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PII: S0040-4039(19)31297-3
DOI: https://doi.org/10.1016/j.tetlet.2019.151498
Reference: TETL 151498

To appear in: *Tetrahedron Letters*

Received Date: 23 October 2019
Revised Date: 4 December 2019
Accepted Date: 5 December 2019

Please cite this article as: Cai, N., Mi, F., Wu, Y., Song, H., Liu, X-Y., Qin, Y., Practical and efficient preparation of the chiral 4-bromotryptophan derivative by Rh-catalyzed hydrogenation, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151498

Graphical Abstract

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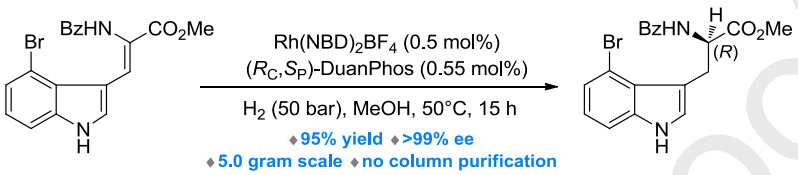

Tetrahedron Letters
journal homepage: www.elsevier.com

Practical and efficient preparation of the chiral 4-bromotryptophan derivative by Rh-catalyzed hydrogenation

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Asymmetric hydrogenation
Tryptophan
Indole alkaloid
Chiral ligand

ABSTRACT

An efficient three-step sequence has been developed for the preparation of a chiral 4-bromotryptophan derivative starting from the commercially available 4-bromoindole. Key to the synthesis was the generation of the chiral center via a Rh-catalyzed asymmetric hydrogenation of a dehydrotryptophan precursor with 95% yield and >99% ee. Notably, the whole synthetic route required no column chromatographic operations and was readily conducted on large scales.

Indole alkaloids represent a large family of natural products with fascinating chemical structures and rich biological activities.[1] Tryptophan (**1**, Figure 1), the important starting point in the biosynthesis of indole alkaloids, corresponds to the "*indole•C_2N*" building block that constitutes the key structural units in these alkaloid molecules.[2] As many complex indole alkaloids contain varied substituents at the C4 position (e.g., **2**–**5**, Figure 1),[3] the chiral 4-halotryptophan derivatives proved to be important starting materials or synthetic intermediates for accessing the corresponding indole alkaloid natural products and

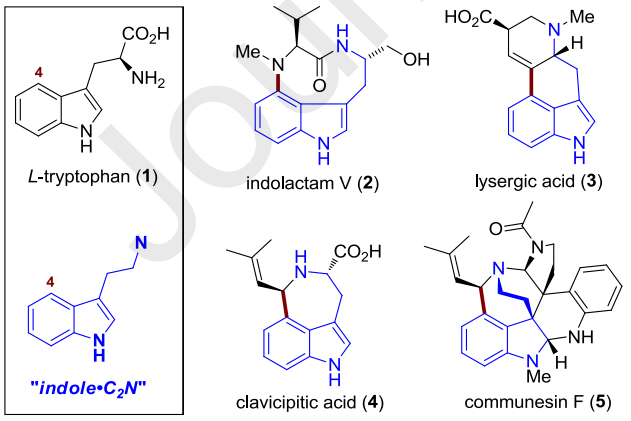

Figure 1. Selected indole alkaloids containing C4 functionalities.

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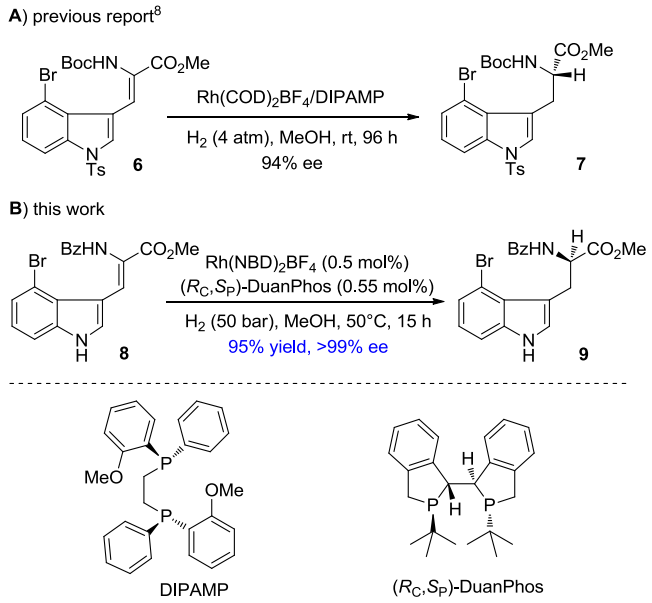
associated analogues in enantiomerically pure forms.[4] First, the halogenate functionality at C4 could act as a synthetic handle for the introduction of requisite groups. Second, the chiral information bearing in these compounds would be transferred to the final products via a substrate-controlled fashion.

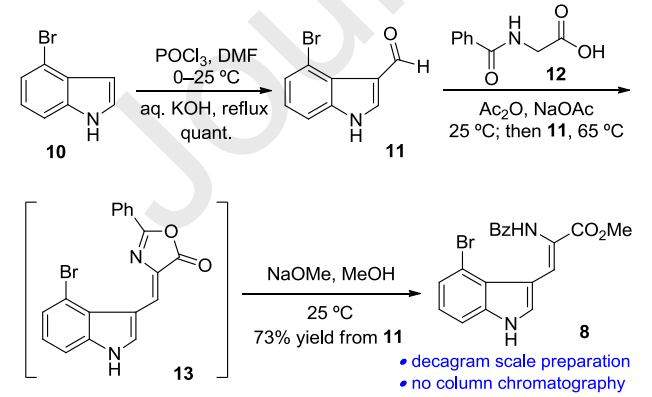
Several methods were previously documented in the literature for the preparation of optically pure 4-halo-tryptophan derivatives. These include, to name a few, an acylase-mediated kinetic resolution approach,[5] Pd-catalyzed annulation[4b,6] or Ni-catalyzed reductive cross-coupling[4d] protocols using chiral starting materials, as well as an alkylation strategy with a proline-based chiral auxiliary.[4f] Asymmetric catalysis based on transition metals has proved to be efficient tools for the generation of chiral molecules.[7] In 1995, Yokoyama and co-workers described the synthesis of a chiral 4-bromotryptophan derivative **7** by asymmetric reduction of the corresponding dehydrotryptophan precursor **6** with the best ee value of 94% using DIPAMP phosphine ligand (Scheme 1A).[8] Not only the enantioselectivity of the key hydrogenation reaction was not perfect, but preparation of the 4-bromodehydrotryptophan substrate **6** required a stoichiometric amount of $Pd(OAc)_2$,[8] which significantly reduced the overall synthetic efficiency. Thus, a simple and efficient method for synthesizing the chiral 4-bromotryptophan derivative is still desirable. Herein, we report an operationally simple and scalable synthesis of the chiral 4-bromotryptophan **9** employing a Rh-catalyzed asymmetric

hy) in chiral ligand allowed the generation of **9** with excellent yield (95%) and enantiomeric purity (>99%) (Scheme 1B).



Scheme 1. Catalytic asymmetric hydrogenation approaches to chiral 4-bromotryptophan derivatives.

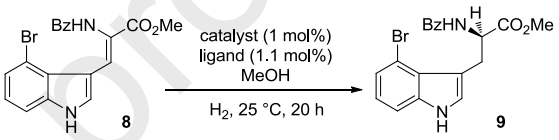
Our synthetic efforts commenced with the preparation of the 4-bromodehydrotryptophan substrate **8** (Scheme 2). According to a known procedure,[9] 4-bromoindole (**10**) was first treated with $POCl_3$/DMF followed by reflux in aqueous KOH to give aldehyde **11** with quantitative yield. Based on a protocol reported by Jursic and colleagues,[10] aldehyde **11** was condensed with an *in situ* generated oxazolone intermediate (not shown) from *N*-benzoylglycine (**12**) in the presence of NaOAc/Ac_2O, leading to the coupling product **13**. Subjection of the crude **13** to the conditions of NaOMe in methanol at room temperature resulted in opening of the oxazolone ring and afforded the desired α,β-unsaturated tryptophan **8** with 73% overall yield (**11**→**8**). Compared to the previously known methods,[8] the above-mentioned protocol was more efficient that avoided the use of transition metals and column chromatographic operations. Thus, this practical approach easily provided us decagram materials of 4-bromodehydrotryptophan **8**, setting the stage for investigating the catalytic asymmetric reduction of the enamide double bond.



Scheme 2. Practical synthesis of 4-bromodehydrotryptophan **8**.

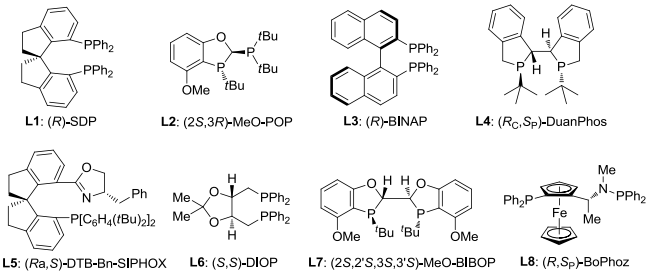
With **8** in hand, we set out to examine the reaction conditions for the catalytic asymmetric reduction of the enamide double bond (Table 1). The relatively cheap catalyst Ru(2-methylallyl)$_2$(COD) was employed in the initial experiments.[11] Subjecting the α,β-unsaturated tryptophan **8** to Ru(2-methylallyl)$_2$(COD) in EtOH under the atmosphere of H_2 (10 bar) at room temperature afforded the desired reduction product **9** with full conversion of the starting material and with 21% ee (entry 1). Different ligands **L2**–**L4** (entries 2–4) were unsuccessful to improve the reaction enantioselectivity. Subsequently, we switched the metal catalyst to $Rh(NBD)_2BF_4$ that was commonly used in the reduction of enamide substrates.[12] Extensive screening of various chiral ligands (entries 5–13) was then conducted under the atmosphere of H_2 (50 bar). Specifically, many ligands including (*R*)-BINAP (**L3**), (*R*)-SDP (**L1**), (*Ra*,*S*)-DTB-Bn-SIPHOX (**L5**), (2*S*,3*R*)-MeO-POP (**L2**), (*S*,*S*)-DIOP (**L6**), (2*S*,2'*S*,3*S*,3'*S*)-MeO-BIBOP (**L7**), and (*R*,S_P)-BoPhoz (**L8**) only led to low conversion and unsatisfactory enantioselectivity (entries 5–11). By contrast, we were delighted to find that (R_C,S_P)-DuanPhos (**L4**) was perfect to deliver a spot-to-spot conversion and excellent ee value (>99%) of the product (entry 12).[13] Of note, use of DIPAMP as the chiral ligand under the same conditions failed to generate any desired product (entry 13).[8,14] The effect of different anions for the Rh-catalyst was also surveyed (entries 14–16) and all the attempted anions gave inferior results compared to BF_4 (entry 12).

Table 1. Exploration and optimization of the reaction conditions[a]

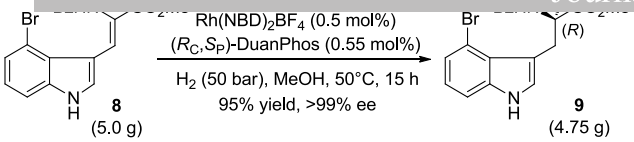


entry	catalyst	ligand	H_2 (bar)	conv. (%)[b]	ee (%)[c]
1[d]	Ru(2-methylallyl)$_2$(COD)	**L1**	10	100	21
2[d]	Ru(2-methylallyl)$_2$(COD)	**L2**	10	100	<5
3[d]	Ru(2-methylallyl)$_2$(COD)	**L3**	10	100	25
4[d]	Ru(2-methylallyl)$_2$(COD)	**L4**	10	100	13
5	$Rh(NBD)_2BF_4$	**L3**	50	17	<5
6	$Rh(NBD)_2BF_4$	**L1**	50	30	25
7	$Rh(NBD)_2BF_4$	**L5**	50	26	18
8	$Rh(NBD)_2BF_4$	**L2**	50	trace	---
9	$Rh(NBD)_2BF_4$	**L6**	50	57	<5
10	$Rh(NBD)_2BF_4$	**L7**	50	60	31
11	$Rh(NBD)_2BF_4$	**L8**	50	25	38
12	$Rh(NBD)_2BF_4$	**L4**	50	100	>99
13	$Rh(NBD)_2BF_4$	**DIPAMP**	50	NR	---
14	$Rh(NBD)_2SbF_6$	**L4**	50	86	94
15	$Rh(NBD)_2PF_6$	**L4**	50	38	90
16	$Rh(NBD)_2CO_2CF_3$	**L4**	50	65	90

[a]Unless otherwise specified, all reactions were performed with 0.25 mmol of **8** in the presence of catalyst (1 mol%) and ligand (1.1 mol%) at room temperature for 20 h. NBD = 2,5-norbornadiene, COD = cyclooctadienyl. [b]Obtained according to HPLC analysis of the crude reaction mixture. [c]Determined by HPLC using a Chiralcel OD-H column. [d]These reactions were carried out in the presence of HBF_4•Et_2O (2 mol%) using EtOH as the reaction solvent.



With the optimal catalyst/ligand combination, we performed a scale-up reaction (Scheme 3) and found that the reaction yield (95%) and enantioselectivity (>99%) maintained on a 5.0 gram scale experiment with less $Rh(NBD)_2BF_4$ (0.5 mol%) and **L4** (0.55 mol%) at a slightly elevated temperature (50 ºC). Simple and direct recrystallization from the reaction mixture (in methanol) provided 4.75 g of the desired 4-bromotryptophan derivative **9**.



Scheme 3. Gram scale catalytic asymmetric hydrogenation of **8**.

To summarize, we have developed a practical and scalable synthetic approach to the optically pure 4-bromotryptophan derivative **9** starting from the commercially available 4-bromoindole (**10**) in three steps with 69% overall yield and without use of any column chromatographic operations. Among these steps, a key Rh-catalyzed asymmetric hydrogenation employing DuanPhos as the chiral ligand furnished the expected product **9** with excellent ee (>99%), which, to the best of our knowledge, represents the highest enantioselectivity obtained in the asymmetric hydrogenation of such dehydrotryptophan substrates. Predictably, the present method would be able to facilitate the asymmetric synthesis of related indole alkaloids and analogues. Such efforts are ongoing in our laboratory and will be reported in due course.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (21871189) and National Major Science and Technology Projects of China (2018ZX09101003-005-004).

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13. The absolute configuration of the generated stereocenter in **9** was assigned as (*R*) by comparison of its CD spectrum with that of a debromo compound derived from *L*-tryptophan. See the Supplementary data for details.
14. Subjecting 4-bromodehydrotryptophan **8** to the same asymmetric hydrogenation conditions as those reported by Yokoyama et al (ref. 8) resulted in no reaction over 96 h.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

- bromotryptophan derivative in three steps
- A key Rh-catalyzed asymmetric hydrogenation with excellent enantioselectivity (>99%)
- Column-chromatography-free in the whole synthetic route