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Total synthesis of (*R*)-tylophorine by using an asymmetric hydrogenation of the allyl alcohol

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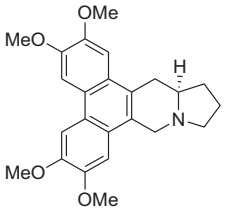
ABSTRACT

An efficient synthesis of naturally occurring (*R*)-tylophorine is described. The alkaloid was prepared in seven steps from a known phenanthryl aldehyde with an overall yield of 14.2%. Asymmetric hydrogenation of an allyl alcohol was employed as a key step for installing a stereogenic center with good enantioselectivity (77% ee), and the ee value of the ω-chloro alcohol was improved to 95% by recrystallization. After azidation and oxidation of the *enantio*-enriched ω-chloro alcohol to the precursor of the Schmidt reaction, the chirality transfer in the stereospecific 1,2-migration furnished the chiral carbon in the alkaloid. Finally, a one-pot deformylation/Pictet-Spengler cyclization completed the total synthesis of (*R*)-tylophorine.

Tylophorine **1** (Fig. 1), a phenanthroindolizidine alkaloid featuring with a pentacyclic motif, was initially isolated from *Tylophora indica* plant family.[1] It exhibits remarkable antitumor,[2] antiinflammatory,[3] and antifungal activities,[4] therefore many groups had reported their synthesis of the racemate tylophorine,[5] naturally occurring (*R*)-tylophorine,[6,7] and its antipode (*S*)-tylophorine.[8,9] Most of the synthetic methods toward the optically active tylophorine were based on the chiral materials or auxiliaries,[6,8] and only four different synthetic routes had been developed for constructing the stereogenic center of tylophorine *via* the catalytic asymmetric reactions. The Pd-[7a] and Cu-catalyzed[9b] asymmetric alkene carboamination reactions were used by Wolfe's group and Chemler's group, and the corresponding intermediates for synthesis of the enanito-enriched tylophorine were produced with good enantioselectivities (88% ee and 81% ee, respectively). Wang's group had reported that the asymmetric allylation of an aldehyde could be used as a key step for synthesis of (*S*)-tylophorine, affording a homoallylic alcohol with 86% ee.[9a] Yamaoka and co-workers had reported the synthesis of (*R*)-tylophorine based on an asymmetric transfer hydrogenation of a cyclic imine for creating the chirality (84% ee).[7b] In this paper, we present an enantioselective synthesis of the (*R*)-tylophorine by using a catalytic asymmetric hydrogenation for installing the stereogenic center.

Our synthesis of (*R*)-tylophorine employed the strategy analogous to our previously reported method for preparation of the



(*R*)-tylophorine **1**

Fig. 1. Structure of naturally occurring tylophorine.

(±)-antofine,[10] another attractive phenanthroindolizidine alkaloid for researchers. An intramolecular Schmidt reaction of the alkyl azide with an aldehyde was served as a key conversion in our previous synthesis of **(±)-**antofine, and the Schmidt rearrangement had been demonstrated as a stereospecific process, where the stereochemistry of the migration group could be maintained.[11] Therefore, the synthesis of optically active tylophorine could be conveniently addressed if the *enantio*-enriched precursor of the Schmidt reaction could be prepared.

With this in mind, we started the synthesis from the known phenanthryl aldehyde **2**[12] and a substituted phosphonate **3** (Scheme 1). The aldehyde could be easily prepared according to the literature[12a] through four steps conversion, and the phosphonate **3** was obtained *via* the synthetic procedure we reported.[10] The Horner-Wadsworth-Emmons condensation of the phenanthryl aldehyde **2** with phosphonate **3** was carried out in the presence of 2.0 equiv of NaH, affording the α,β-unsaturated ester

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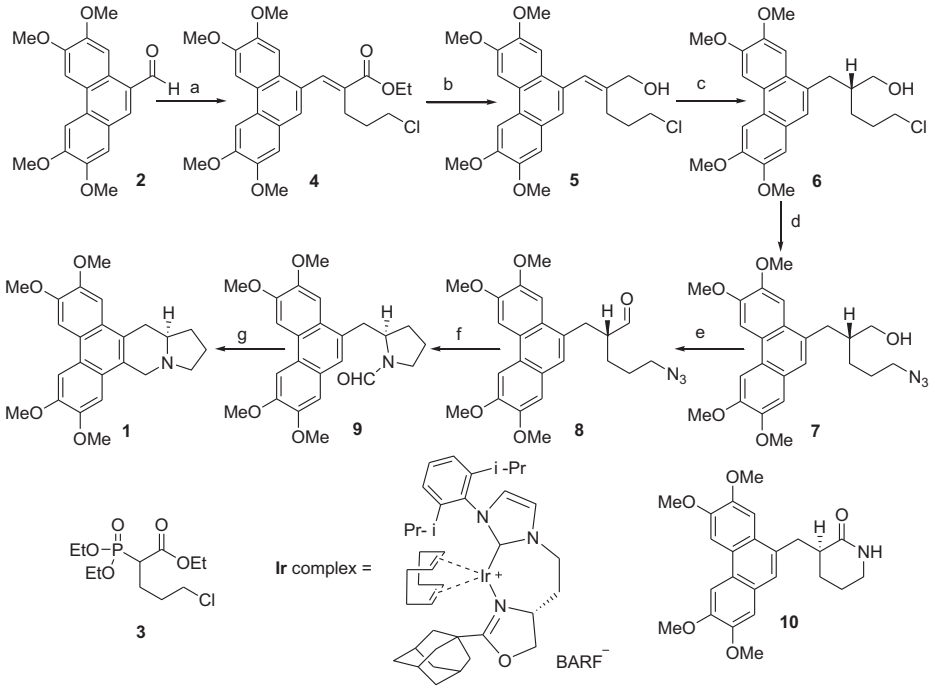
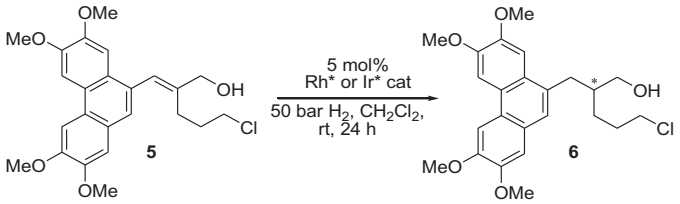
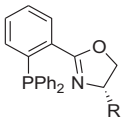


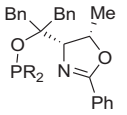
Scheme 1. Synthesis of (*R*)-tylophorine.



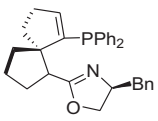
Ligands for the chiral ***Ir*** catalysts:



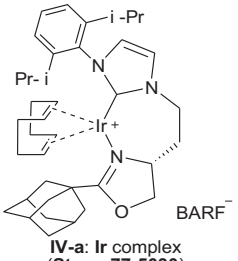
I-a: R = Ph (20% ee, >99% conv.)
I-b: R = ^{i}-Pr (15% ee, >99% conv.)
I-c: R = ^{t}-Bu (24% ee, >99% conv.)



II-a: R = Ph (34% ee, >99% conv.)
II-b: R = Cy (27% ee, >99% conv.)

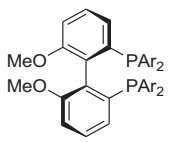


III-a: (20% ee, >99% conv.)

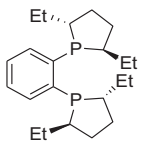


IV-a: **Ir** complex
(**Strem 77-5030**)
[71% ee, >99% conv. (CH_2Cl_2, 50 bar)]
[54% ee, 12% conv. ($CHCl_3$, 50 bar)]
[58% ee, 22% conv. ($ClCH_2CH_2Cl$, 50 bar)]
[55% ee, 85% conv. (CH_2Cl_2, 30 bar)]
[77% ee, >99% conv. (CH_2Cl_2, 60 bar)]
[77% ee, >99% conv. (CH_2Cl_2, 70 bar)]

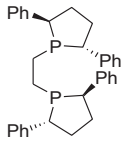
Ligands for the chiral ***Rh*** catalysts :



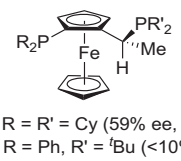
V-a: R = Ph (34% ee, 60% conv)
V-b: R = 4-OMe-3,5-^{t}Bu-Ph (25% conv)



VI-a: (42% ee, 70% conv)



VII-a: (<10% conv)



VIII-a: R = R' = Cy (59% ee, 19% conv)
VIII-b: R = Ph, R' = ^{t}Bu (<10% conv)
VIII-c: R = 4-OMe-3,5-Me-Ph, R' = Cy (<10% conv)

Scheme 2. Optimization for the asymmetric hydrogenation of the allyl alcohol **5**.

4 in 70% yield with absolute control of the stereochemistry of the double bond, and only the *E* isomer of the ester **4** was observed. Reduction of **4** with potassium borohydride and lithium chloride could smoothly offer an allyl alcohol **5** in 65% yield, and the reaction should be carefully monitored, as excess reduction of the C=C bond had been observed. The asymmetric hydrogenation of alkenes provides an efficient and reliable method for producing chiral compounds.[13] The primary screening of the commercially available Rh and Ir catalysts revealed that the *Ir*-complex catalyzed hydrogenation reaction of allyl alcohol **5** gave the ω-chloro alcohol **6** with a bit higher conversion and enantioselectivity, and the results were outlined in Scheme 2. Then the catalytic asymmetric hydrogenation of the allyl alcohol was further explored with several commercially available chiral *Ir*-complexes,[14] where the best enantioselectivity (77% ee) was observed with an *Ir*-oxazoline complex depicted in Scheme 1, efficiently affording the ω-chloro alcohol **6** in 99% yield. To improve the *enantio*-purity, recrystallization of the ω-chloro alcohol from EA/PE (1:2, 98 mg in 15 mL) was performed, and the ω-chloro alcohol was recovered in 56% yield with 95% ee.

Then azidation of the ω-chloro alcohol **6** with sodium azide in DMF delivered the corresponding ω-azido alcohol **7** in nearly quantitative yield (Scheme 1). Oxidation of the alcohol with Dess-Martin reagent smoothly gave the azido aldehyde **8** in 99% yield. The intramolecular Schmidt reaction of the chiral ω-azido aldehyde **8** was carried out with TFA, affording the desired formamide **9** (alkyl migration) in 82% yield. It should be noted that the lactam **10** (hydride migration) was also observed and isolated. Deformylation of **9** followed by a sequenced Pictet-Spengler cyclization of the corresponding amine with the phenanthryl ring could be realized in one pot operation. The formamide **9** was treated with concentrated HCl and aqeous formaldehyde in ethanol at 80 °C, and the (*R*)-tylophorine was finally furnished in 70% yield. The NMR data and the optical rotation of the synthetic sample {$[\alpha]_D^{25} = -101$ (c 1.0, $CHCl_3$)} were in agreement with those reported in literatures {lit.[6b] $[\alpha]_D^{22} = -90.4$ (c 1.0, $CHCl_3$); lit.[6d] $[\alpha]_D^{22} = -99.0$ (c 1.0, $CHCl_3$); lit.[6e] $[\alpha]_D^{20} = -103$ (c 1.0, $CHCl_3$)}. Finally, the ee value of the synthetic tylophorine was determined to be 96% by the chiral HPLC analysis, which also indicates that the Schmidt reaction of the ω-azido aldehyde **8** should be a stereospecific process.

In summary, we have developed an efficient synthetic route to the naturally occurring (*R*)-tylophorine. Asymmetric hydrogenation of an allyl alcohol was employed for installing a stereogenic center, and a stereospecific shift of the chiral carbon finally completed constructing the stereocenter of (*R*)-tylophorine. The (*R*)-tylophorine was prepared through seven steps from the known phenanthryl aldehyde with an overall yield of 14.2%.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.052.

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14. For more information about the screening of the Rh and Ir catalysts, please see the supporting information file for details.