	12 : 1
8	$-OPO(OPh)_2$	THF	-78	80	46 : 1



With the internal alkyne **2** in hand, the palladium-catalyzed heteroannulation reaction with readily available substituted *ortho*-iodoanilines **1**[12] was carried out. The results are summarized in Table 2. Lithium chloride was found to be a crucial component of this coupling process in agreement with the findings of Larock[6] and Yum.[13] Addition of the ligand PPh_3 retarded the reaction rate and resulted in the isolation of recovered starting material and diminished yields. Use of an excess of alkyne **2** in this sequence was beneficial to the process. For the substrate listed in entry 2, the biaryl side product **9** was isolated if only one equivalent of alkyne **2** was used. For electron deficient iodoanilines (entries 4 and 5), the heteroannulations were appreciably faster but with reduced regioselectivity. For both cases, desilyated regioisomers **10** and **11** were isolated in 15% and 22% yield, respectively, along with the desired tryptophans.

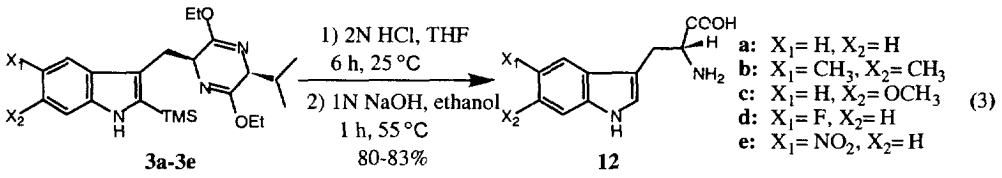
Table 2. Palladium-Catalyzed Heteroannulation of Alkyne **2** and Iodoanilines **1**[a]

entry	X_1	X_2	isolated yield (%)
1	H	H	81%
2	CH_3	CH_3	70%
3	H	OCH_3	61% (77%)[b]
4	F	H	50%
5	NO_2	H	65%

[a]All reactions were run at 100 °C under nitrogen by heating 5 mol% $Pd(OAc)_2$, aryl iodide (0.5 mmol), LiCl (0.5 mmol), Na_2CO_3 (1 mmol), alkyne **2** (0.65 mmol) in 10 mL of DMF. [b]This example is for the TES substituted alkyne and was accompanied by 5% of the desilyated regioisomer.

When the coupling products **3a-3c** (entries 1-3, Table 2) were treated with hydrochloric acid in THF, the bis-lactim ether moiety was hydrolyzed to the amino acid ethyl ester, and the silyl group was concomitantly removed to provide the tryptophan ethyl esters directly. The subsequent saponification furnished L-tryptophan derivatives **12a-12c** in good yields (eq.3). However, for indoles substituted with electron withdrawing groups, acid-mediated desilylation was troublesome, as expected. For the fluorine substituted tryptophan **3d**, 6N HCl instead of 2N HCl was required to cleave the silyl group. For the nitro substituted tryptophan **3e**, desilylation failed under acidic conditions; however, when **3e** was treated with 2N KOH in ethanol at 78°C for 6 h, smooth removal of the silyl group occurred. Acid-mediated hydrolysis of the desilylated intermediate, followed by saponification of the ester moiety, provided the desired 5-nitro L-

tryptophan **12e** in 80% yield (from **3e**). The optical rotation of L-tryptophans obtained in this process were in good agreement with the literature values[14] where available.



(3)

In summary, a Schöllkopf/palladium-catalyzed heteroannulation protocol was developed to synthesize ring-A substituted optically active tryptophans. The present method is short, practical and versatile in operation because of the variety of iodoanilines and the availability of the Schöllkopf chiral auxiliary in both enantiomeric forms.

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