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Synthesis of indole alkaloid (−)-corynantheidol and formal synthesis of (−)-corynantheidine via one-pot asymmetric azaelectrocyclization

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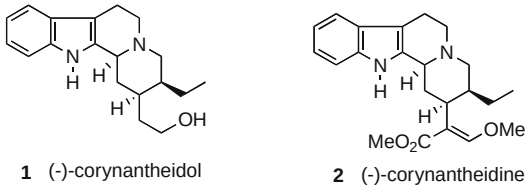
ABSTRACT

The highly efficient asymmetric total synthesis of indole alkaloid, (−)-corynantheidol, containing a 2,4,5-trisubstituted piperidine core, was achieved using a new version of the one-pot azaelectrocyclization reaction. The formal synthesis of (−)-corynantheidine was also achieved using the common synthetic intermediate for these corynantheines.

Corynantheines, which are the family of indole alkaloids related to yohimbine and known as ring E seco equivalents (Fig. 1),[1] have a characteristic tetracyclic skeleton possessing three asymmetric centers, and several total syntheses of these alkaloids have been reported.[2] A few total syntheses of corynantheidol (**1**), which was isolated from *Mitragyna parvifolia (Roxb.) Korth.* (Rubiaceae) in 1973,[3] have been realized,[4] and a number of partial and total syntheses of corynantheidine (**2**), which was isolated from the African plant *Psudocinchona Africana*[5] and whose structure was determined in 1955,[6] were reported.[7] However, in these syntheses, only two approaches were enantioselective.[8] Meyers and co-workers completed the synthesis of (−)-corynantheidol (**1**) using β-carboline formamidine via the intramolecular Blaise reaction, and also performed the formal synthesis of (−)-corynantheidine (**2**).[8a] Cook and co-workers achieved the total syntheses of (−)-corynantheidol (**1**) and (−)-corynantheidine (**2**) in 2000 using the asymmetric Pictet–Spengler reaction in a key bond-forming step.[8b]

Recently, we realized the highly stereoselective asymmetric 6π-azaelectrocyclization of the conformationally flexible linear 1-azatrienes using 7-isopropyl-*cis*-aminoindanol, and the substituted chiral tetrahydropyridine derivatives were successfully obtained in high yields and selectivities.[9] Furthermore, in order to develop the asymmetric 6π-azaelectrocyclization as a new strategy for alkaloid synthesis, we reported a unique one-pot protocol, which led to the facile and stereoselective preparation of the chiral tetracyclic 2,4-disubstituted 1,2,5,6-tetrahydropyridine derivative (R^1 = H)



1 (-)-corynantheidol **2** (-)-corynantheidine

Figure 1. The structures of the corynantheine family of alkaloids.

(Fig. 2).[10] In addition, based on this protocol, the stereoselective syntheses of chiral 2,4,6-trisubstituted piperidines and an

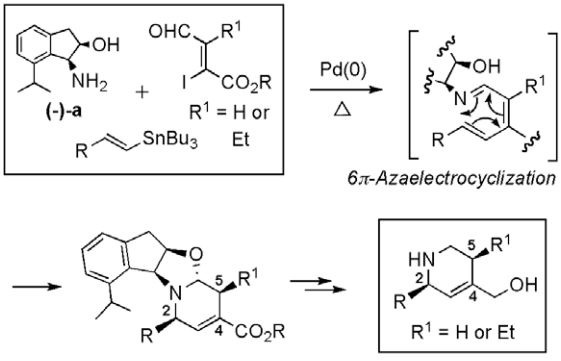


Figure 2. Synthesis of chiral tetrahydropyridines using one-pot asymmetric azaelectrocyclization protocol.

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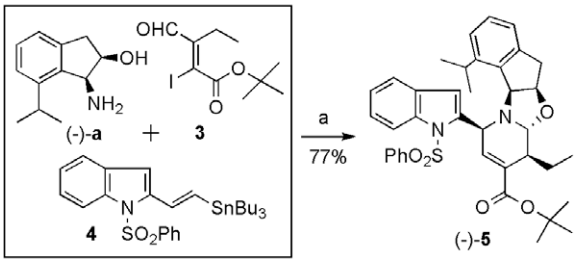


Scheme 1. One-pot azaelectrocyclization. Reagents and conditions: (a) **3**, (−)-**a**, MS5A, 1,4-dioxane, 80 °C, 30 min then **4**, $Pd_2(dba)_3$, trifurylphosphine, LiCl, reflux, 11 h, 77%.

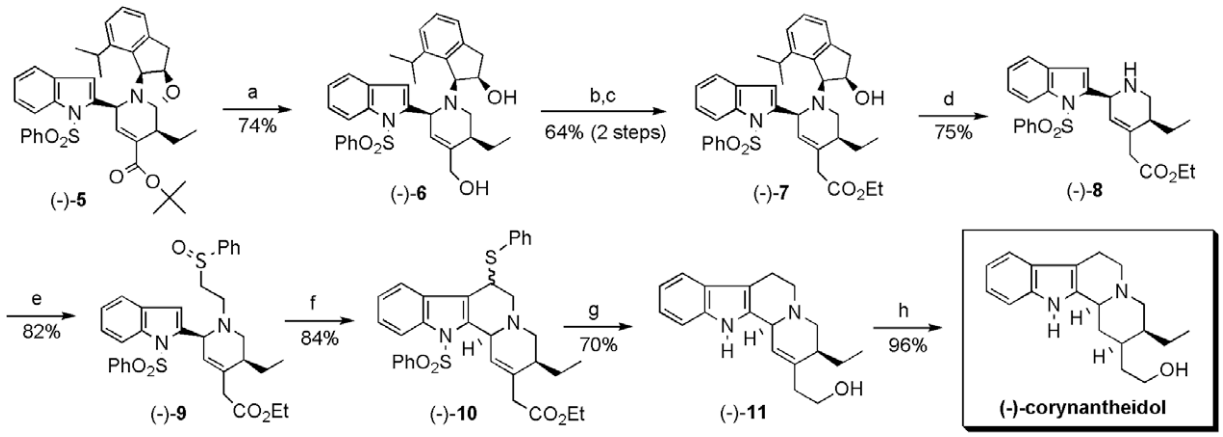
indolizidine alkaloid, (−)-dendroprime, were achieved.[11] Moreover, we also realized a new version of the one-pot procedure for the synthesis of 2,4,5-trisubstituted 2,5-chiral 1,2,5,6-tetrahydropyridines (R^1 = Et) (Fig. 2) by the further developed one-pot asymmetric azaelectrocyclization using tetrasubstituted vinyl iodide having a *t*-butyl ester group (R^2 = *t*-Bu) (Fig. 2).[12]

In this Letter, the highly stereocontrolled asymmetric total synthesis of (−)-corynantheidol (**1**) and formal synthesis of (−)-corynantheidine (**2**) are described as a demonstration of a new version of the one-pot asymmetric azaelectrocyclization protocol using tetrasubstituted vinyl iodide **3** through the intermediates of (−)-**5** and (−)-**8** (Schemes 1 and 2).

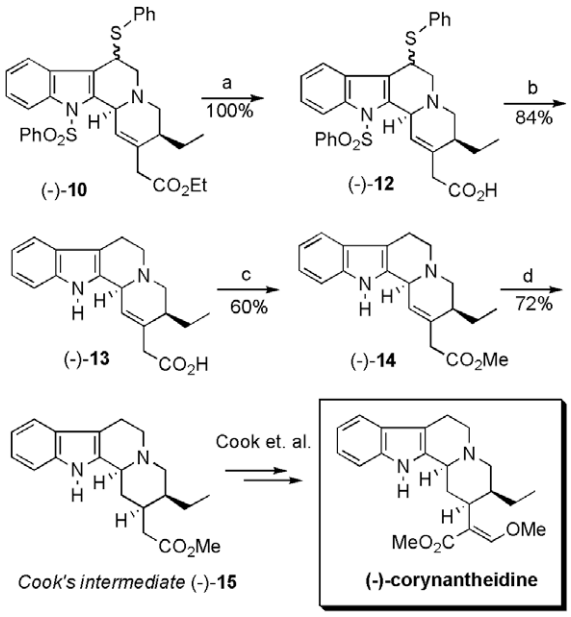
According to the established reaction conditions described in the previous Letter,[12] the tetrasubstituted vinyl iodide **3**,[13] aminoindanol derivative (−)-**a,** and MS5A were mixed in 1,4-dioxane, and the mixture was heated at 80 °C for 30 min. After checking the consumption of **3** by TLC, the indolyl vinyl stannane **4**, which was prepared from 1-benzenesulfonyl-2-formylindole[14] by a sequence of the Cory-Fucks alkyne synthesis, base treatment (LiHMDS and then BuLi in THF, −78 °C), and hydrostanylation with tributyltin hydride (AIBN in benzene, reflux) in 53% yield for three steps, was added, and the resulting mixture was refluxed in the presence of a catalytic amount of $Pd_2(dba)_3$, trifurylphosphine, and LiCl (Scheme 1). The desired tetracyclic aminoacetal (−)-**5** was obtained in 77% yield as a single diastereomer. Thus four new bonds were created by controlling the stereochemistry at three asymmetric centers in a single operation.

The synthesis of (−)-corynantheidol (**1**) from compound (−)-**5** is shown in Scheme 2. In order to optimize the efficiency of the synthesis, we selected the synthetic route in which the one-carbon elongation at the four position of the tetrahydropyridine nucleus of compound (−)-**5** was first accomplished in preference to the construction of the C ring. Thus, reduction of both the ester group and the aminoacetal moiety with diisobutylaluminum hydride (DIBAL-H) at −78 °C provided the corresponding diol (−)-**6** in 74% yield. The primary hydroxy group of (−)-**6** was selectively converted into the corresponding carbonate by the reaction with ethyl chloroformate. The successful one-carbon elongation was achieved by the CO insertion using a catalytic amount of $Pd(OAc)_2$ and Ph_3P in EtOH under a carbon monoxide atmosphere to produce the corresponding ethyl ester (−)-**7** in 64% yield in two steps. Elimination of the indanol moiety of (−)-**7**, which was a chiral nitrogen source and a protecting group at the tetrahydropyridine nitrogen, was achieved by the established procedure.[10] Thus, the ethyl ester (−)-**7** was oxidized with lead tetraacetate in the presence of *n*-propylamine at −50 °C to afford the tetrahydropyridine derivative (−)-**8** in 75% yield. With the key intermediate (−)-**8** in hand, the remaining objectives were the construction of the tetracyclic ring system and stereoselective reduction of the double bond in the piperidine ring. After several trials, we achieved the construction of the tetracyclic ring system using the Bosch's Pummerer cyclization sequence.[15] Thus, the sulfoxide (−)-**9** was prepared in 82% yield as a 1:1 mixture of diastereomers by the alkylation of amine (−)-**8** with phenyl vinyl sulfoxide in methanol under reflux. Treatment of the sulfoxide (−)-**9** with trimethylsilyl triflate in the presence of diisopropylethylamine at room temperature for 30 min provided the expected tetracyclic sulfide (−)-**10** in 84% yield.

Next was the removal of the resulting thiophenyl group and the phenylsulfonyl group at the nitrogen of the indole. After several trials, we found that the Birch reduction was extremely effective for this removal. The treatment of (−)-**10** in liquid NH_3 and THF with lithium successfully produced the alcohol (−)-**11** in 70% yield resulting from the reduction of the ethyl ester group in addition to removal of both the thiophenyl and phenylsulfonyl groups. Thus, three functional groups were nicely reduced by one operation. In order to achieve the stereoselective reduction of the double bond in the tetrahydropyridine ring, we attempted the catalytic hydrogenation using several catalysts, such as Pd-C, Ra-Ni, and $Rh(PPh_3)_3Cl$. Among them, we found that platinum dioxide was most suitable for this purpose. The synthesis of (−)-corynantheidol (**1**) was achieved by the hydrogenation of (−)-**11** in the presence of a catalytic amount of platinum dioxide in MeOH in 96% yield as a single diastereomer. The optical rotation and the spectral (^1H and ^{13}C NMR) data of the synthesized (−)-corynantheidol (**1**) were in good correspondence with those published in the literatures.[8a,b,16]



Scheme 2. Total synthesis of (−)-corynantheidol. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 74%; (b) $ClCO_2Et$, pyridine, THF, −20 °C, 15 min, then rt, 30 min, 88%; (c) $Pd(OAc)_2$, Ph_3P, CO, EtOH, 50 °C, 18 h, 88%; (d) $Pb(OAc)_4$, *n*-$PrNH_2$, $CHCl_3$, −50 °C, 30 min, 75%; (e) $PhS(O)CH{=}CH_2$, MeOH, reflux, 27 h, 82%; (f) TMSOTf, DIPEA, CH_2Cl_2, rt, 30 min, 84%; (g) Li, NH_3, THF, −78 °C then −33 °C, 70%; (h) H_2, PtO_2, MeOH, rt, 30 min, 96%.



Scheme 3. Reagents and conditions: (a) $Ba(OH)_2$, H_2O, THF/MeOH (2:1), 50 °C, 30 min, 100%; (b) Li, NH_3, THF, −78 °C then −33 °C, 84%; (c) thionyl chloride, MeOH, reflux, 1 h, 60%, (d) H_2, PtO_2, MeOH, rt, 30 min, 72%.

The formal synthesis of (−)-corynantheidine (**2**) from the intermediate (−)-**10** was also achieved (Scheme 3). After (−)-**10** was hydrolyzed with $Ba(OH)_2$ in THF and MeOH, the Birch reduction of the quantitatively produced (−)-**12** provided the desired acid (−)-**13** in 84% yield resulting from the removal of the thiophenyl and benzenesulfonyl groups without reduction of the carboxyl group. Esterification of the obtained (−)-**13** with thionyl chloride in MeOH gave the corresponding ester (−)-**14** in 60% yield. The catalytic hydrogenation of the resulting (−)-**14** with platinum dioxide in MeOH successfully provided the Cook's intermediate (−)-**15** in 72% yield as a single diastereomer. The spectral characteristics of the synthesized (−)-**15** were in good agreement with those reported by Cook and co-workers.[8b] According to the precedence established by Cook and co-workers for the synthesis of corynantheidine **2**, (−)-**15** could be carried through to (−)-corynantheidine (**2**) in two steps.

In summary, we achieved the asymmetric total synthesis of (−)-corynantheidol (**1**) and the formal synthesis of (−)-corynantheidine (**2**) using the highly efficient and stereoselective one-pot azaelectrocyclization protocol as the key step. Thus, the one-pot asymmetric 6π-azaelectrocyclization reaction developed by us can be regarded as a powerful strategy for the synthesis of alkaloids possessing a 2,4,5-trisubstituted piperidine core. Further applications toward related natural alkaloids are currently being pursued in our laboratory.

Acknowledgments

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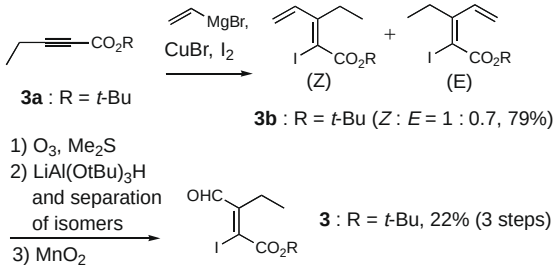
13. Tetrasubstituted vinyl iodide **3** was prepared as follows:



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