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Asymmetric [4 + 3] Cycloadditions between Benzofuranyldiazoacetates and Dienes: Formal Synthesis of (+)-Frondosin B

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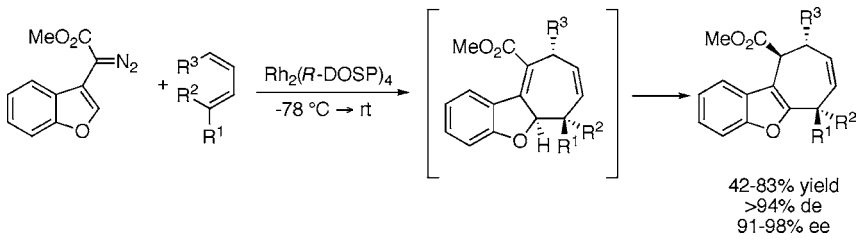
ABSTRACT

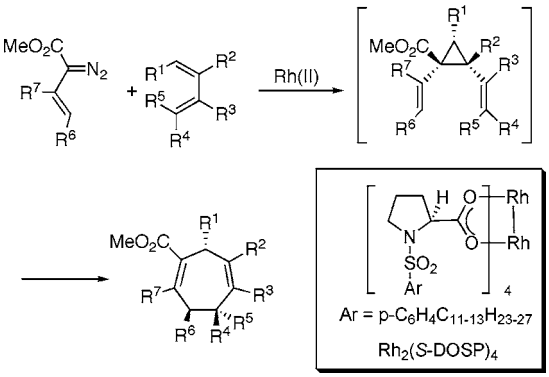


The reaction of benzofuranyldiazoacetates with 1,3-dienes catalyzed by the dirhodium tetracarboxylate Rh_2(*R*-DOSP)$_4$, generates formal [4 + 3] cycloadducts with >94% de and 91−98% ee. The reaction proceeds by a tandem cyclopropanation/Cope rearrangement followed by a stereoselective tautomerization. This methodology was extended to a formal synthesis of (+)-frondosin B.

The tandem cyclopropanation/Cope rearrangement between vinyldiazoacetates and dienes is a general method for the stereoselective synthesis of highly functionalized seven-membered rings (Scheme 1).[1] The reaction, which results in a formal [4 + 3] cycloaddition, is of broad scope and has been applied to a range of dienes, including furans,[2] pyrroles,[3] pyridones,[4] and even benzene derivatives.[5] By using chiral dirhodium catalysts such as Rh_2(DOSP)$_4$, high enantioselectivity can be achieved.[6]

Inspired by the recent synthetic interest[7−12] in frondosin B (**1**),[13] we became intrigued with the possibility of using a tandem cyclopropanation/Cope rearrangement sequence for the synthesis of its core 6,5,7-tricyclic system (Scheme 2). A specific target would be tricycle **2** which has been previously converted to frondosin B by Danishefsky.[7] For this approach to be successful, benzofuranyldiazoacetate **4**

Scheme 1. Tandem Cyclopropanation/Cope Rearrangement



(1) (a) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. (b) Davies, H. M. L. *Advances in Cycloaddition*; JAI Press, Greenwich, CT, 1999: Vol. 5, pp 119−164.

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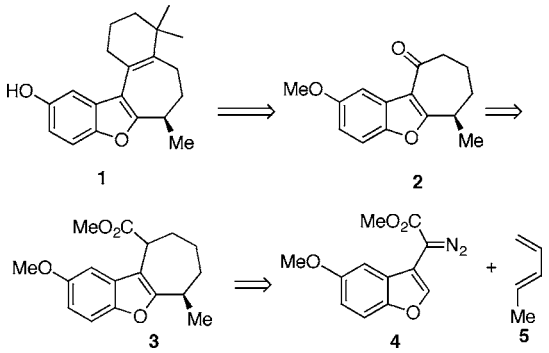
Scheme 2. Frondosin B Retrosynthetic Analysis

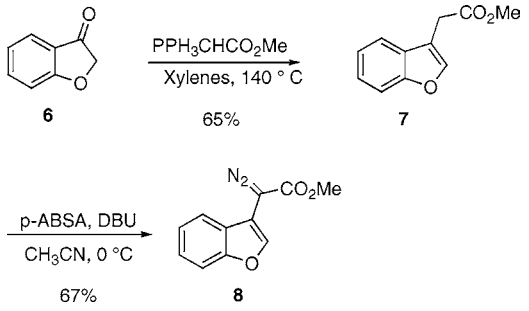


and diene **5** would be needed as substrates in the initial cyclopropanation and the benzofuran moiety would need to be a reactive component in the subsequent Cope rearrangement. A further requirement would be the regeneration of the benzofuran ring by means of tautomerization. This paper describes the successful development of the tandem cyclopropanation/Cope rearrangement between benzofuranyldiazoacetates and dienes and its application to the synthesis of **2**.

To test the effectiveness of this reaction, the benzofuranyldiazoacetate **8** was synthesized and reacted with a series of conjugated dienes. **8** was readily synthesized from the commercially available coumaran-3-one **6** by treatment with methyl(triphenylphosphoranylidene)acetate in refluxing xylenes[14] followed by a diazo transfer reaction on the resulting benzofuranacetate **7** with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (Scheme 3).

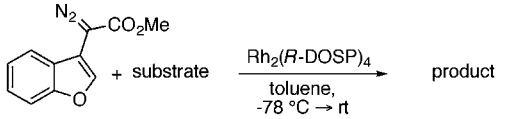
With the desired benzofurandiazoacetate **8** in hand, its reactions with a variety of cyclic and acyclic conjugated dienes were examined under Rh_2(*R*-DOSP)$_4$-catalyzed conditions (Table 1). The standard reaction was conducted with 1 mol % of Rh_2(*R*-DOSP)$_4$, to which **8** was added to the reaction mixture at −78 °C, and then the mixture was warmed to room temperature. In some cases where the diene has a *cis*-substituent, more vigorous conditions were required to drive the Cope rearrangement of the *cis*-divinylcyclopropane.[15] A significant amount of the *trans*-divinylcyclopropane

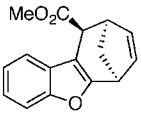
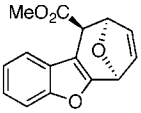
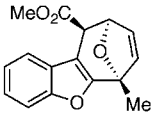
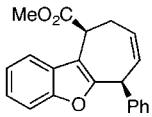
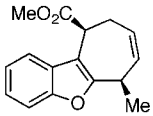
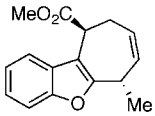
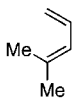
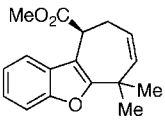
Scheme 3. Synthesis of Benzofuranyldiazoacetate **8**



was generated only in the case of *cis*-piperylene. In all instances, the formal [4 + 3] cycloadducts were obtained in moderate to high yield (43−92%) and high diastereoselectivity (>94% de) and enantioselectivity (91−98% ee). The relative configuration of the products was determined by

Table 1. Rh_2(*R*-DOSP)$_4$-Catalyzed Reactions of **8** with Dienes



substrate	yield (%)	de (%)[a]	ee (%)	product
	83[b]	>94	98	 **9**
	92	>94	96	 **10**
	83	>94	96	 **11**
	68	>94	98	 **12**
	66	>94	98	 **13**
	43[c, d]	>94	93	 **14**
	82[b]	—	91	 **15**

[a] Diastereoselectivity determined from the ^{1}H NMR of the crude reaction mixture. [b] Cope rearrangement required heating to 110 °C. [c] Cope rearrangement required heating to 140 °C. [d] Initial cyclopropane was produced in a 2.7:1 diastereomeric ratio.

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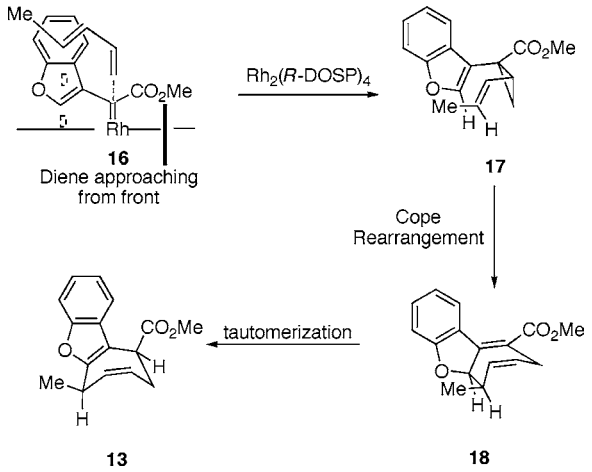
NOE, which had distinctive across ring signal enhancements. Further confirmation of the relative stereochemistry in the annulated products from the reaction with cyclopentadiene and furan (**9**−**11**) was obtained from the distinctive coupling constants for the endo products in the bicyclo[3.2.1]octadiene subunit.[16]

The high enantioselectivity observed in the formation of the [4 + 3] cycloadducts is not surprising because it is well-established that Rh_2(*R*-DOSP)$_4$ is capable of high enantioselectivity with a range of donor/acceptor-substituted carbenoids.[17] More unexpected is the fact that the [4 + 3] cycloadducts are produced with very high diastereoselectivity. The most reasonable mechanism to explain this reaction would be a diastereoselective cyclopropanation, followed by a Cope rearrangement and then a stereoselective proton transfer (Scheme 4). The asymmetric induction is achieved

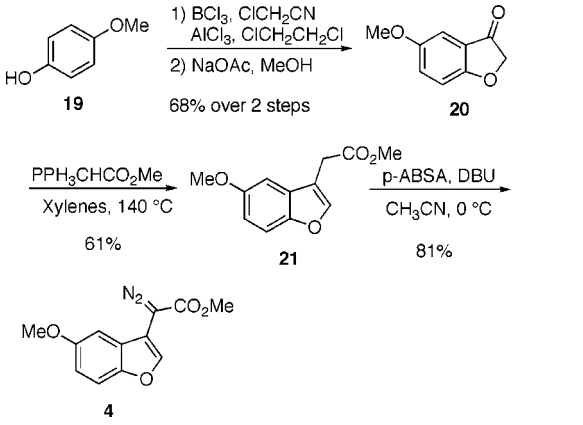
Scheme 4. Stereochemical Analysis



in the initial cyclopropanation, and donor/acceptor carbenoids are known to result in highly diastereoselective cyclopropanations.[18] The model for the Rh_2(*R*-DOSP)$_4$ cyclopropanation predicts the formation of the enantiomer **17** shown in Scheme 4,[19] and as will be described later, this was confirmed in the frondosin B synthetic studies. The ring expansion of **17** via the Cope rearrangement to form **18** occurs through a boat transition state, and it proceeds with well-defined stereocontrol.[1] The less precedented step is the tautomerization of **18** to **13** to regenerate the benzofuran ring, which occurs without any observable isomerization. The configuration of the new stereocenter after tautomerization is not controlled by other stereocenters in the molecules as is evident from the formation of the diastereomeric products **13** and **14** with *trans*- and *cis*-piperylene, respectively, and the formation of **15** in 91% ee.

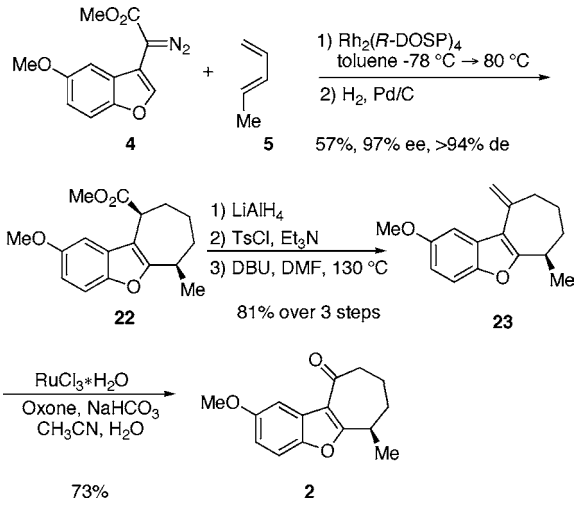
The application of the [4 + 3] cycloaddition to a formal synthesis of (+)-frondosin B would require the availability of methoxy derivative **4** as the carbenoid precursor. As shown in Scheme 5, **4** was conveniently prepared from the commercially available 4-methoxyphenol **19**. Cyclization of **19** with chloroacetonitrile generated the benzofuranone **20**, which was then converted under the standard procedure to **21** and then the benzofuranyldiazoacetate **4**.

Scheme 5. Synthesis of Benzofuranyldiazoacetate **4**



When **4** was reacted with *trans*-piperylene **5** in the presence of Rh_2(*R*-DOSP)$_4$, a mixture of the desired [4 + 3] cycloadduct as well as some of the cyclopropane was obtained. Upon heating to 80 °C, the mixture was completely converted to the desired [4 + 3] cycloadduct. Because this product rapidly decomposed, it was immediately subjected to hydrogenation to produce compound **22** in 57% yield, 97% ee, and >94% de. This product was reduced with lithium aluminum hydride, and the resulting alcohol was eliminated using toluenesulfonyl chloride and triethylamine, followed by heating in the presence of DBU to produce **23**. The exocyclic olefin was cleaved using ruthenium-catalyzed oxidative cleavage to produce the desired intermediate **2** (Scheme 6).[20] The predicted absolute configuration of **2**,

Scheme 6. Synthesis of (+)-Frondosin B Intermediate



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according to the model shown in Scheme 4, was confirmed by optical rotation and chiral HPLC analysis.[7a]

In conclusion, we have broadened the scope of the tandem cyclopropanation/Cope rearrangement sequence by using benzofuranyldiazoacetates as substrates. The formal [4 + 3] cycloadducts are produced in high diastereoselectivity and enantioselectivity with a variety of dienes. The potential of this methodology was demonstrated by its application to a formal enantioselective synthesis of (+)-frondosin B.

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Supporting Information Available: Experimental data for the reported reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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