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Total Synthesis of (−)-Herbindoles A, B, and C via Transition-Metal-Catalyzed Intramolecular [2 + 2 + 2] Cyclization between Ynamide and Diynes

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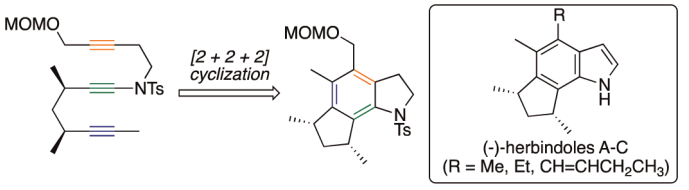
ABSTRACT



The total syntheses of (−)-herbindoles A, B, and C as naturally occurring forms were accomplished for the first time through transition-metal-catalyzed intramolecular [2 + 2 + 2] cyclization between ynamide and diynes. This strategy provided a highly efficient synthetic route to all three herbindoles from an identical indoline derivative as a common intermediate.

(−)-Herbindoles A, B, and C (Figure 1), belonging to polylalkylated cyclopent[*g*]indole alkaloids, were isolated in 1990 from a Western Australian sponge, *Axinella* sp., and were shown to exert cytotoxicity against KB cells as well as general antifeedant activity against fishes.[1,2] In 1992, Natsume reported the first total synthesis of (+)-herbindoles A, B, and C through an indole cyclization of pyrrole derivatives, by which the absolute configurations of the naturally occurring herbindoles A, B, and C were unambiguously determined to be antipodes of their synthetic ones.[3] Although syntheses of racemic herbindoles A and B were independently reported by Kerr's group[4a,b] and Buszek's group,[4c] there have been no reports on the total synthesis of natural (−)-herbindoles.

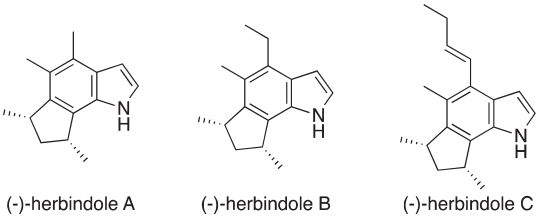


Figure 1. (−)-Herbindoles A, B, and C.

Transition-metal-catalyzed inter- and intramolecular [2 + 2 + 2] cycloaddition of three unsaturated bonds has been recognized as a useful and promising methodology for the synthesis of polycyclic compounds in recent organic synthesis.[5,6] In particular, the [2 + 2 + 2] cycloaddition of triynes is known to be an efficient synthetic protocol for the synthesis of various aromatic compounds. In this context, the [2 + 2 + 2] cycloaddition of three alkynes including an ynamide[7−9] (**1** and **2**) has been recently established as a new method for the construction of indole skeleta **3** (Scheme 1).[10]

With this as a background, we planned the total synthesis of (−)-herbindoles A, B, and C by intramolecular

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(2) For recent reviews on synthetic studies of herbindoles and their structurally related indole alkaloids, trikentrins, see: Silva, L. F., Jr.; Craveiro, M. V.; Tébéka, I. R. M. *Tetrahedron* **2010**, *66*, 3875.

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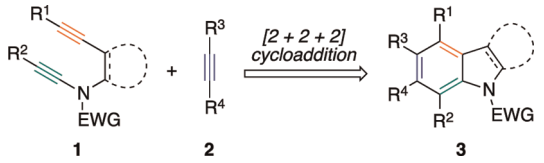
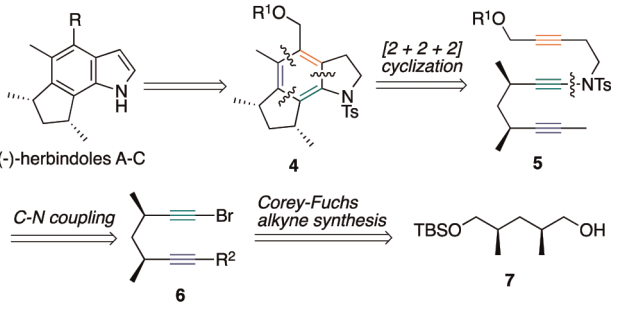
Scheme 1. Construction of an Indole Skeleton via [2 + 2 + 2] Cycloaddition of *Alkyne–Alkyne–Ynamide*



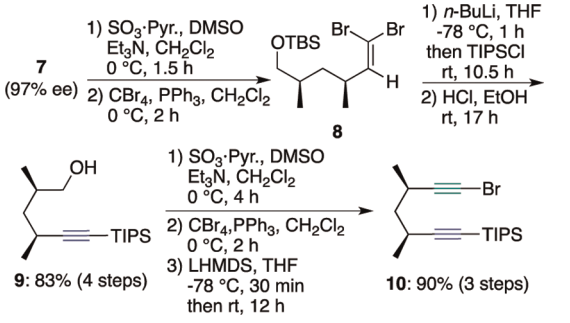
[2 + 2 + 2] cyclization of ynamide-diynes using a transition metal catalyst. Our retrosynthetic analysis of them is shown in Scheme 2. All three herbindoles could potentially be synthesized from the identical cyclopentane-fused indoline derivative **4** as a key intermediate, whose aromatic ring would be constructed by transition metal-catalyzed [2 + 2 + 2] cyclization of the dialkynylynamide **5**. Construction of the ynamide part of **5** could be performed by C–N coupling between bromoalkyne **6** and the corresponding nitrogen nucleophile. Furthermore, the bromoalkyne **6** could be easily synthesized from the known optically active alcohol **7**[11] via Corey–Fuchs alkyne synthesis.

Scheme 2. Retrosynthesis of (−)-Herbindoles A, B, and C



Preparation of the bromoalkyne unit is shown in Scheme 3. First, the known alcohol **7** (97% ee) was transformed into dibromoalkene **8**, from which alkyne formation followed by deprotection of the TBS group was conducted to give an alcohol **9**. Then dibromoalkene prepared from **9** via

Scheme 3. Preparation of Bromoalkyne Part



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(10) For examples of transition-metal-catalyzed [2 + 2 + 2] cycloaddition of *alkyne–alkyne–ynamide* leading to an indole skeleton, see: (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (b) Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965. (c) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. For related transition-metal-catalyzed [2 + 2 + 2] cycloaddition of *alkyne–nitrile–ynamide* leading to hetroaromatic comounds, see: (d) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464. (e) Garcia, P.; Moulin, S.; Miclo, Y.; Leboeuf, D.; Gandon, V.; Aubert, C.; Malacria, M. *Chem.—Eur. J.* **2009**, *15*, 2129. (f) Nissen, F.; Detert, H. *Eur. J. Org. Chem.* **2011**, 2845. (g) Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. *Chem. Commun.* **2011**, *47*, 6656. (h) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030.

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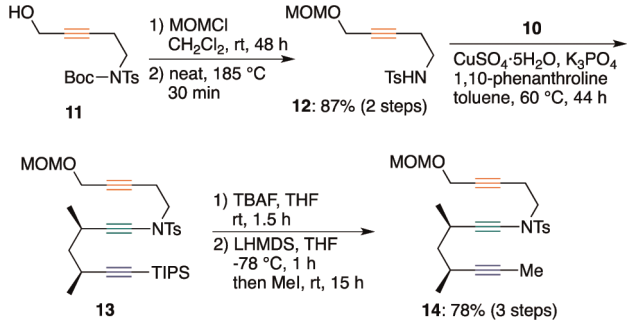
oxidation−dibromoalkenylation was treated with LHMDS[12] to afford the bromoalkyne unit **10**.

The hydroxy group of the known compound **11**[13] was protected by the MOM group, and deprotection of the Boc group by heating gave tosylamide **12** (Scheme 4). In the presence of a copper catalyst,[14] bromoalkyne **10** and amide **12** were coupled to give dialkynylynamide **13**, which was converted into the [2 + 2 + 2] cyclization precursor **14** in good yield.

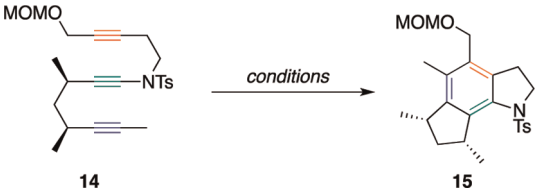
Next, we examined the [2 + 2 + 2] cyclization of **14** using various transition metal catalysts, which have been employed previously in a variety of inter- and intramolecular [2 + 2 + 2] cycloadditions[5] (Table 1). The cyclization of **14** in the presence of a Cp*RuCl(cod) catalyst proceeded at room temperature to give the expected indoline derivative **15** in 91% yield (run 1). Group 9 metal complexes, $CpCo(CO)_2$ and $RhCl(PPh_3)_3$, also showed good catalytic activity for the [2 + 2 + 2] cyclization of ynamide derivative **14**, and the cyclized product **15** was obtained in excellent yields (runs 2 and 3). The reaction of **14** by using an Ni(0)-PPh_3 catalyst also afforded **15** in good yield (run 4). On the other hand, a Pd(0)-PPh_3 catalyst did not promote the cyclization, and the starting **14** was recovered in almost quantitative yield (run 5). Thus, we decided to employ the Wilkinson's catalyst to synthesize herbindoles.

Scheme 4. Synthesis of Dialkynylynamide **14** as a [2 + 2 + 2] Cyclization Precursor



With the supposed common intermediate **15** in hand, we set out to conduct the transformation of **15** into three herbindoles. The cyclized product **15** was treated with BBr_3, giving benzylic bromide derivative **16** which, after radical reduction, gave **17** in high yield (Scheme 5). Finally, deprotection of the tosyl group followed by aromatization in the presence of a cobalt(II) catalyst[15] produced (−)-herbindole A, whose spectral data were identical to those reported for naturally occurring herbindole A. The value of $[\alpha]_D$ was also identical with the synthetic (+)-herbindole A except for the sign of $[\alpha]_D$.[3] It it noteworthy that the overall yield of (−)-herbindole A from the known compound **7** was 49% yield in 15 steps (average ca. 95.3% yield in each step).

Table 1. Construction of a Cyclopent[*g*]indole Skeleton by Transition-Metal-Catalyzed [2 + 2 + 2] Cyclization of **14**

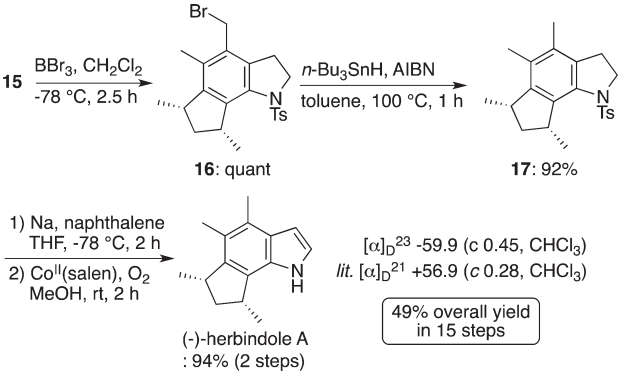


run	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)
1	Cp*RuCl(cod) (5)	toluene	rt	48	91
2	$CpCo(CO)_2$ (10)	*p*-xylene	140	24	95[a]
3	$RhCl(PPh_3)_3$ (4)	toluene	50	5	97
4	$Ni(cod)_2$ (5) PPh_3 (10)	THF	50	24	80
5	$Pd_2dba_3 \cdot CHCl_3$ (2.5) PPh_3 (10)	toluene	50	24	(98)[b]

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [b] The values in parentheses are the yields of starting dialkynylynamide **14**.

The synthesis of (−)-herbindole B was also achieved as shown in Scheme 6. Thus, after removal of the MOM group of **15**, oxidation of the corresponding alcohol **18** by Dess-Martin periodinane (DMP) followed by methylenation using Tebbe reagent and hydrogenation afforded indoline derivative **19**. Finally, (−)-herbindole B was synthesized through deprotection of **19** followed by aromatization in excellent yield (average ca. 94.2% yield in each step).

Scheme 5. Synthesis of (−)-Herbindole A from **15**



As shown in Scheme 7, the above alcohol **18** was easily converted into **20** in 91% yield through oxidation,

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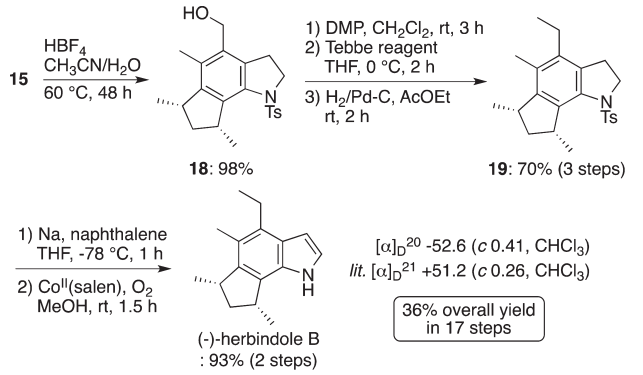
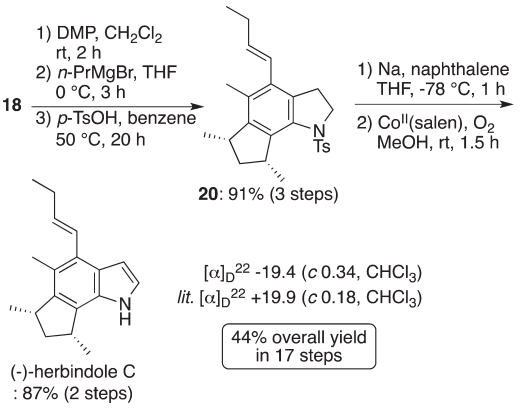
Scheme 6. Synthesis of (−)-Herbindole B from **15**



Scheme 7. Synthesis of (−)-Herbindole C from **18**



Grignard reaction and subsequent dehydration. The synthesis of (-)-herbindole C was also achieved by similar transformation from **20** as the above-described procedure (average ca. 95.3% yield in each step).

In summary we have achieved, for the first time, an efficient synthesis of (−)-herbindoles A, B, and C in naturally occurring forms. The key reaction of the total syntheses was transition metal-catalyzed [2 + 2 + 2] cycloaddition of an ynamide-diyne, with ruthenium, cobalt, and rhodium as well as nickel complexes catalyzing the cyclization to give the cyclopent[*g*]indole skeleton in high yield. This strategy provides a highly efficient synthetic route to all three herbindoles from an identical indoline derivative as a common intermediate.

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Supporting Information Available. Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.