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Enantioselective preparation of C-ring fragment of cotylenin A via catalytic asymmetric intramolecular cyclopropanation of α-diazo β-keto ester

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ABSTRACT

A synthetic pathway to the C-ring fragment of cotylenin A which emerged from our retrosynthetic analysis of cotylenin A is described. The catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of the α-diazo-β-keto ester bearing 2,4,6-trimethylphenyl group as the ester part has been found to afford the crystalline product with high *ee*, which allowed to establish the approach to the C-ring fragment which required ten-pot operations. The developed approach would be beneficial to a large scale synthesis of the C-ring fragment for the total synthesis of cotylenin A

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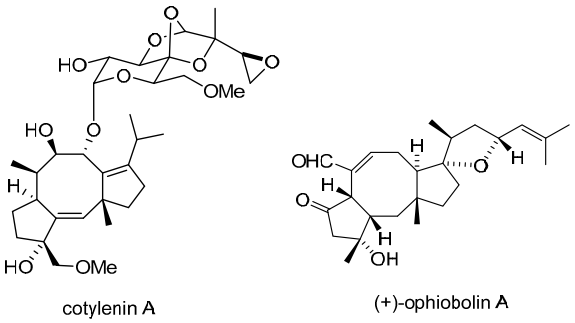


Figure 1. Structures of cotylenin A and (+)-ophiobolin A.

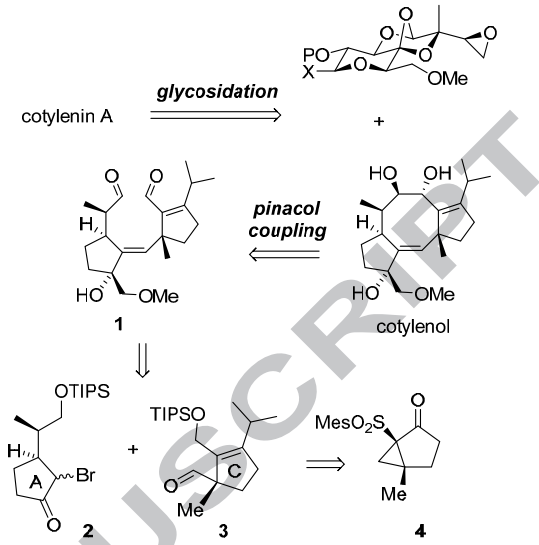
The dicyclopenta[*a*,*d*]cyclooctane ring system is a common carbon scaffold embedded in some classes of natural products such as ophiobolins[1] and fusicoccins[2]. In our previous paper, we reported the first total synthesis of (+)-ophiobolin A (Figure 1) via a convergent approach, in which two cyclopentane building blocks were successfully assembled to form the cyclooctane ring[3]. Although the structures of ophiobolins and fusicoccins involve the dicyclopenta[*a*,*d*]cyclooctane ring system, the structural differences arising from their embedded diverse functionalities pose synthetic challenges. Moreover, some members of the ophiobolin and the fusicoccin families show intriguing and significant bioactivity[4].

Cotylenin A is a glycosylated diterpene, which was isolated from the metabolites of Cladosporium sp. 501-7W, as a plant growth regulator[5]. Biological studies on cotylenin A have revealed that it induces apoptosis in a wide range of human cancer cell lines by combined treatment with interferon-α[6]. The promising bioactivity and the interesting mechanism of binding to the 14-3-3 complex of cotylenin A have attracted many researchers[7]. However, because the cotylenin A producer, Cladosporium sp. 501-7W, loses its ability to proliferate during preservation on a slant culture[8], it is necessary to develop a method to supply cotylenin A for further biological investigation of cotylenin A.

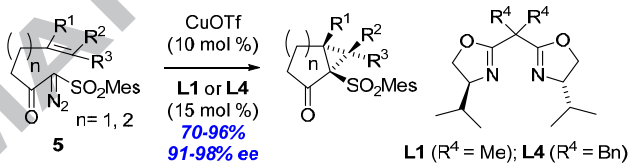
The challenging structures and intriguing biological properties of cotylenin A have attracted many research groups, and Kato et al. reported the total synthesis of cotylenol (Scheme 1)[9]. However, a total synthesis of cotylenin A has never been reported. Hence, we started the synthetic studies on cotylenin A and herein report the enantioselective preparation of the C-ring fragment of cotylenin A.

Our retrosynthetic analysis of cotylenin A is shown in Scheme 1. The glycosylation of cotylenol with the sugar moiety afforded cotylenin A because the glycosylation of the allylic alcohol proceeds preferentially owing to its enhanced reactivity. Cotylenol was synthesized by the intramolecular pinacol coupling of the dialdehyde **1**, though the resultant stereogenic centers needed to be transformed to the correct configuration. Dialdehyde **1** was obtained by the coupling of the two fragments: A-ring fragment **2** and C-ring fragment **3**, and subsequent transformations.

Fragments **2** and **3** were expected to be synthesized from the cyclopropanes prepared via the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-keto sulfone developed by us (Scheme 2)[10]. We studied the CAIMCP of various α-diazo-β-keto sulfones and found that CAIMCP proceeded with high yield and enantioselectivity. Thus, the CAIMCP of α-diazo-β-keto sulfone **5** (n = 1, $R^3 = R^4 = H$, $R^5 = CH_3$) using CuOTf (10 mol %) and ligand **L** (15 mol %) in toluene at 50 °C afforded cyclopropane **4** in 90% yield and 98% *ee*. Compound **4** was easily converted to an enantiomerically pure compound by a single recrystallization and its absolute structure was unambiguously elucidated by X-ray crystallographic analysis[10a].



Scheme 1. Retrosynthetic analysis of cotylenin A

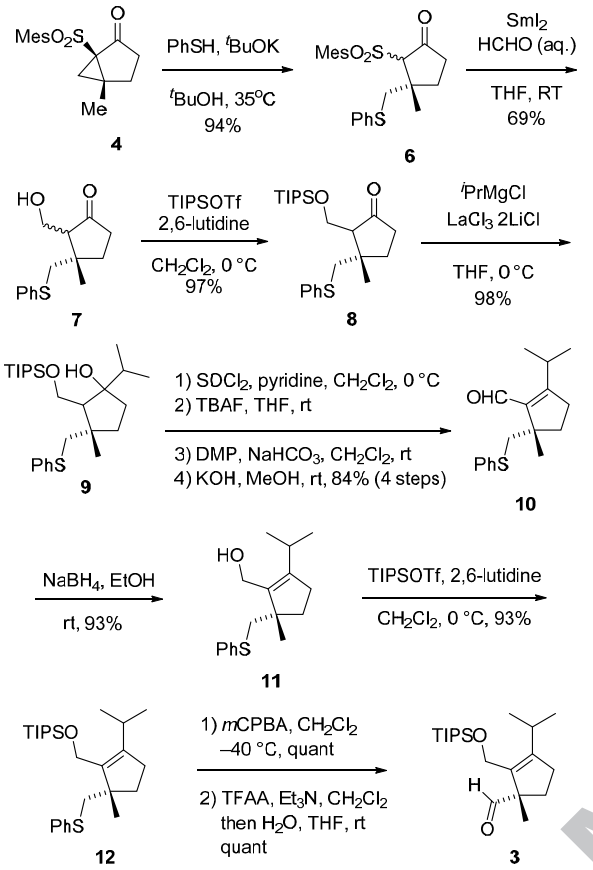


Scheme 2. CAIMCP of α-diazo-β-keto sulfones developed by us

Cyclopropane **4** possesses an all-carbon quaternary stereogenic center, which correlates with that in the C-ring fragment. Hence, the transformation of **4** into the C-ring fragment was investigated. The reaction of **4** with thiophenol and potassium *tert*-butoxide caused the ring opening of the cyclopropane, to afford compound **6** in 94% yield (Scheme 3)[11]. Because **6** lacks a one-carbon unit that is required for the transformation into the C-ring fragment, the conversion of **6** to **7** was examined. The reductive removal of the aryl sulfonyl group of **6** generated the corresponding enolate, which could be used for the introduction of the one-carbon unit. Therefore, the reaction of **6** with SmI_2 or lithium naphthalenide was examined and was found to afford the corresponding desulfonated product; however, interestingly, subsequent reactions with paraformaldehyde, MOMCl, BOMCl, and $PivOCH_2I$ afforded no desired product. Because the desulfonated product was obtained, the corresponding enolate was formed in situ, so that further optimization could be carried out. After several experiments, we found that the reaction of **6** with SmI_2 in a mixture of aqueous formaldehyde and THF at room temperature successfully afforded the desired product **7** in 69% yield.

To introduce the isopropyl group into **7**, the primary alcohol was protected as TIPS ether **8**, and then treated with isopropyl magnesium chloride. However, a large amount of **7** was recovered probably because **8** underwent enolization with the Grignard reagent. Fortunately, the use of an organolanthanum reagent, prepared in situ, solved the problem. Isopropyl magnesium chloride was treated with $LaCl_3 \cdot 2LiCl$ in THF and

this solution was added to a solution of **8** to successfully afford compound **9** in 98% yield[12].

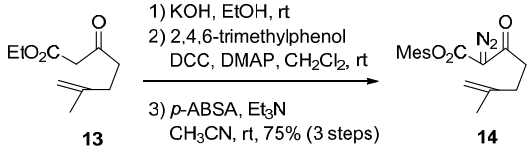


Scheme 3. Synthesis of the C-ring fragment **3**

To introduce the alkene in the C-ring fragment, **9** was treated with thionylchloride and pyridine; however, the tetrasubstituted alkene was not formed. Instead, the trisubstituted alkene was formed. Hence, to isomerize the double bond to the desired position, the TIPS group was removed by the addition of TBAF, subsequent oxidation of the primary alcohol with Dess-Martin periodinane, and treatment with KOH in methanol to successfully afford **10**, which possesses a double bond at the correct position. Compound **10** was reduced with $NaBH_4$, and the resultant alcohol **11** was protected as a TIPS ether to give **12**, which was oxidized to the sulfoxide, and the subsequent Pummerer rearrangement successfully afforded the desired C-ring fragment **3**.

The yield of each reaction in the above synthesis was generally excellent; however, the problem in a large-scale synthesis was that the preparation of the C-ring fragment from the starting material required a relatively large number of steps (16 steps).

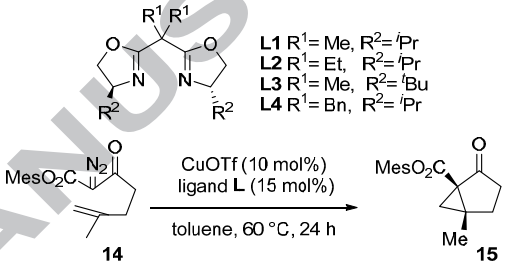
To lessen the number of steps, we examined the CAIMCP of α-diazo-β-keto ester, because the corresponding product possesses an ester group as the one-carbon unit, which had to be introduced in the above synthesis. We found that the CAIMCP of the α-diazo-β-keto ester hardly showed any enantioselectivity, even when the ester group was large[10a]. However, we have also observed that the CAIMCP of the α-diazo-β-keto ester sometimes showed high enantioselectivity. In other words, the CAIMCP of the α-diazo-β-keto ester depends on the structures of the substrate and the chiral ligand.



Scheme 4. Preparation of **14** from **13**

We prepared α-diazo-β-keto ester **14** bearing 2,4,6-trimethylphenyl group because excellent enantioselectivity was observed in the CAIMCP of α-diazo-β-keto sulfone bearing 2,4,6-trimethylphenyl group[13]. The CAIMCP of **14**, which was prepared from the known **13** by the hydrolysis of the ester, dehydrative coupling with 2,4,6-trimethylphenol, and diazo-transfer reaction using *p*-acetamidebenzenesulfonyl azide (*p*-ABSA) (Scheme 4), was carried out using CuOTf (10 mol %) and ligand **L1-4** (15 mol %) in toluene (Table 1), which were the conditions used in the CAIMCP of α-diazo-β-keto sulfones.

Table 1. The CAIMCP of **14**



entry	ligand	yield (%)[a]	*ee* (%)[b]
1	**L1**	91	62
2	**L2**	quant	72
3	**L3**	97	68
4	**L4**	95	80

[a]Isolated yield. [b]*Ee* was determined by HPLC.

The reaction using **L1** was very slow at room temperature but it was completed at 60 °C after 24 h to afford the product in 91% yield and 62% *ee* (entry 1). The reaction using **L2** afforded **15** quantitatively and increased the *ee* to 72% *ee* (entry 2), but the reaction using **L3**, which bears *tert*-butyl group on the oxazoline, gave inferior results (97%, 68% *ee*, entry 3). The reaction using **L4**, which bears two benzyl groups at the junction of the oxazolines, afforded the product in 95% yield and 80% *ee*.

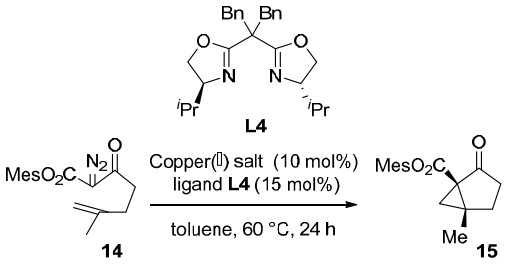
The CAIMCP of **14** was next examined using **L4** and other Cu(I) salts (Table 2). The use of $Cu(CH_3CN)_4PF_6$ slightly increased the ee (82% *ee*, entry 2) and the reaction using $Cu(CH_3CN)_4BF_4$ afforded the product with 86% *ee* (entry 3). Finally, use of 20 mol % of $Cu(CH_3CN)_4BF_4$ and 30 mol % of **L4** increased the yield to 98% with 93% *ee* (entry 4).

The enantioselectivity of the CAIMCP of **14** was higher when $Cu(CH_3CN)_4BF_4$ was used. This result could be attributed to the highly cationic nature of the Cu-carbene complex, which is induced by the coordinating ability of the counteranion.[14] That is, BF_4, with more anionic character, renders a Cu-carbene complex with more cationic character, and the increased cationic character of the Cu(I) in the complex could attract the nitrogen-coordinating ligand and the carbene center, thus shortening the coordination bonds and resulting in a more compact transition state leading to higher enantioselectivities.

The CAIMCPs of other substrates bearing a large ester **14a** and **14b** (Figure 2) were examined under the same reaction conditions as those in entry 4 of Table 2, but interestingly, only inferior results were obtained when compared with the reaction of **14** in terms of yield or enantioselectivity.

Because the product **15** was crystalline, it could be purified by recrystallization to afford enantiomerically pure **15**, and the absolute of which was successfully elucidated by X-ray crystallographic analysis[15]. The crystal structure shown in Fig. 3 indicated that **15** has suitable absolute configuration for the preparation of the C-ring fragment. Hence, transformation of **15** to the C-ring fragment **3** was examined.

Table 2. Effect of the counter anion of Cu(I) salt



entry	Cu(I) salt	yield (%)[a]	*ee* (%)[b]
1	CuOTf	95	80
2	$Cu(CH_3CN)_4PF_6$	54	82
3	$Cu(CH_3CN)_4BF_4$	68	86
4[c]	$Cu(CH_3CN)_4BF_4$	98	93

[a]Isolated yield. [b]*Ee* was determined by HPLC. [c]20 mol % of $Cu(CH_3CN)_4BF_4$ and 30 mol % of **L4** was used.

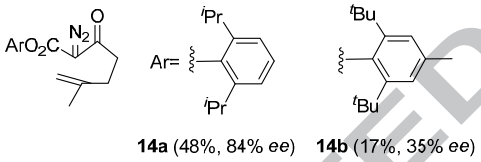


Figure 2. Structures of **14a** and **14b**.

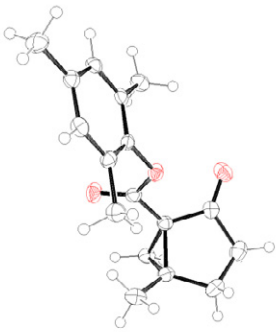
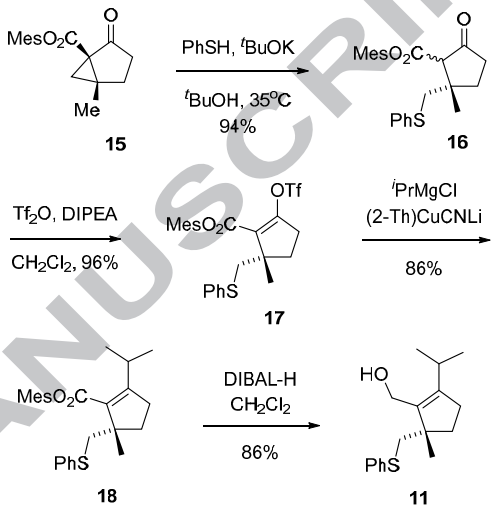


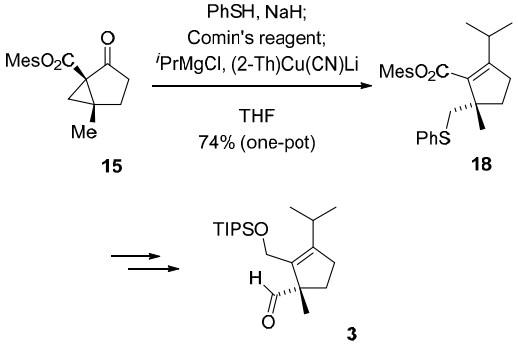
Figure 3. X-Ray crystal structure of **15**.

The reaction of **15** with thiophenol and sodium hydride induced the ring-opening of the cyclopropane to afford β-keto ester **16**. The reaction of **16** with isopropyl magnesium chloride only caused enolization owing to the acidic methyne proton. Hence, **16** was converted to the enol triflate **17** by the reaction with Tf_2O and DIPEA, and then, the coupling reaction with isopropyl magnesium bromide was examined[16]. After several optimizations, the reaction of **17** with isopropyl magnesium chloride and thienyl cuprate was found to afford **18** in 86 % yield. Subsequent DIBAL-H reaction of **18** afforded allylic alcohol **11** (86%) which was used for the preparation of the C-ring fragment as shown in Scheme 2.

The second synthesis required less steps to reach the C ring fragment when compared with the first synthesis but we found that the transformation from **15** to **18**, the ring-opening reaction, the enol triflate formation, and the coupling reaction, could be carried out in a one-pot manner in 74% yield. Thus, the C-ring fragment was successfully prepared from the commercially available compound by ten-pot operations.



Scheme 5. Preparation of **11** from **15**



Scheme 6. Short synthesis of the C-ring fragment

In summary, we have successfully developed the synthetic pathway to the C-ring fragment which emerged from our retrosynthetic analysis of (+)-cotylenin A. The CAIMCP of the α-diazo-β-keto ester bearing 2,4,6-trimethylphenyl group as the ester part has been found to afford the crystalline product with high *ee*, which allowed to establish the approach to the C-ring fragment which required ten-pot operations. The developed approach would be beneficial to a large scale synthesis of the C-ring fragment for the total synthesis of (+)-cotylenin A, and further synthetic studies on (+)-cotylenin A in now under way and will be reported in due course.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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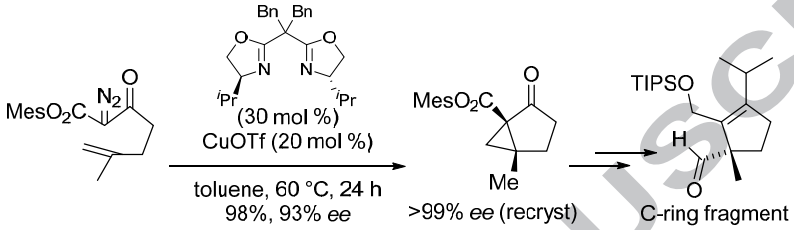

Highlights

·Highly enantioselective catalytic asymmetric cyclopropanation is described.
·Asymmetric synthesis of the C-ring fragment of cotylenin A has been achieved.
·The C-ring fragment of cotylenin A has been prepared by ten-pot operations.