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Total Synthesis of *ent*-Dihydrocorynantheol by Using a Proline-Catalyzed Asymmetric Addition Reaction

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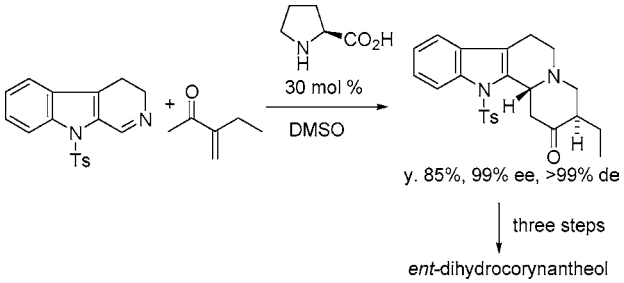
ABSTRACT



9-Tosyl-3,4-dihydro-β-carboline reacted with 3-ethyl-3-buten-2-one in the presence of (*S*)-proline to give (3*R*,12b*R*)-3-ethyl-12-tosyl-3,4,6,7,8,9,-10,11,12,12b-decahydro-1*H*-indolo[2,3-*a*]quinolizin-2-one in complete enantio- and diastereoselectivity. The compound thus obtained was readily transformed to *ent*-dihydrocorynantheol in three steps.

In recent years, asymmetric syntheses with organic compounds as catalysts have attracted much attention[1] due to their environmentally benign nature compared with conventional transition metal catalysts, and there have been many reactions in which chiral amines such as proline,[2] amino acids, and their derivatives[3] are used as catalysts. Despite intense studies of this area, however, there are few reports[4] which adopted the methodology as a tool for asymmetric total synthesis of natural products.

In the course of our research for the synthesis of chiral 1-substituted 1,2,3,4-tetrahydro-β-carboline derivatives,[5] we found that 9-tosyl-3,4-dihydro-β-carboline (**1**)[6] is a good substrate for the asymmetric addition of methyl ketones in the presence of (*S*)-proline.[7] We further investigated the reaction using various methyl ketone derivatives, and found that the use of 3-ethyl-3-buten-2-one resulted in concise asymmetric synthesis of *ent*-dihydrocorynantheol. This paper describes these results.

Although there are many reports concerning diastereoselective synthesis of indole alkaloids,[8] to carry out the synthesis in an enantioselective manner remains a formidable challenge.[9] 1,2,3,4-Tetrahydro-β-carboline derivatives having

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(2) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(3) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(4) (a) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (b) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696.

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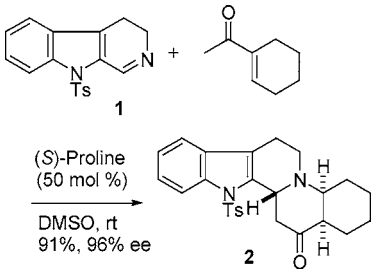
a substituent at the C-1 position widely exist in nature as a constituent of indole alkaloids, but construction of the chiral center at an early stage is a minor approach[10] for the total synthesis of indole alkaloids. We planned to reinvestigate such an approach because these compounds are thought to be general precursors for asymmetic synthesis of the alkaloids, and found that *N*-tosyl-3,4-dihydro-β-carboline (**1**) reacted with methyl vinyl ketones in a highly enantioselective mannner catalyzed by (*S*)-proline.[7] Thus, we extended our attention to the synthesis of the addition products which have more than two chiral centers. The first attempt was carried out with commercially available 1-acetylcyclohexene as a methyl ketone, and it was found that the addition product **2** was solely obtained in a completely stereoselective manner.[11] Thus, the three chiral centers were formed in a single step (Scheme 1).

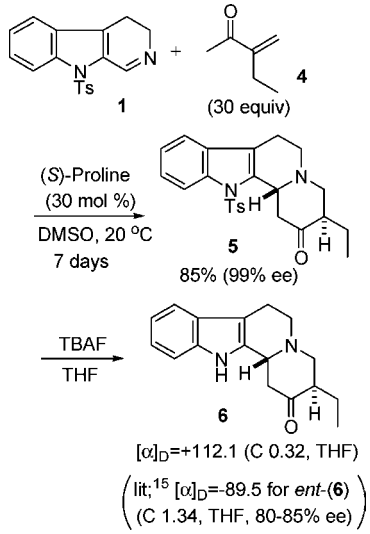
Scheme 1. Reaction of 9-Tosyl-3,4-dihydro-β-carboline (**1**) with 1-Acetylcyclohexene in the Presene of (*S*)-Proline



The result prompted us to apply the process to both enantioselective and diastereoselective reactions using an enamine derived from (*S*)-proline and 3-ethyl-3-buten-2-one as a nucleophile to construct the D-ring of an alkaloid, which has an ethyl group on the C-3 position to give corynanthe alkaloids. Thus, the addition reaction was carried out with 3-ethyl-3-buten-2-one aiming at the synthesis of dihydrocorynantheol (**3**),[12] which was isolated from Aspidosperma marcgravianum, and shows activity against gram-positive bacteria. In a recent paper,[13] Martin et al. performed a concise diastereoselective synthesis of the compound in excellent overall yield using ring-closing metathesis as a key reaction. There are several total syntheses of **3**,[14] and three of them are asymmetric synthesis with the chiral pool,[15] a chiral auxiliary,[16] or a resolution step.[17]

Our reaction was commenced with the reaction of **1** with 3-ethyl-3-buten-2-one (**4**)[18] in the presence of (*S*)-proline (Scheme 2), and the use of 30 equiv of **4**[19] and 30 mol % of

Scheme 2. Reaction of 9-Tosyl-3,4-dihydro-β-carboline (**1**) with 3-Ethyl-3-buten-2-one in the Presene of (*S*)-Proline



(*S*)-proline afforded the product **5** in a good yield of 85% with 99% ee in the DMSO solvent.[20]

Since there were no intermediates observed in the reaction, we could not conclude whether the reaction proceeded via Mannich−Michael reaction or a Diels−Alder-type addition. It was thought, however, that the present reaction is a Mannich−Michael reaction rather than a hetero-Diels−Alder reaction, because the reaction proceeded in the same manner as with simple methyl ketones as reagents.[7] The reaction of **1** and **4** proceeded smoothly when the excess amount (3 equiv) of proline was used in the presence of 10 equiv of the enone to give quantitative yield of the product in 99% ee in 3 days. The result suggested that the first addition step is a rate-determining process. The stereochemistry of the product **5** was determined by the elimination of the tosyl group to give a ketone **6**, which was synthesized by Meyers et al.[16] Thus, the formation of the D ring of the target

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(11) The relative configuration of **2** was determined by using the NOE analysis (see the Supporting Information). The absolute configuration was speculated according to those of the other addition products.

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(14) (a) Ziegler, F. E.; Sweeny, J. G. *Tetrahedron Lett.* **1969**, *14*, 1097. (b) Kametani, T.; Kanaya, N.; Honda, T.; Ihara, M. *Heterocycles* **1981**, *16*, 1937. (c) Ihara, M.; Taniguchi, N.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1438. (d) Lounasmaa, M.; Jokela, R.; Tirkonnen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 321. (e) Diez, A.; Villa, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M. *Tetrahedron Lett.* **1993**, *34*, 733.

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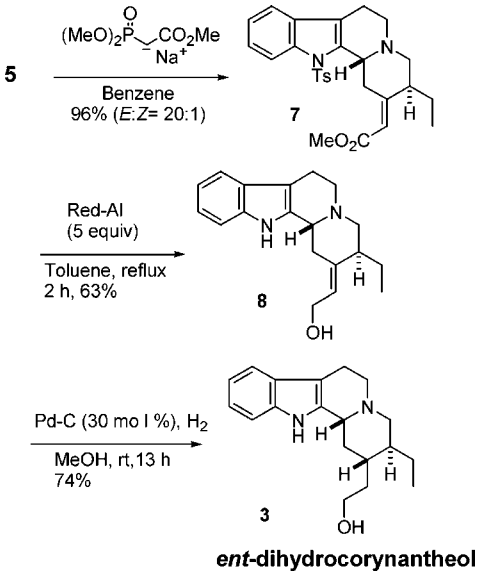
(17) Ohba, M.; Ohashi, T.; Fujii, T. *Heterocycles* **1991**, *32*, 319.

(18) Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 553.

(19) Since the present reaction was slow, the excess amount of the enone was necessary for the progress of the reaction in tolerable time. The self-reaction of enones in the presence of proline catalyst was not observed in the present reaction; see: Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Tetrahedron Lett.* **2002**, *43*, 6743.

(20) Although the other solvents such as CH_2Cl_2, CH_3CN, DMF, and THF were used for the reaction, the results were inferior to that of the DMSO solvent.

Scheme 3. Synthesis of *ent*-Dihydrocorynantheol



molecule was accomplished in a single step with the correct configuration and in a high yield. Compound **5** was then allowed to react with a Wittig reagent to give an alkene **7** quantitatively in the ratio of $E/Z = 20$. The reaction of **7** with Red-Al occurred at two reactive sites, that is, the reductive elimination of the tosyl group and the reduction of the ester group to an alcohol. Finally, hydrogenation of alcohol **8** afforded *ent*-dihydrocorynantheol (**3**) in 74% yield. Therefore, the asymmetric total synthesis of **3** was performed in 38% overall yield via 4 steps.While our synthesis targeted the enantiomer of the natural product, the natural series is equally accessible by using (*R*)-proline as a catalyst.

In this paper, we described a new method for the asymmetric synthesis of *ent*-dihydrocorynantheol using proline-catalyzed asymmetric addition of 3-ethyl-3-buten-2-one to compound **1**. The procedure was readily carried out in the presence of air and moisture to give a single stereoisomer. With use of the addition product, the target compound was obtained in short steps with complete stereoselectivity. Application of the present reaction to the synthesis of other alkaloids is under investigation in our laboratory, and the results will be published in due course.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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