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Combined C−H Activation/Cope Rearrangement as a Strategic Reaction in Organic Synthesis: Total Synthesis of (−)-Colombiasin A and (−)-Elisapterosin B

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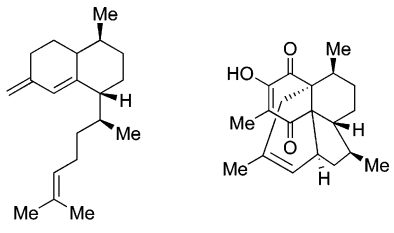
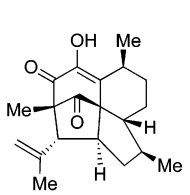
Abstract: The total synthesis of (−)-colombiasin A (**2**) and (−)-elisapterosin B (**3**) has been achieved. The key step is a C−H functionalization process, the combined C−H activation/Cope rearrangement, between methyl (*E*)-2-diazo-3-pentenoate and 1-methyl-1,2-dihydronaphthalenes. When the reaction is catalyzed by dirhodium tetrakis((*R*)-(*N*-dodecylbenzenesulfonyl)prolinate), Rh_2(*R*-DOSP)$_4$, an enantiomer differentiation step occurs where one enantiomer of the dihydronaphthalene undergoes the combined C−H activation/Cope rearrangement while the other undergoes cyclopropanation. This sequence controls the three key stereocenters in the natural products such that the remainder of the synthesis is feasible using standard chemistry.

Natural product synthesis continues to be a fertile area and proving ground for the development of new synthetic methods. On occasion, certain classes of natural products with a rich combination of promising biological activity and intriguing structural architecture become highly attractive synthetic targets. A class of compounds that is generating much current interest is a super-family of diterpenes that were isolated from gorgonian corals.[1−8] The diverse family of diterpenes, comprising from bicyclic to hexacyclic systems, is completely derived biosynthetically from (+)-elisabethatriene (**1**).[2] Examples of these natural products are (−)-colombiasin A (**2**),[3,4] (−)-elisapterosin B (**3**),[5] and (+)-erogorgiaene (**4**).[6] Many members of this superfamily display substantial biological activity as anti-inflammatory, anticancer, antitubercular, and/or general antibacterial agents.[9] Due to the common biosynthetic ancestry of these natural products,[2] all have three distinctive stereocenters. From a synthetic perspective, these three stereocenters have represented considerable challenges[1,3−8] because there are no convenient neighboring functional groups available to assist in their stereocontrol. This paper will describe a C−H functionalization strategy that has the potential to be a universal solution of the stereochemical issues associated with the synthesis of the three stereocenters in these natural products.

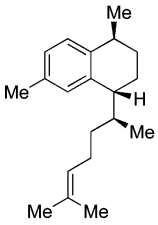


1 elisabethatriene

2 colombiasin A



3 elisapterosin B



4 erogorgiaene

The problems associated with the stereochemical issues of these natural products can be readily seen in the published

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(6) (+)-Erogorgiaene, (a) Isolation: Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100−102. Total synthesis: (b) Cesati, R. R.; Armas, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96−101. (c) Davies, H. M. L.; Walji, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1733−1735. Formal synthesis: (d) Harmata, M.; Hong, X. *Tetrahedron Lett.* **2005**, *46*, 3847−3849.
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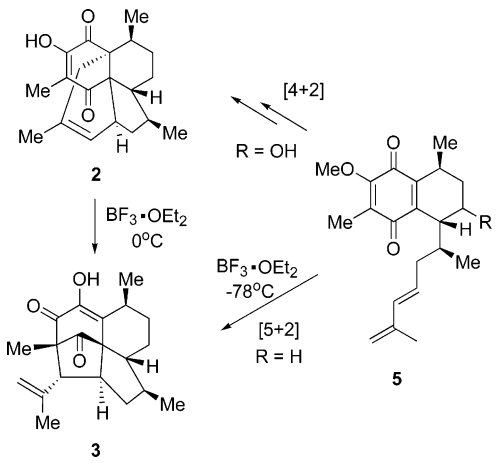
Scheme 1

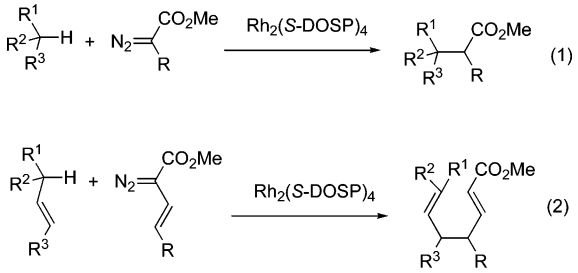


syntheses of (−)-colombiasin A (**2**) and (−)-elisapterosin B (**3**).[3−5] The end game in the syntheses of these compounds has been elegantly achieved by means of cycloaddition approaches (Scheme 1). Nicolaou et al. demonstrated that (−)-colombiasin A could be readily prepared by an intramolecular [4 + 2] cycloaddition from the diene **5**,[3b,3c] while Kim and Rychnovsky developed a rapid entry into (−)-elisapterosin B by a Lewis acid catalyzed [5 + 2] cycloaddition from **5**.[3d] Recently, Jacobsen and co-workers have shown that (−)-colombiasin A can be converted into (−)-elisapterosin B by a Lewis acid catalyzed reaction, possibly occurring by a retro [4 + 2] cycloaddition followed by a [5 + 2] cycloaddition.[3f]

Even though the end game solution for the synthesis of (−)-colombiasin A and (−)-elisapterosin B is very elegant and efficient, the stereoselective synthesis of the three distinctive stereogenic centers has been much more challenging (Scheme 2). In the synthesis related to (−)-colombiasin A, three main retrosynthetic strategies have been developed. The first approach employed a Tsuji allylation from **7** but this suffered from poor regiocontrol, producing a 1:2.4 mixture of the 1,3- and 3,3-rearrangement (**8**) products.[3b,3c] Furthermore, **8** is formed as the wrong diastereomer, and several additional steps were required to achieve the necessary epimerization. An alternative strategy has been an intermolecular Diels−Alder reaction of benzoquinone **9** with a diene **10**. Due to the lack of stereocontrol, the exocyclic stereocenter in the diene needed to be stereospecifically introduced prior to the cycloaddition. In the initial process reported by Kim and Rychnovsky, the diastereoselectivity in the cycloaddition was low (1:1.7),[3d] but recently, Jacobsen and co-workers have greatly improved this process by using chiral Lewis acids to influence the diastereoselectivity of this cycloaddition.[3f] Due to the stereochemical challenges of these natural products, many groups have avoided the problem by starting their syntheses with commercially available monoterpenes.[8a,8b,10] This strategy has been recently used by Harrowven et al. starting from the monoterpene **12** which is converted to **13** and includes a nice cascade to complete the total synthesis of (−)-colombiasin A.[3e] This approach is effective but it does have the drawback that a different annulation strategy would have to be designed for each natural product synthesis.

In this paper we describe a very different approach to control the three stereocenters in these natural products. The approach is based on a "combined C−H activation/Cope rearrangement" between the vinyldiazoacetate **15** and dihydronaphthalenes **14**, which generates the three stereocenters in one step.[6c]

Our group has been developing new strategic reactions for organic synthesis, which are based on regioselective intermolecular C−H functionalization processes.[11] Our approach to achieve the C−H functionalization is by means of intermolecular C−H insertions of rhodium carbenoids. Two major variants of this theme have been discovered. The first is the direct C−H insertion which can be conducted in a highly enantioselective manner using the dirhodium tetraprolinate complex Rh_2(*S*-DOSP)$_4$ as catalyst (eq 1).[11] With use of this reaction, equivalent transformations have been achieved to several of the classic reactions of organic synthesis, such as the Aldol reaction,[12] Mannich reaction,[13] Michael addition,[14] and the Claisen rearrangement.[15] The second is the "combined C−H activation/Cope rearrangement", a transformation that often occurs in >98% ee and >98% de (eq 2).[16] This reaction occurs during allylic C−H functionalization by vinyldiazoacetates.



The combined C−H activation/Cope rearrangement also has the potential of being a surrogate for some of the classic reactions of organic synthesis.[17] This can be illustrated by considering a hypothetical approach for the synthesis of (−)-colombiasin A that would in principle be applicable to many other members of these diterpenes (Scheme 3). A flexible precursor to (−)-colombiasin A would be the ester **17**. If **17** is derived from the diene **18**, a hypothetical approach to generate **18** with controlled stereochemistry would be a tandem Claisen rearrangement/Cope rearrangement from **19**. Both reactions would be expected to proceed through a chair transition state where the ester stereogenic center in **19** would dictate the stereochemistry in the formation of the two new stereogenic centers in **18**. This scheme has to be considered hypothetical because there would be no driving force for the Cope

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(14) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2070−2071.
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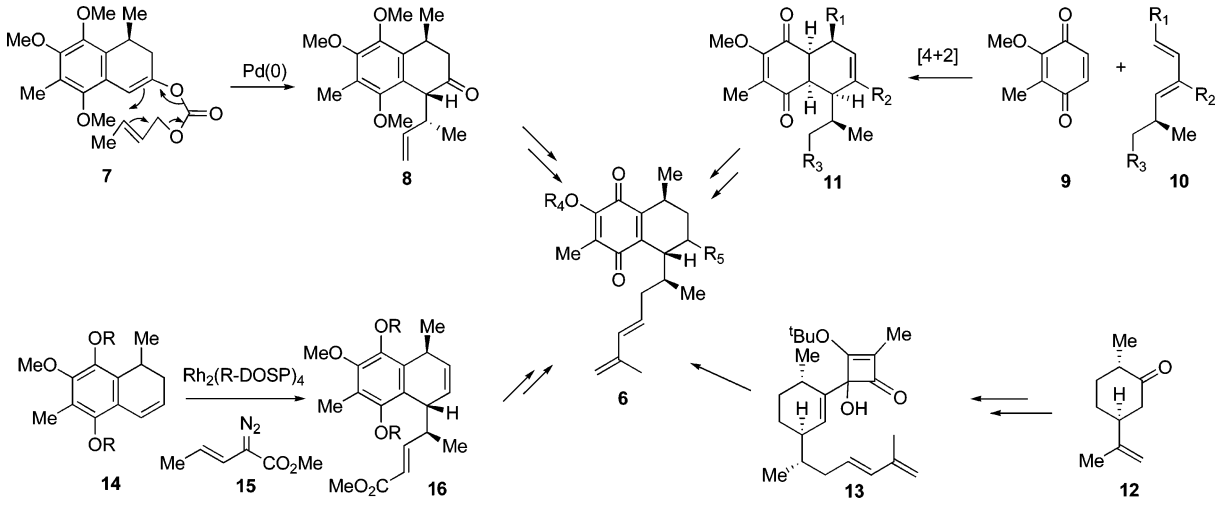
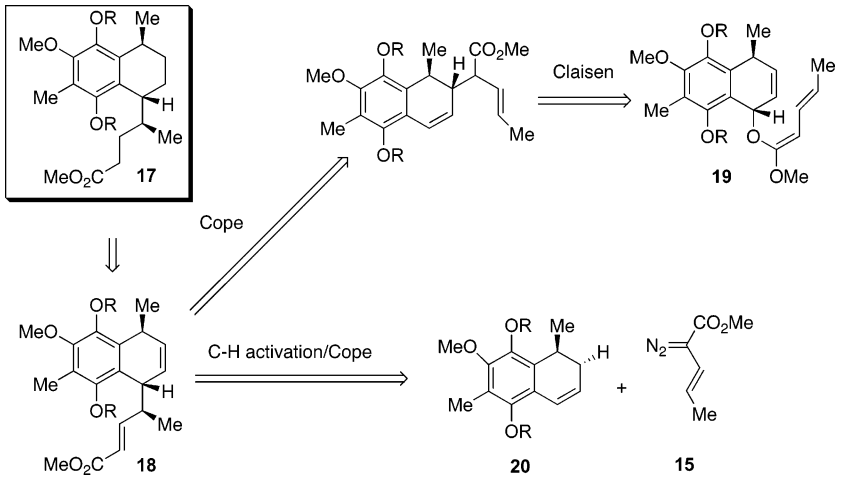
(17) Davies, H. M. L.; Beckwith, R. E. J. *J. Org. Chem.* **2004**, *69*, 9241−9247.

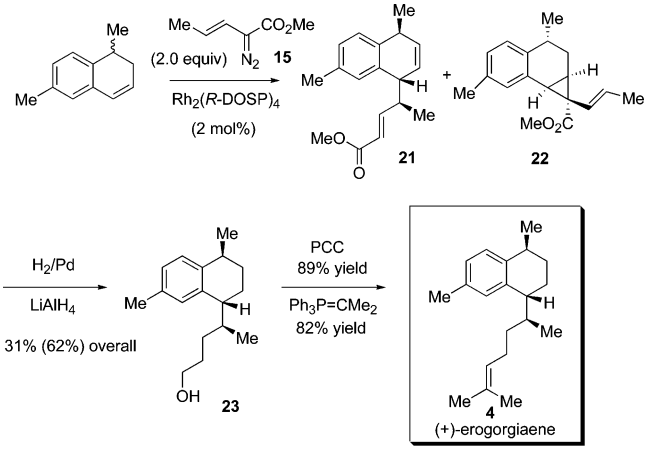
Scheme 2



Scheme 3



Scheme 4

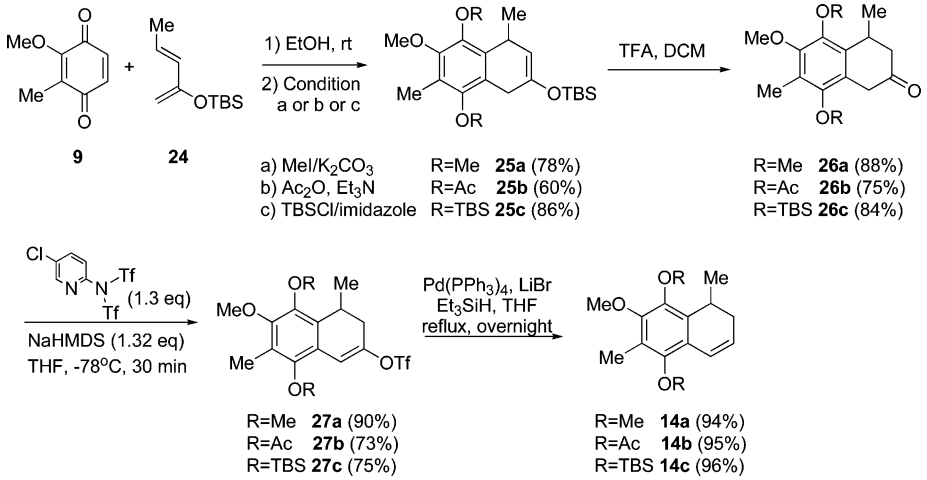


rearrangement.[16a] The "combined C−H activation/Cope rearrangement" would be an equivalent of this hypothetical reaction, as illustrated in the conversion of **20** to **18**.

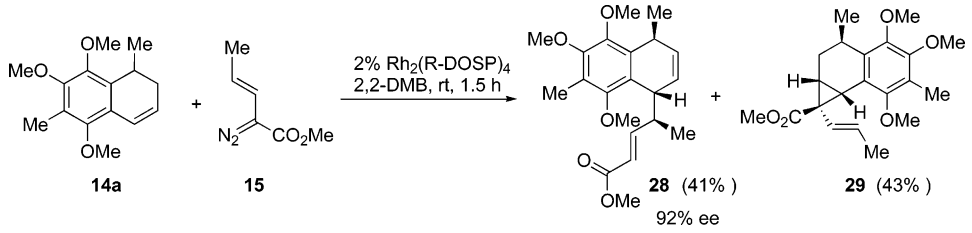
We have communicated a proof-of-concept study which demonstrated that the combined C−H activation/Cope rearrangement can be effectively applied to the rapid construction of (+)-erogorgiaene (Scheme 4).[6c] The C−H functionalization with the vinyldiazoacetate **15** is especially impressive because it is an enantiodivergent step. One enantiomer of the dihydronaphthalene undergoes the C−H activation/Cope rearrangement to form **21** while the other enantiomer undergoes a cyclopropanation to form **22**. Completion of the synthesis of (+)-erogorgiaene (**4**) was readily achieved in four additional steps from **21**. As the C−H functionalization begins at a site well away from the aromatic ring, we made the hypothesis that this reaction would be little influenced by the aromatic ring functionality. In this paper we demonstrate that a highly oxygenated aromatic ring is equally compatible with this carbenoid chemistry, leading to very direct access to (−)-colombiasin A and (−)-elisapterosin B.

Three dihydronaphthalenes with different protecting groups, methyl (**14a**), acetyl (**14b**), and *tert*-butyldimethylsilyl (**14c**) were chosen as appropriate substrates for the crucial combined C−H activation/Cope rearrangement. The synthesis of **14** started from the *p*-quinone **9** following a [4 + 2] cycloaddition sequence described by Nicolaou et al. (Scheme 5).[3b,3c] Reaction of the quinone **9** with the diene **24** generated the cycloadduct which on isomerization to the corresponding quinol could be trapped under different conditions to afford the dimethyl derivative ether **25a**, the diacetyl derivative **25b**, and the disilyl derivative **25c**. Acidic hydrolysis of the resulting TBS-enol ether in **25** gave rise to the ketone **26** in good yields. Initially, we investigated utilizing a reduction/elimination strategy to form the C=C double bond of **14** from the β-tetralone **26**, but this gave a

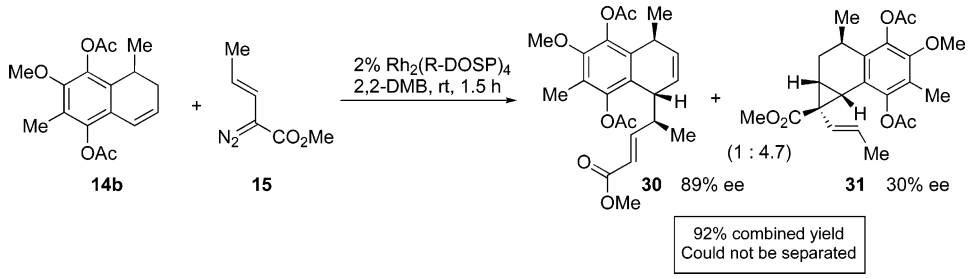
Scheme 5



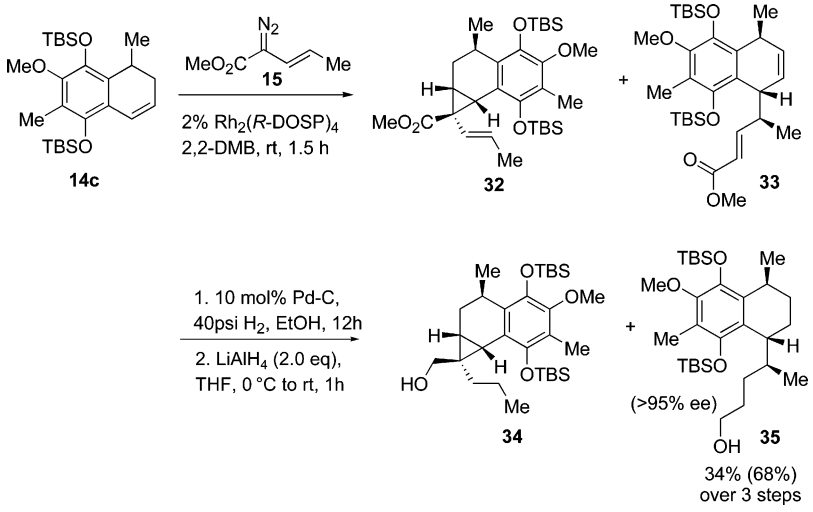
Scheme 6



Scheme 7



Scheme 8



mixture of double-bond isomers. The overall transformation could be achieved through initially converting the β-tetralone **26** to the corresponding vinyl triflate **27** using Comins' reagent,[18] before carrying out a palladium-catalyzed reductive coupling.[19]

With quantities of the three dihydronaphthalenes **14** in hand, the key rhodium carbenoid step was examined. From the

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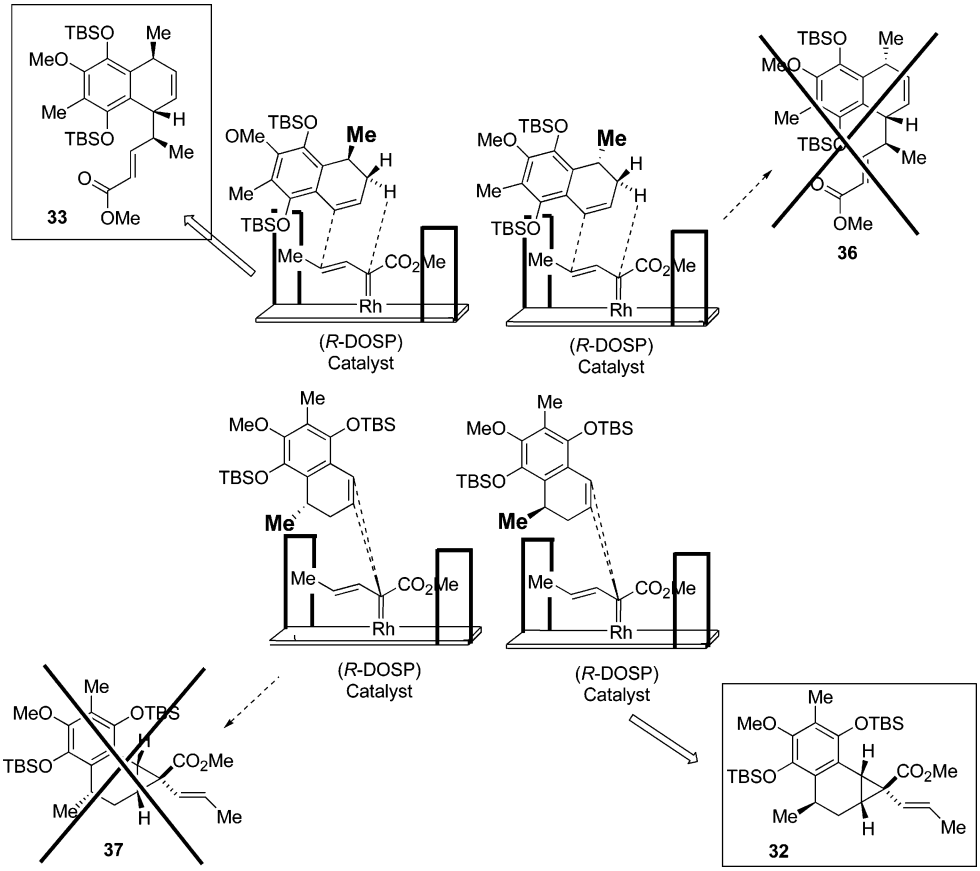
Scheme 9



conception of the project, it was proposed that the functionality on the aromatic ring would not interfere with the combined C−H activation step. This was definitely the case with the dimethoxy derivative **14a** as the Rh_2(*R*-DOSP)$_4$-catalyzed reaction of **14a** with the vinyldiazoacetate **15** gave a 1:1 mixture of the C−H functionalization product **28** and the cyclopropane **29** as single diastereomers (Scheme 6). Furthermore, the C−H functionalization product **28** was formed with the correct relative stereochemistry for the natural products and in 92% ee.

The C−H functionalization chemistry of the diacetyl derivative **14b** gave a surprising result (Scheme 7). The Rh_2(*R*-DOSP)$_4$-catalyzed reaction between **15** and **14b** proceeded in high yield (92%) but the 1:4.7 ratio of the C−H functionalization product **30** to the cyclopropane **31** was much different from the 1:1 ratio of the reaction with **14a**. Even so, both **30** and **31** were produced with very high diastereoselectivity (>95% de) but the enantioselectivity for the C−H functionalization product **30** was 89% ee, while the cyclopropane **31** was formed in only 30% ee. This result is not consistent with our previous observations and is indicative that the acetoxy groups interfere with the chiral discrimination by the prolinate catalyst on the cyclopropanation, although the C−H functionalization selectivity is not markedly changed. A possible explanation for this strange effect is that the acetoxy group coordinates to the carbenoid prior to the cyclopropanation event and this interferes with the chiral influence of the catalyst. Ester coordination to a carbenoid has been implicated in asymmetric cyclopropanations with chiral ester auxilaries[20a] and the presence of methyl benzoate as an additive greatly enhances the turnover numbers of rhodium-catalyzed cyclopropanations.[20b] Further studies are in progress to fully understand the nature of the acetoxy effect.

In contrast to the diacetoxy system, the disilyl derivative **14c** was an exceptional substrate for the combined C−H activation/Cope rearrangement. The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of **15** with **14c** gave a 1:1 mixture of the C−H functionalization product **32** and the cyclopropane **33** (Scheme 8). Since the two products could not be separated at this stage, the mixture was hydrogenated and then reduced to the alcohols **34** and **35**. The desired C−H functionalization product **35** was isolated in 34% yield (68% in theory) as a single diastereomer in >95% ee over three steps.

The enantiomer differentiation in these reactions can be rationalized as illustrated in Scheme 9. Excellent predictive models have been developed for both the rhodium prolinate-catalyzed C−H activation/Cope rearrangement[16b] and the cyclopropanation.[21] The chiral catalysts are considered to adopt a D_2 symmetric arrangement and can be viewed simply with a blocking group in the front and another in the back. Applying these models to the 4-methyl-1,2-dihydronaphthalenes as substrates leads to an interesting prediction. The matched enantiomer for the C−H activation/Cope rearrangement is opposite to the matched enantiomer for the cyclopropanation. Consequently, a situation exists for enantiomer differentiation in which one enantiomer preferentially undergoes the C−H activation/Cope rearrangement to form **33**, while the other undergoes cyclopropanation to form **32**. From a practical perspective, this

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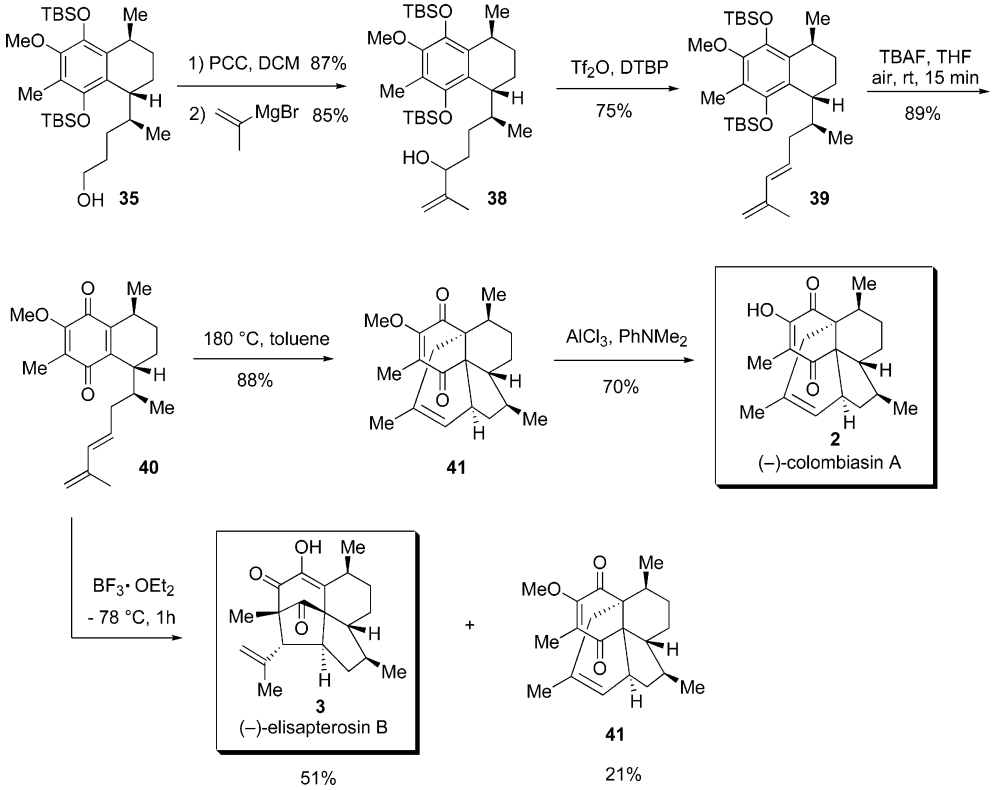
Scheme 10



is even better than kinetic resolution because the complex dihydronaphthalene can be used as the limiting agent.

Although both dihydronaphthalene **14a** and **14c** gave excellent results in the C−H activation/Cope rearrangement, **14c** was used to complete the total synthesis since it would be easier to unveil the quinone moiety by deprotection of TBS ethers rather than methyl ethers. Thus, conversion of the alcohol **35** to the key diene **40** was achieved using very standard steps (Scheme 10). PCC oxidation of **35** followed by a Grignard addition generated the allylic alcohol **38**. Conversion of **38** to the triflate followed by elimination generated the diene **39**, which was readily desilylated and air-oxidized to the quinone **40**.

Kim and Rychnovsky have previously shown that the diene **40** can be converted to (−)-colombiasin A by an intramolecular Diels−Alder reaction, while treatment of **40** with boron trifluoride etherate generates (−)-elisapterosin B by means of a [5 + 2] cycloaddition.[3d] Thus, when diene **40** was heated at 180 °C in toluene, (−)-colombiasin A methyl ether (**41**) was isolated in 88% yield).[3b,3c] The total synthesis of (−)-colombiasin A (**2**) was completed by demethylation of **41** with $AlCl_3$.[3d] Exposing diene **40** to boron trifluoride etherate at −78 °C for 1 h resulted in a [5 + 2] cycloaddition to give (−)-elisapterosin B in 51% yield. Under these conditions (−)-colombiasin A methyl ether **41** was generated as a side product in 21% yield. The spectral data for (−)-colombiasin A and (−)-elisapterosin B were in full agreement with the literature data.[3,5]

In conclusion, the total synthesis of (−)-colombiasin A (**2**) and (−)-elisapterosin B (**3**) has been achieved in 14 and 13 steps, respectively, from quinone **9**. The key step is the combined C−H activation/Cope rearrangement, which is an excellent method for the construction of the three stereogenic centers common to the various diterpenes isolated from *Pseudopterogorgia elisabethae*.

Acknowledgment. The National Science Foundation (CHE-0350536) is gratefully acknowledged.

Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

JA056877L

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