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# Total Synthesis of (-)-Corynantheidine by Nickel-Catalyzed Carboxylative **Cyclization of Enynes**

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The total synthesis of (-)-corynantheidine has been achieved through Ni<sup>0</sup>-mediated carboxylative cyclization as the key reaction step with incorporation of CO<sub>2</sub>, and this cyclization

Introduction

Carbon dioxide  $(CO_2)$  has attracted much attention as an abundant carbon resource. Thus, the development of reactions that utilize  $CO_2$  as a C1 unit is one of the important challenges in synthetic organic chemistry.<sup>[1]</sup> However, the utilization of CO<sub>2</sub> as a C1 unit is limited due to its chemical stability. It is known that transition metals can activate the C=O bond of CO<sub>2</sub>, and various reactions that incorporate CO<sub>2</sub> into organic molecules by employing transition-metal complexes have been reported.<sup>[2,3]</sup> In this context, we have recently reported the nickel-mediated carboxylative cyclization of enynes, and the reaction mechanism is shown in Scheme 1.<sup>[4,5]</sup>



Scheme 1. Ni<sup>0</sup>-mediated carboxylative cyclization of enynes.

Envne 1, having an electron-withdrawing group on the terminus of the alkene, reacts with a zero-valent nickel complex to form oxanickelacyclopentene I. Nickelacycle I un-

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was also successfully expanded to the catalytic reaction by using Et<sub>2</sub>Zn in the presence of an excess amount of DBU.

dergoes insertion of CO2 at the Csp3-nickel bond under an atmosphere of  $CO_2$  to give nickelacycle II. After hydrolysis of II, the corresponding carboxylic acid 2 was produced along with CO<sub>2</sub> incorporation.

### **Results and Discussion**

Since plants produce various organic compounds using CO<sub>2</sub> as a carbon source through photosynthesis, the synthesis of natural products, especially those derived from plants such as alkaloids, by a CO<sub>2</sub> incorporation reaction is a stimulating objective. Thus, we decided to utilize the abovementioned nickel-mediated carboxylative cyclization of enynes for the synthesis of (-)-corynantheidine.<sup>[6,7]</sup> The retrosynthetic plan is shown in Scheme 2. (-)-Corynantheidine would be derived from 3, which would be synthesized from



Scheme 2. Retrosynthetic analysis of (-)-corynantheidine.

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enyne **4** by nickel-mediated carboxylative cyclization accompanied by  $CO_2$  incorporation. Chiral enyne **4** would be formed from tetrahydro-β-carboline **5**, which would be accessed from L-tryptophan methyl ester and aldehyde **6** by a *cis*-selective Pictet–Spengler reaction.<sup>[8]</sup>

Initially, *cis*-selective Pictet–Spengler reaction of L-tryptophan methyl ester (7) and aldehyde **8** was investigated (Scheme 3). As a result, two tetrahydro- $\beta$ -carboline products were produced, and they could be easily separated by silica gel chromatography to give the major product in 74% yield and the minor product in 18% yield. As expected, the stereochemistry of the major product was unambiguously assigned to have the *cis* configuration by comparison of its <sup>13</sup>C NMR spectrum with that of the minor product, in which the <sup>13</sup>C carbon signals for C1 and C3 of the major product [*cis*-**9**:  $\delta$  = 53.2 (C1), 56.8 (C3) ppm] were downfield relative to those of the minor product [*trans*-**9**:  $\delta$  = 48.9 (C1), 52.1 (C3) ppm].<sup>[9]</sup>



Scheme 3. cis-Selective Pictet-Spengler reaction.

Desired enyne 16 was readily synthesized from *cis*-9 in an optically active form in good yield through a sequence of usual transformations: *N*-propargylation of *cis*-9 with 10, protection of 11 with Boc, followed by hydrolysis of the ester moiety, decarboxylation by using the Barton reaction, deprotection of the TBDSP group, and oxidation with Dess-Martin periodinane followed by Wittig reaction (Scheme 4).

With substrate 16 in hand, we turned our attention to the construction of the fourth ring in (-)-corynantheidine by a nickel-mediated carboxylative cyclization. According to the optimal conditions previously reported by us,<sup>[4]</sup> treatment of enyne 16 with a stoichiometric amount of Ni- $(cod)_2$  and DBU (2 equiv.) as a ligand in the presence of 4 Å molecular sieves (MS) in dioxane at 40 °C under an atmosphere of gaseous  $CO_2$  (1 atm) gave crude materials. The crude materials were treated with diazomethane, resulting in desired product 17 in 73% yield as a single isomer along with 18 in 2% yield (Scheme 5). Apparently,  $CO_2$  incorporation product 17 was produced via nickelacycles  $III^{[10]}$  and IV; the former was formed from 16 and the Ni<sup>0</sup> complex through oxidative cycloaddition, and the latter was formed by insertion of  $CO_2$  between the  $C_{sp^3}$ -nickel bond in III. The stereochemistry of the ring junction in 17 was unequivocally determined to be in the syn configuration by an NOE experiment between H<sup>a</sup> and H<sup>b</sup> (see V in Scheme 5), which means that nickelacycle IV was stereo-



Scheme 4. Synthesis of enyne 16 from cis-9.

selectively formed from 16 and the  $Ni^0$  complex. On the other hand, product 18 would be directly formed from III without  $CO_2$  incorporation.



Scheme 5. Ni<sup>0</sup>-mediated carboxylative cyclization of 16.

It is noteworthy that carboxylative cyclization of **16** also proceeded by using a catalytic amount of Ni(cod)<sub>2</sub> (20 mol-%) in the presence of an excess amount of DBU (6.4 equiv.) and Et<sub>2</sub>Zn (3.0 equiv.) to give desired product **17** in 58% yield (Scheme 6).<sup>[11]</sup>

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Scheme 6. Ni<sup>0</sup>-catalyzed carboxylative cyclization of 16.

The possible mechanism of the catalytic carboxylative cyclization of **16** is shown in Scheme 7. As mentioned above, nickelacycles **III** and **IV** would be successively formed from substrate **16** and Ni<sup>0</sup> complex. Then, transmetalation between nickelacycle **IV** and Et<sub>2</sub>Zn would occur to give complex **19**, and  $\beta$ -elimination from the ethyl group on nickel metal in **19** would produce nickel–hydride complex **20** along with the evolution of ethylene. Reductive elimination from **20** gives zinc–carboxylate **21** along with regeneration of a zero-valent nickel complex. Then, methyl ester **17** is obtained through hydrolysis of **21** by acidic workup followed by methylation with diazomethane. It is known that the use of an excess amount of DBU is important in the catalytic reaction because DBU can coordinate to both the Ni<sup>0</sup> complex and the zinc reagent as a ligand.



Scheme 7. Mechanism of Ni<sup>0</sup>-catalyzed carboxylative cyclization of **16**.

Key synthetic intermediate 17 was converted into (–)-corynantheidine by the following four steps (see Scheme 8). Deprotection of the Boc group in 17 by treatment with formic acid produced 22 in 93% yield, which was reduced with DIBALH (1.5 equiv.) to give Z-geissoschizinene (23) in 58% yield along with recovery of unreacted 22 in 35% yield. Conversion of  $(\pm)$ -Z-geissoschizinene into  $(\pm)$ -corynantheidine has already been reported by Lounasmaa.<sup>[6g]</sup> Thus, the final two steps from 23 toward (–)-corynantheidine have been successfully conducted according to the literature, giving (–)-corynantheidine in 47% yield (two steps). The spectroscopic data, including the sign and value of  $[a]_{D}$ , for our synthetic (–)-corynantheidine agreed with those reported in the literature.<sup>[7c]</sup>



Scheme 8. Synthesis of (-)-corynantheidine from 17.

#### Conclusions

In summary, the total synthesis of (–)-corynantheidine has been achieved through Ni<sup>0</sup>-mediated carboxylative cyclization as the key reaction step with incorporation of  $CO_2$ . We have also succeeded in expanding the Ni<sup>0</sup>-mediated reaction of enynes to the catalytic reaction by using Et<sub>2</sub>Zn as a transmetalation reagent in the presence of an excess amount of DBU. The present results indicate that  $CO_2$  is one of the useful carbon resources in synthetic organic chemistry, and further studies for development of new reactions accompanied by  $CO_2$  incorporation and their applications are now in progress.

**Supporting Information** (see footnote on the first page of this article): Experimental details, characterization data, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for key compounds.

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