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CONCISE SYNTHESES OF HARMICINE AND A PYRROLIDINO-ISOQUINOLINE DERIVATIVE USING CHIRAL 1-ALLYL ADDUCTS OF β-CARBOLINE AND ISOQUINOLINE AS STARTING MATERIALS [1]

Takashi Itoh, Michiko Miyazaki, Kazuhiro Nagata, Masashi Yokoya, Shigeru Nakamura, and Akio Ohsawa*

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

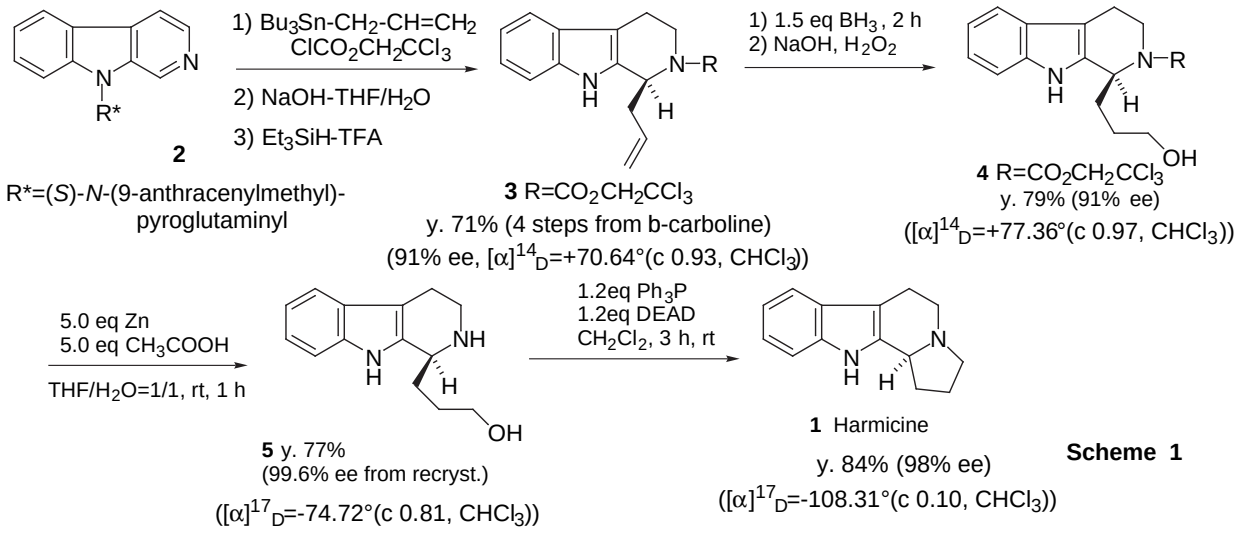
Abstract – Total syntheses of (*S*)-harmicine and (*R*)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline were carried out using chiral 1-allyl-1,2,3,4-tetrahydro-β-carboline and 1-allyl-1,2-dihydroisoquinoline as starting materials, respectively.

In recent years, we have developed a new method by which allyl group was introduced at C-1 position of β-carboline or isoquinoline derivatives using chiral auxiliaries derived from readily available amino acids. Thus, 1-allyl-1,2-dihydro derivatives of isoquinolines[2] and β-carbolines[3] were obtained in a highly diastereoselective manner. Allyl group is a versatile tool for syntheses of other functional groups,[4] and there are several reports concerning the application of racemic allyl group of β-carboline to the synthesis of various alkaloids.[5] In order to prove the usability of the chiral allyl adducts obtained by our method, we have investigated straightforward transformation of the compounds to natural and/or useful compounds, and found that the allyl adducts were transformed to fused five-membered rings through a hydroboration-Mitsunobu reaction procedure. From a 1-allyl-β-carboline, an alkaloid named harmicine was synthesized in an optically pure form, and it was also found that the initially suggested stereochemistry was incorrect.[6] From a 1-allylisoquinoline derivative, an optically active pyrrolidinoisoquinoline derivative was obtained. This paper describes these results.

2,3,5,6,11,11b-Hexahydro-1*H*-indolizino[8,7-*b*]indole (**1**) has been used as a starting material of racemic total synthesis of many alkaloids such as tubifoline, condyfoline, fluorocurarine *etc*.,[6] thus the synthetic utility of the compounds was established. Although **1** had been thought to be a non-natural product, it was isolated recently from the leaf extract of *Kopsia griffithii*, and the absolute configuration of C-11b chiral center was suggested to be (*S*) from the spectrum data.[7] The compound was named as harmicine. The verification of the absolute configuration, however, was not reported so far.

In the course of our research for asymmetric synthesis of 1-allyl-1,2,3,4-tetrahydro-β-carboline, we found that both enantiomers were obtained in high yields and good stereoselectivity.[3] In these

precedents in hand, we have applied these compounds to the synthesis for indole alkaloids, and at first, determined to synthesize harmicine for the determination of the absolute configuration. The synthetic scheme is shown in Scheme 1.



2 R*=(*S*)-*N*-(9-anthracenylmethyl)-pyroglutaminyl

3 R=$CO_2CH_2CCl_3$
y. 71% (4 steps from b-carboline)
(91% ee, $[\alpha]^{14}_D$=+70.64°(c 0.93, $CHCl_3$))

4 R=$CO_2CH_2CCl_3$
y. 79% (91% ee)
($[\alpha]^{14}_D$=+77.36°(c 0.97, $CHCl_3$))

5 y. 77%
(99.6% ee from recryst.)
($[\alpha]^{17}_D$=-74.72°(c 0.81, $CHCl_3$))

1 Harmicine
y. 84% (98% ee)
($[\alpha]^{17}_D$=-108.31°(c 0.10, $CHCl_3$))

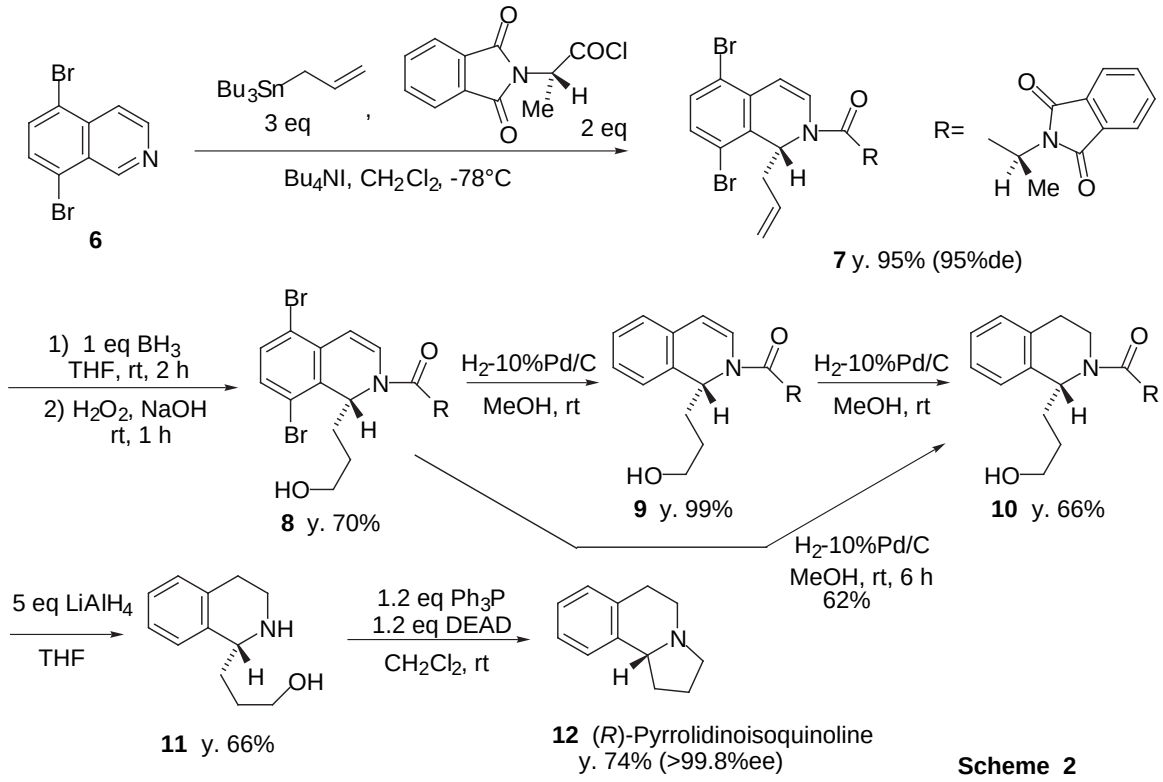
Scheme 1

Since the report[7] suggested the structure of **1** as the (*S*) isomer, we selected an (*S*)-allyl adduct (**3**) as a starting material. The compound (**3**) was obtained from the method reported earlier in 91%ee (overall yield 71% from β-carboline *via* 4 steps).[8] A standard hydroboration-oxidation procedure afforded a 1-(3-hydroxypropyl)-β-carboline (**4**) without any noticeable racemization. The reduction of trichloroethoxycarbonyl group by zinc/acetic acid readily eliminated the group to give 1-(3-hydroxypropyl)-1,2,3,4-tetrahydro-β-carboline (**5**). The compound (**5**) was recrystallized from hexane-AcOEt to give an optically pure form. Then a Mitsunobu procedure[9] was applied to **5** and the ring-closed product (**1**) was obtained in a good yield with high enantiopurity. All the values of the ee were obtained from the chiral HPLC analysis. We started the synthesis using the (*S*) isomer, and the racemization did not occur in the reaction process. The value of the specific rotation was, however, showed $[\alpha]^{17}_D$= –108.31° (c 0.10, $CHCl_3$), which has an opposite sign for the reported value of (+)-(*S*)-harmicine. Therefore, the present study revealed that the naturally occurring harmicine has an (*R*) configuration.

Next, a similar procedure was applied to the synthesis of a pyrrolidinoisoquinoline (**12**) using a 1-allyl-1,2-dihydroisoquinoline as a starting material (Scheme 2). The derivatives of **12** widely exist in plant products and many of them have been reported to exhibit interesting biological activity.[10] Accordingly, many studies have focused on development of general approaches to these compounds.[11] However, there are not many general methods for the asymmetric synthesis of them,[12] and Lee *et al*. recently reported the total synthesis of both enantiomers of parent **12**.[13] Therefore, we decided to apply our method to the asymmetric synthesis of (*R*)-**12**.

We already reported that the introduction of bromo group(s) to isoquinoline ring raised the stereoselectivity of the addition reaction of isoquinoline with nucleophiles in the presence of chiral acyl chloride derived from L-alanine.[2] Thus, the compound (**6**), which was readily obtained from the

reaction of isoquinoline and bromine, was adopted as a starting material. When **6** was allowed to react with allyltributyltin and *N*-phthaloyl-L-alanyl chloride in the presence of tetrabutylammonium iodide, the 1-allyl-1,2-dihydro adduct (**7**) was obtained in 95% yield (95% de). Then hydroboration-oxidation protocol was carried out using BH_3-THF complex to give **8** in a moderate yield of 70%. The reduction of **8** under catalytic hydrogenation conditions rapidly proceeded to give a debrominated derivative (**9**) in a quantitative yield. Further reduction under the same conditions slowly transformed **9** to **10** in a moderate yield.[14] The compounds (**8**, **9**, and **10**) were obtained as a single diastereomer, which were confirmed by the ^1H and ^{13}C NMR spectra. Then the chiral auxiliary was eliminated with $LiAlH_4$ reduction in THF to afford **11** without any racemization, and the compound was subjected to the ring-closing reaction to give the compound (**12**) in an optically pure form.



Scheme 2

In this paper, we described the application of the chiral allyl adducts derived from β-carboline and isoquinoline to the synthesis of harmicine and a pyrrolidinoisoquinoline in short straightforward steps. The results showed that the reported configuration of (+)-harmicine was reversed. Application of the allyl adducts to syntheses of other chiral alkaloids is now under investigation.

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REFERENCES AND NOTES

1. This paper is dedicated to Professor A. I. Meyers on the occasion of his 70th birthday.
2. a) T. Itoh, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, **1999**, 1154. b) T. Itoh, K. Nagata, M. Miyazaki, K. Kameoka, and A. Ohsawa, *Tetrahedron*, 2001, **57**, 8827.
3. a) T. Itoh, Y. Matsuya, Y. Enomoto, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, **1999**, 1799. b) Y. Matsuya, T. Itoh, Y. Enomoto, and A. Ohsawa, *Heterocycles*, 2000, **53**, 2357. c) T. Itoh, Y. Matsuya, Y. Enomoto, and A. Ohsawa, *Tetrahedron*, 2001, **57**, 7277.
4. Y. Yamamoto and N. Asao, *Chem. Rev*., 1993, **93**, 2207, and references cited therein.
5. a) S. F. Martin, B. Benage, and J. E. Hunter, *J. Am. Chem. Soc*., 1988, **110**, 5925. b) S. F. Martin, B. Benage, L. S. Geraci, J. E. Hunter, and M. Mortimore, *J. Am. Chem. Soc*., 1991, **113**, 6161. c) R. Yamaguchi, T. Hamasaki, T. Sasaki, T. Ohta, K. Utimoto, S. Kozima, and H. Takaya, *J. Org. Chem*., 1993, **58**, 1136. d) V. B. Birman and V. H. Rawal, *Tetrahedron Lett*., 1998, **39**, 7219. e) V. B. Virman and V. H. Rawal, *J. Org. Chem*., 1998, **63**, 9146.
6. a) B. A. Dadson, J. Harler-Mason, and G. H. Foster, *J. Chem. Soc., Chem. Commun*., **1968**, 1233. b) J. Harley-Mason and C. G. Tayler, *J. Chem. Soc., Chem. Commun*., **1970**, 812. c) G. C. Crawley and J. Harley-Mason, *J. Chem. Soc., Chem. Commun*., **1971**, 685. d) W. R. Ashcroft, S. J. Martinez, and J. A. Joule, *Tetrahedron*, 1981, **37**, 3005.
7. T.-S. Kam and K.-M. Sim, *Phytochemistry*, 1998, **47**, 145.
8. Modification of the reported method in ref. 2 raised the ee to 91% using an *N*-pyroglutamic acid derivative as a chiral auxiliary. The detailed procedure will be reported in a due course.
9. R. C. Bernotas and R. V. Cube, *Tetrahedron Lett*., 1991, **32**, 161.
10. B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, and P. E. Setler, *J. Med. Chem.*, 1987, **30**, 1433, and references cited therein.
11. a) Y. Tsuda, Y. Sakai, M. Kaneko, and Y. Ishiguro, *Heterocycles*, 1981, **15**, 431. b) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367. c) E. Lete, A. Egiarte, N. Sotomayor, T. Vicente, and M.-J. Villa, *Synlett*, **1993**, 41.
12. a) B. E. Maryanoff and D. F. McComsey, *J. Heterocycl. Chem*., 1985, **22**, 911. b) B. E. Maryanoff, D. F. McComsey, H. R. Almond Jr., M. S. Mutter, G. W. Bemis, R. R. Whittle, and R. A. Olofson, *J. Org. Chem*., 1986, **51**, 1341. c) B. E. Maryanoff, D. F. McComsey, M. S. Mutter, K. L. Sorgi, and C. A. Maryanoff, *Tetrahedron Lett*., 1988, **29**, 5073. d) K. L. Sorgi, C. A. Maryanoff, D. F. McComsey, D. W. Graden, and B. E. Maryanoff, *J. Am. Chem. Soc*., 1990, **112**, 3567.
13. Y. S. Lee, D. W. Kang, S. J. Lee, and H. Park, *J. Org. Chem*., 1995, **60**, 7149.
14. Direct formation of **10** from **8** was also possible by elongation of the reaction time (6 h) to give a comparable yield of 62%.