Asymmetric Synthesis of (−)-Dictyopterene C' and its Derivatives via Catalytic Enantioselective Cyclopropanation

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An efficient and simple method for enantioselective synthesis of (−)-dictyopterene C' and its derivatives was developed on the basis of chiral oxazaborolidinium ion-catalyzed enantioselective cyclopropanation and divinylcyclopropane-cycloheptadiene rearrangement. Utilizing the Julia-Kocienski reaction and Sonogashira and Suzuki coupling reactions, various 1,4-cycloheptadiene compounds were synthesized with good results.

Keywords: *cis*-Cyclopropane, Enantioselectivity, Lewis acid catalyst, Rearrangement, 1,4-Cycloheptadiene

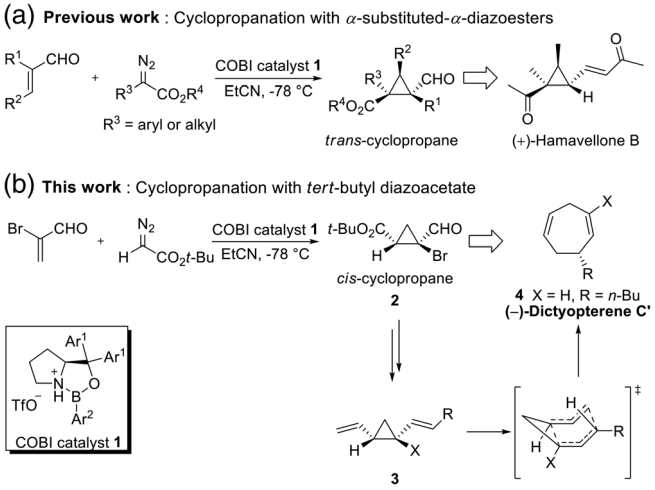
Cyclopropane, a strained small ring, is a structural unit found in various natural products and bioactive molecules.[1] Enantioselective formation of multisubstituted cyclopropanes has become a powerful strategy as such compounds serve as versatile building blocks in organic synthesis through ring-opening reactions. Among substituted cyclopropanes, optically active dicarbonyl-substituted cyclopropanes have been applied to various synthetic methodologies as important intermediates.[2] Therefore, considerable attention has been devoted to development of catalytic asymmetric methods for easy access to multisubstituted dicarbonyl cyclopropanes. Metal carbenoid-mediated reactions such as Simmons−Smith type, transition-metal-catalyzed reactions, and ylide-based cyclopropanation have been studied intensively. However, the two carbonyl groups on the cyclopropane are usually in the *trans*-configuration with each other. Synthetic methods forming *cis*-dicarbonyl-substituted cyclopropanes have rarely been reported.[3] Feng's group utilized a chiral diamine catalyst to promote cyclopropanation between α,β-unsaturated ketones and sulfonium ylides.[4]

In 2011, we reported enantioselective cyclopropanation between diazoacetates and α,β-unsaturated aldehydes in the presence of chiral oxazaborolidinium ion (COBI)[5] catalyst (Scheme 1(a)).[6a] Furthermore, we extended the substrate scope to alkyl substituents (R^3 = alkyl) and accomplished total synthesis of (+)-hamavellone B (Scheme 1(a)).[6b] Encouraged by these results, we planned to synthesize the 1,4-cycloheptadiene derivatives **4** from *cis*-divinyl cyclopropane compound **3** via divinylcyclopropane-cycloheptadiene rearrangement (DVCPR)[7] and anticipated that the optically active *cis*-dicarbonyl cyclopropane **2** would be a suitable precursor to various divinyl cyclopropane compounds **3**. Herein, we describe catalytic enantioselective cyclopropanation for the synthesis of *cis*-dicarbonyl cyclopropanes and their application to total synthesis of (−)-dictyopterene C' and 1,4-cycloheptadiene derivatives (Scheme 1(b)).

Enantioselective cyclopropanation was first examined with α-bromoacrolein and *tert*-butyl diazoacetate in the presence of 20 mol% of COBI catalyst **1a**. When the cyclopropanation was performed at −78 °C in propionitrile as solvent, *cis*-**2** was obtained as the major product instead of *trans*-**2** (Table 1, entry 1) in 66% yield with moderate diastereomeric ratio. The *cis* relationship between the aldehyde and ester groups was confirmed by nuclear Overhauser effect (NOE) analysis. This result differed from our previous cyclopropanation result with α-alkyl-α-diazoesters, that produce *trans*-cyclopropane as the major product (Scheme 1(a)). When the catalyst with a 3,5-dimethylphenyl Ar^1 substituent was used, the desired product was obtained with >99% *ee* and a small increase than phenyl Ar^1 substituted **1a** in diastereomeric ratio (Table 1, entry 2). Next, the effect of changing the boracycle substituent (Ar^2) of COBI catalyst **1** was investigated (Table 1, entries 3–6). Gratifyingly, using COBI **1f**, which has an 1-naphthyl substituent at the boron center,[8] greatly improved the yield to 93% and the diastereomeric ratio is 8:1 (Table 1, entry 6). The sterically bulkier diazo *tert*-butyl ester gave higher enantio- and diastereoselectivity than the corresponding diazo ethyl ester (Table 1, entries 6 and 7). The cyclopropanation reaction with α-chloroacrolein under optimized conditions provided the corresponding *cis*-**2** in 78% yield with 88% *ee* (Table 1, entry 8).[9]

To identify the absolute structure of *cis*-cyclopropane **2**, chemical transformation of **2** to lactone **6** was performed (Scheme 2). After radical debromination using Et_3B as an initiator, reduction of the aldehyde at low temperature led to alcohol product **5** in 54% overall yield. Trifluoroacetic

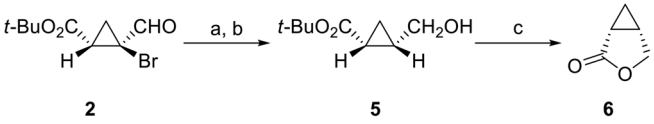
†These authors contributed equally to this work.



Scheme 1. Enantioselective cyclopropanation (a) α-substituted-α-diazoesters with α,β-unsaturated aldehydes, (b) *tert*-butyl diazoacetate with α-bromoacrolein and synthetic route to (−)-dictyopterene C'.

acid (TFA)-catalyzed intramolecular cyclization of **5** gave chiral cyclopropyl lactone product **6** in 81% yield. Comparison of the optical rotation data of **6** to the literature value[10] confirmed the absolute (1*S*,2*R*)-configuration of **2**.

The observed stereochemistry for the enantioselective cyclopropanation reaction with COBI catalyst **1** can be rationalized by the transition-state model shown in Figure 1. The coordination mode of α,β-unsaturated aldehydes to catalyst **1** is the same as has been previously suggested for



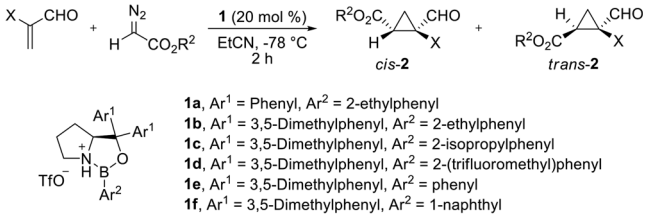
$[\alpha]^{20}_D$ = +59.1 (*c* = 1.00, $CHCl_3$)
lit. $[\alpha]^{20}_D$ = +60.2 (*c* = 1.01, $CHCl_3$)

Scheme 2. Synthetic method to optically active lactone **6**. Reagents and conditions: (a) Et_3B, *n*-Bu_3SnH, *n*-hexane, −78 °C, 4 h; (b) $NaBH_4$, MeOH, −78 °C, 1 h, 54% (2-step overall yield); (c) TFA, CH_2Cl_2, −78 °C, 4 h, 81%.

enantioselective Diels–Alder[11] and cyclopropanation[6] reactions. In the pretransition-state assembly **7** shown in Figure 1, the *re* face of acrolein is effectively blocked by the 3,5-dimethylphenyl group of COBI **1**. As the diazoacetate approaches the β-position of acrolein, the *tert*-butyl ester moiety is situated away from the aldehyde moiety of α-bromoacrolein due to a dipole–dipole interaction between the carbonyl groups. Therefore, nucleophilic addition of *tert*-butyl diazoacetate from the *si* face of the α-bromoacrolein is facilitated and leads to intermediate **8**. Cyclization with loss of nitrogen gas provides (1*S*,2*R*)-*cis*-cyclopropane **2** as the major product.

To demonstrate the utility of this stereoselective *cis*-dicarbonyl cyclopropane synthesis, the total synthesis of (−)-dictyopterene C' was carried out (Scheme 3). Since a (*Z*)-configuration of the substrates results in a significant increase of the activation barrier[12] for the DVCPR, Julia-Kocienski olefination[13] was considered to introduce

Table 1. Optimization of enantioselective cyclopropanation of *tert*-butyl diazoacetate and α-bromoacrolein.[a]



Entry	1	2	X	R^2	*cis*/*trans*[b]	Yield (%)[c]	*ee* (%)[d]
1	**1a**	**2a**	Br	*t*-Bu	4.7:1	66	93
2	**1b**	**2a**	Br	*t*-Bu	5:1	66	>99
3	**1c**	**2a**	Br	*t*-Bu	5:1	66	>99
4	**1d**	**2a**	Br	*t*-Bu	4:1	55	>99
5	**1e**	**2a**	Br	*t*-Bu	5.9:1	62	95
6	**1f**	**2a**	Br	*t*-Bu	8:1	93	97
7	**1f**	**2b**	Br	Et	4.2:1	99	87
8	**1f**	**2c**	Cl	*t*-Bu	3.8:1	78	88

[a] The reactions of *tert*-butyl diazoacetate (0.24 mmol) with α-bromoacrolein (0.28 mmol) were performed in the presence of **1** (20 mol%) in propionitrile at −78 °C for 2 h.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Yield of isolated products.
[d] Determined by HPLC analysis on a chiral stationary phase.

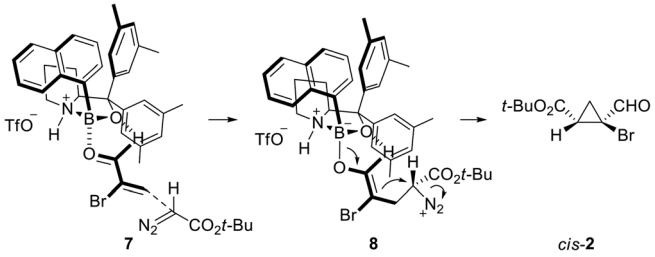
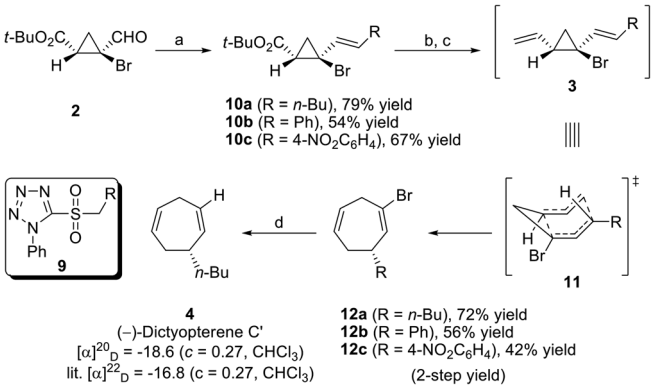
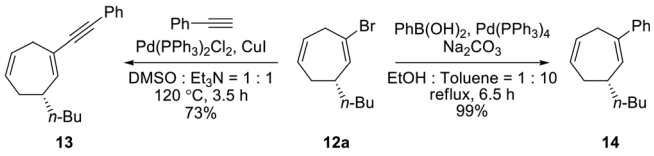


Figure 1. Transition-state model for the enantioselective cyclopropanation reaction.

the (*E*)-alkene substituents of **10** instead of the Wittig reaction, which is known to give (*Z*)-alkenes. Highly *trans*-selective Julia-Kocienski olefination with 1-phenyl-1*H*-tetrazole **9** and potassium bis(trimethylsilyl)amide (KHMDS) provided (*E*)-alkenes **10** in good to high yields. After reduction of the *tert*-butyl ester group to aldehyde by diisobutylaluminum hydride (DIBAL-H), the Wittig reaction with a methylphosphonium salt using *n*-butyllithium introduced the vinyl group to produce divinylcyclopropane products **3** for DVCPR. Interestingly, while there are some reports that high temperature is required for DVCPR, cyclopropane **3** was not observed under the Wittig olefination conditions at 0 °C. Apparently all the *cis*-**3** was transformed to 1,4-cycloheptadienes **12** through the DVCPR *endo*-boat-like transition-state **11**.[6c] Finally, reduction of vinyl bromide **12a** in the presence of palladium catalyst afforded desired (−)-dictyopterene C' **4** in 5 steps and 42% overall yield. Confirmation of the synthetic (−)-dictyopterene C' was fully established through comparison of its physical data including ^{1}H and ^{13}C NMR spectra and optical rotation data to the reported data.[14] Based on the synthetic route in Scheme 3, various chiral 1,4-cycloheptadiene derivatives **12a–c** were synthesized in moderate to high yields.



Scheme 3. Stereoselective synthesis of (−)-dictyopterene C' from optically active cyclopropane **2**. Reagents and conditions: (a) **9**, KHMDS, DME, −78 °C, 30 min; (b) DIBAL-H (1.0 M in toluene), toluene, −78 °C, 10 min; (c) $MePPh_3Br$, *n*-BuLi (2.5 M in *n*-hexane), Et_2O, 0 °C, 24 h; (d) $PdCl_2(PPh_3)_2$, $NaBH_4$, TMEDA, THF, reflux, 3 h, 80%.



Scheme 4. Synthesis of various 1,4-cycloheptadiene derivatives.

Since the bromo substituent of 1,4-cycloheptadienes **12** is easily transformed into a large variety of other moieties with Pd(0) catalysis, further chemical transformations of **12a** were carried out to prepare (−)-dictyopterene C′ derivatives **13** and **14** (Scheme 4). Sonogashira coupling[15] of **12a** with phenyl acetylene under modified reaction conditions[16] provided **13** in 73% yield. Suzuki coupling[17] of **12a** with phenyl boronic acid in the presence of $Pd(PPh_3)_4$ proceeded smoothly to give phenyl 1,4-cycloheptadienes **14** in 99% yield without obvious loss of enantiopurity.

In conclusion, we developed a COBI-catalyzed enantioselective cyclopropanation for the synthesis of optically active *cis*-dicarbonyl cyclopropanes, which were successfully applied to a convenient synthetic route to chiral 1,4-cycloheptadiene derivatives. The efficient synthetic process for enantioselective synthesis of (−)-dictyopterene C' was accomplished in 42% overall yield and five steps from α-bromoacrolein and *tert*-butyl diazoacetate. Moreover, we synthesized various 1,4-cycloheptadiene derivatives from 2-bromo-1,4-cycloheptadienes using Sonogashira and Suzuki coupling reactions. Further chemical transformations of *cis*-dicarbonyl cyclopropane compounds are underway in our laboratory.

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