EurJOC
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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900610

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900610

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One-Pot Synthesis of Cycloocta[*b*]indole through Formal [5+3] Cycloaddition Using Donor-Acceptor Cyclopropanes

Akito Okabe,[a] Shinji Harada,*[a],[b] Takuya Takeda,[a] and Atsushi Nishida*[a],[b]

Abstract: A new approach to cycloocta[*b*]indole through formal [5+3] cycloaddition was developed. This methodology was realized by using an indole derivative as a C5 unit and a cyclopropane derivative as a C3 unit. These two units have both donor and acceptor properties. Two carbon-carbon bonds were formed stepwise by the successive addition of a Lewis acidic catalyst and a Brønsted base. The reaction could be performed as a one-pot process. Optically active cycloocta[*b*]indole was also synthesized by using this methodology with a chiral cyclopropane as a C3 substrate.

Introduction

Cycloocta[*b*]indole is a tricyclic heterocycle, and its cyclooctane ring shares two carbons of indole at the C2 and C3 positions. The cycloocta[*b*]indole skeleton is seen in many natural and biologically active compounds.[1] For example, iprindole (Figure 1) has been used for the treatment of depression,[2] and talcarpine[3] is a macroline alkaloid,[4] which is a family of more than 150 compounds with potent hypotensive and antibiotic activities. While cycloocta[*b*]indoles have been shown to have attractive biological activities, there are few examples of the synthesis of the skeleton.[5] This is due to the general difficulty of constructing 8-membered carbocycles.[1d],[6],[7]

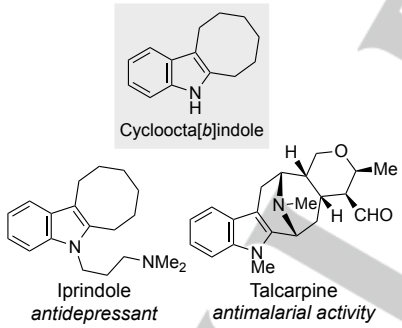
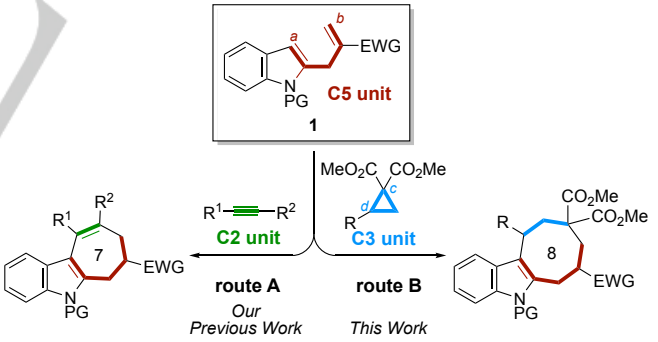


Figure 1. Biologically Active Alkaloids with a Cycloocta[*b*]indole Skeleton

Recently, we designed a novel donor-acceptor (D-A) indole derivative **1** as a C5 unit and developed intermolecular [5+2] cycloheptannulation using alkyne as a C2 unit (Scheme 1, route A).[8] This C5 indole **1** contains both nucleophilic carbon (C_a) and electrophilic carbon (C_b). We then envisioned that the combination of this D-A indole with an appropriate C3 unit would afford 8-membered ring compounds. Among C3 units, we chose D-A cyclopropane.[9] D-A cyclopropane contains both nucleophilic carbon (C_c) and electrophilic carbon (C_d), and has been widely used for intermolecular cycloaddition.[10] It is typically activated by Lewis acid to form 1,3-dipolar species, where the negative charge at C_c is stabilized by the acceptor substituent (e.g., electron-withdrawing group) while the positive charge at C_d is stabilized by the donor substituent (e.g., electron-donating group and/or conjugated system). Although there are several reports on the use of a combination of indole derivatives and D-A cyclopropane to construct indole-fused 5- and 6-membered ring systems,[11] to the best of our knowledge there have been no reports on the construction of an 8-membered ring through an intermolecular reaction. Herein, we report a one-pot synthesis of cycloocta[*b*]indole skeleton through formal [5+3] cycloaddition by a stepwise alkylation/Michael addition process between D-A indole and D-A cyclopropane (Scheme 1, route B).



Scheme 1. Construction of Indole-Fused Carbocycles Using a Common C5 Unit.

Results and Discussion

We screened Lewis acids using indole **1a** and cyclopropane **2a** as substrates (Table 1). When metal triflates were used as Lewis acids at 80 °C in 1,2-dichloroethane (DCE), only ring-opening and subsequent alkylation took place to afford alkylated product **3aa** in good yields (entries 1-4). No cycloadduct was observed for every entry, therefore we first examined the optimal catalyst for the alkylation. $Yb(OTf)_3$ promoted the alkylation in the highest yield, and other lanthanide triflates were examined. However, both lanthanum and europium triflates required a longer reaction

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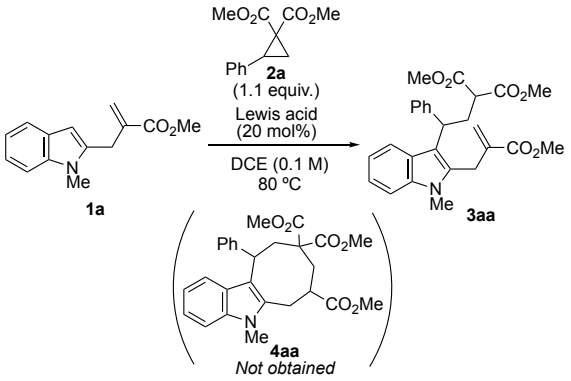
10.1002/ejoc.201900610

time to consume indole **1a** (entries 5 and 6). Although InI_3 was the optimal catalyst in our previous report,[8] it gave **3aa** in 78% yield (entry 7). $TiCl_4$ was not a suitable catalyst, and most of **1a** was recovered (entry 8). BF_3•OEt_2 required a longer reaction time to consume **1a**, and the yield of **3aa** was 74% (entry 9). The desired cyclization was not realized under these conditions, however, $Yb(OTf)_3$ was selected as a suitable catalyst for alkylation. When the amount of $Yb(OTf)_3$ was decreased to 5 mol% (entry 10), the yield of **3aa** was comparable to the result in entry 4.

Table 1. Screening of Lewis Acids for the Activation of D-A Cyclopropane

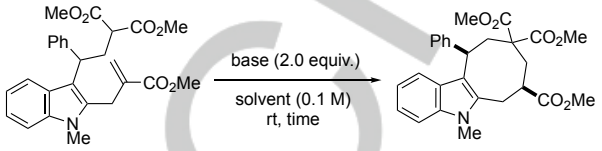


Entry	Lewis Acid	Time (h)	Yield (%)	Recov. of **1a** (%)
1	$Cu(OTf)_2$	0.5	78	0
2	$Zn(OTf)_2$	4	87	trace
3	$Sc(OTf)_3$	0.5	79	0
4	$Yb(OTf)_3$	0.5	92	0
5	$La(OTf)_3$	8	92	0
6	$Eu(OTf)_3$	1	92	0
7	InI_3	1	78	0
8	$TiCl_4$	4	5	<92
9	BF_3•OEt_2	9	74	0
10[a]	$Yb(OTf)_3$	4	94	0

[a] 5 mol% of Lewis acid was used.

We then tried to construct an 8-membered ring using **3aa** as a cyclization precursor (Table 2). The desired reaction proceeded under basic conditions. With the addition of two equivalents of NaH, cycloocta[*b*]indole **4aa** was obtained in 92% yield with 7.2:1 (*cis*-**4aa**:*trans*-**4aa**) diastereoselectivity after stirring for 24 hours at room temperature (entry 1).[12] KHMDS also afforded cyclized product **4aa** in comparable yield, however the selectivity was decreased to only 1:1.1 (entry 2). In entries 3-8, milder inorganic bases were examined, but the yields of **4aa** were less than the yield in entry 1. Notably, the diastereoselectivity changed drastically with the choice of base. This might be due to a change in the conformation of the intermediate, but further investigation is still necessary. Amine bases were not appropriate for this reaction (entries 9 and 10). Therefore, we chose NaH, which gave the best yield and diastereoselectivity, for cyclization.

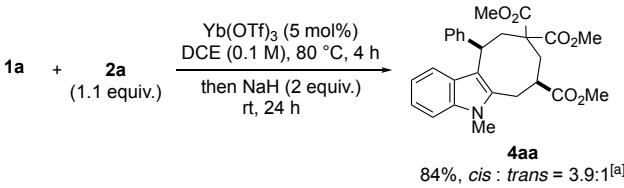
Table 2. Cyclization under Basic Conditions



Entry	Base	Solvent	Time (h)	Yield (%)	*cis* : *trans*[a]
1	NaH	DCE	24	92	7.1 : 1.0
2	KHMDS	DCE	24	86	1.0 : 1.1
3	NaOH	THF	24	67	3.5 : 1.0
4	CsOH	THF	24	78	1.5 : 1.0
5	KOH	THF	6	69	1.4 : 1.0
6[b]	KOH	THF	6	80	1.0 : 1.0
7	K_2CO_3	THF	24	0	–
8[b]	K_2CO_3	THF	24	79	2.9 : 1.0
9	NEt_3	DCE	24	0	–
10[c]	DBU	DCE	18	0	–

[a] Determined by ^{1}H NMR of the Crude Material. These isomers can be separated by multiple elution with preparative TLC. [b] 18-Crown-6 (2.0 equiv.) was added. [c] Carried out at 80 ºC.

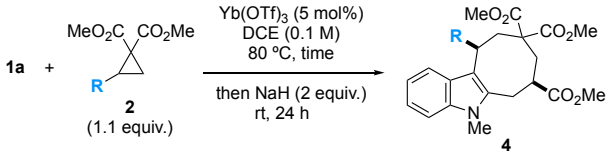
We realized the stepwise synthesis of cycloocta[*b*]indole from C5 indole **1** and C3 cyclopropane **2** by using a catalytic amount of ytterbium triflate and then a stoichiometric amount of Brønsted base. We then tried a one-pot process. After we confirmed that **1a** was consumed by TLC and cooled the reaction mixture, we added NaH to the mixture. The one-pot synthesis of cycloocta[*b*]indole was successfully achieved to give **4aa** in 84% yield (Scheme 2).

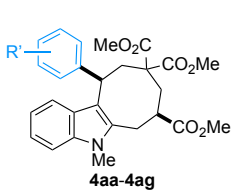


Scheme 2. One-Pot Synthesis of Cycloocta[*b*]indole. [a] Determined by ^{1}H NMR of the Crude Material.

The scope of the substrates was examined following the one-pot process in Scheme 2. D-A cyclopropanes **2** with various types of donor substituents are summarized in Table 3. When electron-donating and -withdrawing groups were installed on the benzene ring as a donor substituent, cyclized products **4** were obtained in high yields (**4ab**-**4ad**). Cyclopropanes with a methyl group on the benzene ring afforded **4ae**-**4ag** in good to high yields, though the reaction time of alkylation (1st step) varied according to the position of the methyl group. A heteroaromatic ring and styryl group were applicable, and desired cyclized products **4ah** and **4ai** were obtained in moderate yields. When vinylcyclopropane derivative **2j** was used, thermal activation was necessary for the completion of cyclization. The cyclized product **4aj** was obtained in 52% yield.

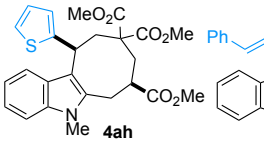
Table 3. Scope of Substituents on Cyclopropane[a]



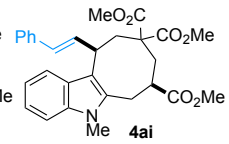


4aa-**4ag**

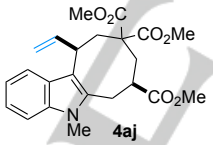
R'		Time	Yield (%)	*cis*:*trans*
H	(**4aa**)	4 h	84	3.9:1.0
4-MeO	(**4ab**)	10 min	84	3.3:1.0
4-Cl	(**4ac**)	5 h	85	8.3:1.0
4-CF_3	(**4ad**)	15 h	87	1.6:1.0
4-Me	(**4ae**)	45 min	61	2.4:1.0
3-Me	(**4af**)	1.5 h	91	3.6:1.0
2-Me	(**4ag**)	6.5 h	88	1.7:1.0



4ah
1 h, 51%
cis:*trans* = 2.0:1.0



4ai
30 min, 59%
cis:*trans* = 5.2:1.0

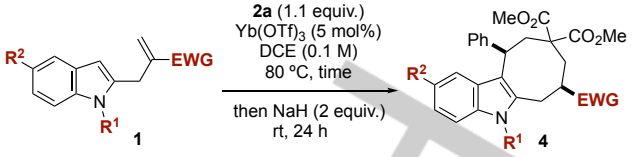


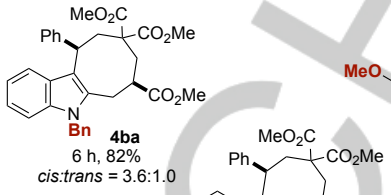
4aj
23 h, 52%[b]
cis:*trans* = 1.4:1.0

[a] Diastereomeric ratio was determined by ^{1}H NMR of the crude material.
[b] The second cyclization step was carried out at 80 °C.

Next, we surveyed the scope of C5 indole derivatives **1** (Table 4). A benzyl group instead of methyl on indole nitrogen gave **4ba** in comparable yield. When non-protected substrate (R^1=H) was used, the alkylation step proceeded in 62% yield (4 h), although the second cyclization step gave a complex mixture and we could not identify the corresponding cyclized product. A methoxy group at the C5 position on the indole ring accelerated the alkylation step, but **4ca** was obtained in moderate yield. An indole substrate with ketone as an electron-withdrawing group was also applicable, and cyclized product **4da** was obtained in 77% yield.[13]

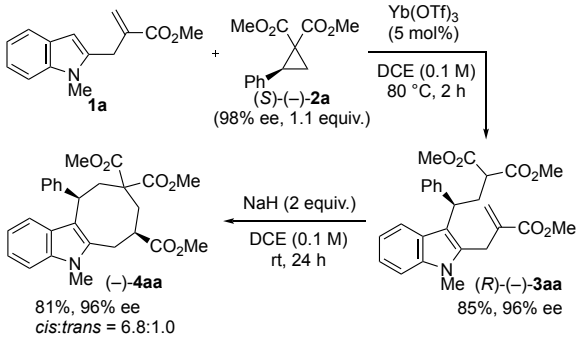
Table 4. Scope of C5-indole Substrates[a]





[a] Diastereomeric ratio was determined by ^{1}H NMR of the crude material.

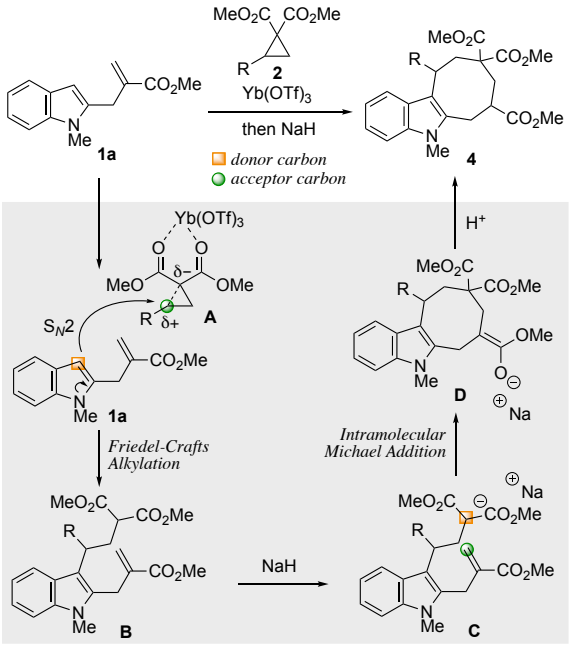
To elucidate the reaction mechanism, optically active cyclopropane (*S*)-(–)-**2a**[11e],[14] was applied to the stepwise synthesis of cycloocta[*b*]indole (Scheme 3). First, the chiral alkylated product (*R*)-(–)-**3aa** was obtained in 85% yield without a significant loss of enantiopurity. After cyclization under basic conditions, the enantiopurity of (–)-**4aa** was comparable to that of (–)-**3aa**. The enantiomeric excess of (–)-**4aa** could be enriched by a single recrystallization operation, and the relative and absolute configuration of the enantiomerically-pure (–)-**4aa** was unambiguously confirmed by X-ray crystallographic analysis.[15] From the structural information of the X-ray analysis, the stereochemistry of the chiral carbon of (*S*)-(–)-**2a** was revealed to be inversed. This result strongly supported that the alkylation step proceeded in an S_N2 fashion. It has been reported that the nucleophilic ring-opening of D-A cyclopropane took place *via* an S_N2-like reaction pattern,[9] thus our result agreed with those in previous reports.



Scheme 3. Stepwise Synthesis of Optically Active Cycloocta[*b*]indole.

The proposed mechanism of this process is shown in Scheme 4. Ytterbium salt was coordinated by a dicarbonyl moiety of the cyclopropane substrate to form an activated species **A**. Subsequent Friedel-Crafts alkylation between **A** and D-A indole

substrate occurred in an S_N2 manner to give alkylated indole **B** as an intermediate. Next, sodium hydride gave an anionic species **C**, intramolecular Michael addition took place to construct the 8-membered ring (**D**), and the protonation of **D** afforded product **4**.



Scheme 4. Plausible Reaction Mechanism.

Conclusions

We developed a novel synthetic approach toward a cycloocta[*b*]indole skeleton. The combination of a pair of D-A substrates enabled the construction of an 8-membered ring through formal [5+3] cycloaddition in a one-pot process. Various substituents could be installed on the substrate. Optically active cycloocta[*b*]indole was also synthesized. With C5 D-A indole **1** as a common substrate, a synthetic approach to indole-fused both 7- and 8-membered rings can be realized. Work on the development of asymmetric reaction and the construction of 8-membered *hetero*cycles is ongoing.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI [Grant Numbers 16K08154 (SH), 19K06991 (SH), 17J03524 (TT), and 17H03969 (AN)], and the Tokyo Biochemical Research Foundation [Grant Number 16-B1-5 (SH)]. We acknowledge the Institute for Global Prominent Research, Chiba University, for providing financial support.

Keywords: Medium-ring compounds • Synthetic methods • Cyclization • Catalysis • Indole

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10.1002/ejoc.201900610

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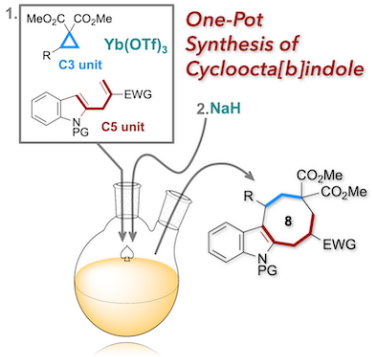
A new approach to cycloocta[*b*]indole through formal [5+3] cycloaddition was developed. This methodology was realized by using an indole derivative as a C5 unit and a cyclopropane derivative as a C3 unit. Two carbon-carbon bonds were formed stepwise by the addition of a Lewis acidic catalyst and a Brønsted base. The reaction could be performed as a one-pot process.



Eight-membered Ring

Akito Okabe, Shinji Harada, Takuya Takeda, and Atsushi Nishida**

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One-Pot Synthesis of Cycloocta[*b*]indole through Formal [5+3] Cycloaddition Using Donor-Acceptor Cyclopropanes