Natural Product Synthesis

Direct Synthesis of (+)-Erogorgiaene through a Kinetic Enantiodifferentiating Step**

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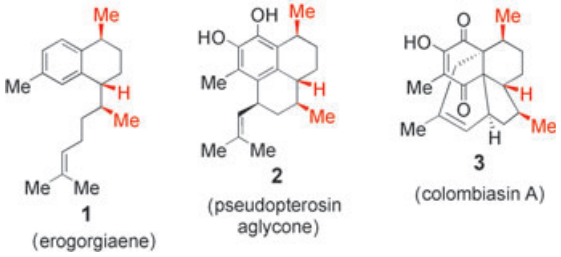
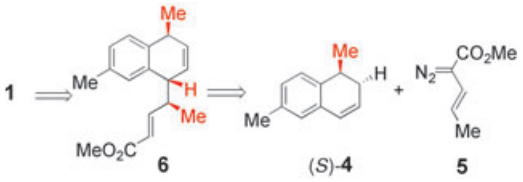
(+)-Erogorgiaene is a member of the marine diterpenes isolated from the West Indian sea whip *Pseudopterogorgia elisabethae* and displays promising activity against *Mycobacterium tuberculosis* H37Rv.[1] Several important biologically active secondary metabolites have been isolated from the *Pseudopterogorgia* corals.[2] Consequently, there has been extensive activity directed towards the synthesis of these natural products.[3] Even though these compounds are not especially complex, a major challenge associated with their synthesis has been the control of the three stereocenters (marked in red, **1**–**3**, Scheme 1), common to all of them. The



Scheme 1. Diterpenes isolated from *Pseudopterogorgia elisabethae*.

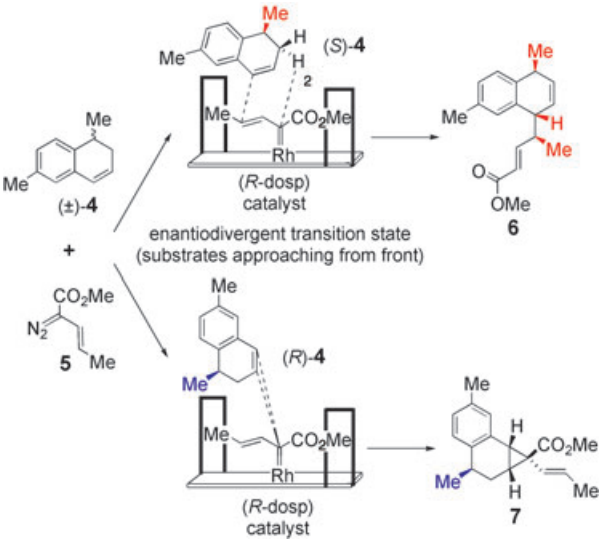
stereocontrol has been challenging because of the lack of functional groups near to the stereogenic centers. This has meant that many of the syntheses have been very lengthy with considerable functional group interconversions, and even then the stereocontrol has been less than satisfactory.[3] The only reported synthesis of (+)-erogorgiaene (**1**), described by Hoveyda and co-workers, employed a chiral-catalyst-controlled conjugate addition in a sequential manner to set up the desired stereocenters.[4]

Here we illustrate through the enantioselective synthesis of (+)-erogorgiaene (**1**) a potentially general strategy to the synthesis of this class of diterpenes. The key step is our recently discovered combined C–H activation/Cope rearrangement catalyzed by dirhodium tetraprolinate $[Rh_2(dosp)_4]$ (dosp = (*N*-dodecylbenzenesulfonyl)prolinate), a reaction that is notable for its very high diastereoselectivity and enantioselectivity.[5] Application of this methodology to the retrosynthetic analysis of (+)-erogorgiaene revealed that the unsaturated ester **6** would be a very desirable precursor to **1**. Reaction of the vinyldiazoacetate **5** with the dihydronaphthalene (*S*)-**4** would be expected to readily form **6** with the desired relative stereochemistry (Scheme 2).



Scheme 2. Retrosynthetic analysis of (+)-erogorgiaene (**1**).

During the analysis of this synthetic problem, we recognized that the synthesis offered a very exciting opportunity for enantiomer differentiation, such that the racemic dihydronaphthalene (±)-**4** could be used as starting material. Even though the exact mechanism of these carbenoid reactions is not known, we have developed models that are excellent at predicting the stereochemical outcome of this chemistry.[5b,6] Applying these models to the $[Rh_2(R\text{-dosp})_4]$-catalyzed reaction of (±)-**4** with **5**, it was revealed that only (*S*)-**4** would be capable of a matched combined C–H activation/Cope rearrangement to form **6** whereas (*R*)-**4** would be matched for a cyclopropanation to form **7** (Scheme 3). This



Scheme 3. Stereochemical prediction for combined C–H activation/Cope rearrangement strategy.

would be a very exciting outcome because the dihydronaphthalene (±)-**4** could potentially be used as the limiting agent, as both enantiomers would be consumed but would form different products.

To test this possibility, the reaction of dihydronaphthalene **8** with the phenylvinyldiazoacetate **9** was used as a model reaction (Scheme 4). We were delighted that the reaction

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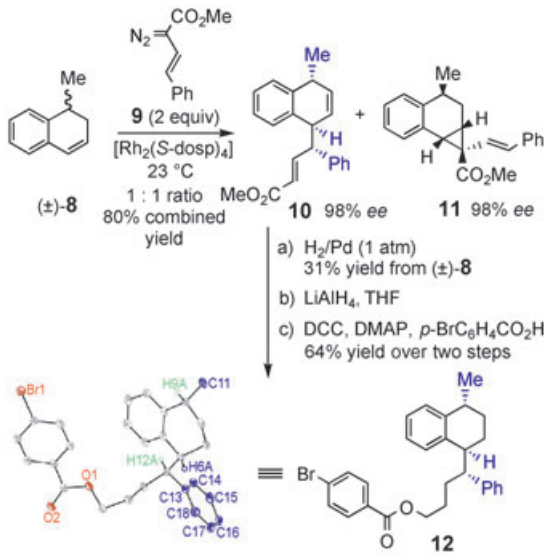
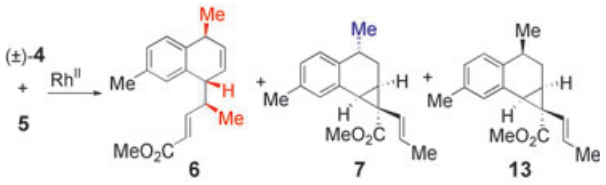


Scheme 4. Preliminary modeling studies and determination of absolute configuration: ORTEP drawing of **12**. DCC = dicyclohexyl carbodiimide, DMAP = 4-dimethylaminopyridine.

catalyzed by $[Rh_2(S\text{-dosp})_4]$ gave a 1:1 mixture of the combined C–H activation/Cope rearrangement product **10** and the cyclopropane **11** in a combined yield of 80%. Remarkably, both products were produced in 98% *ee* and essentially as single diastereomers. The relative and absolute stereochemistry of **10** was confirmed by conversion of **10** into the crystalline *p*-bromobenzoate **12** whose configuration was confirmed by X-ray crystallography.[7]

Having successfully completed the model studies, attention was then directed towards the total synthesis of erogorgiaene. The key step is the rhodium-catalyzed reaction between the vinyldiazoacetate **5** and the dihydronaphthalene (±)-**4** (Scheme 5). A comparison between the reaction of **5**

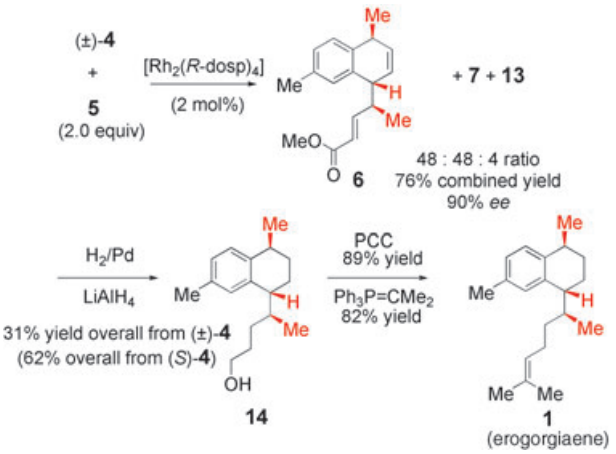


Rh^{II}	Yield [%] (6 + 7 + 13)	Ratio 6 : 7 : 13
$[Rh_2(OOct)_4]$	73	3 : 61 : 36
$[Rh_2(R\text{-dosp})_4]$	76	48 : 48 : 4

Scheme 5. Influence of catalyst $[Rh_2(R\text{-dosp})_4]$ on product distribution.

with (±)-**4** catalyzed by either rhodium octanoate or $[Rh_2(R\text{-dosp})_4]$ is very informative because it demonstrates the important role of $[Rh_2(R\text{-dosp})_4]$ not only to induce the enantioselectivity but also to achieve an effective C–H transformation. The reaction between **5** and (±)-**4** catalyzed by rhodium(II) octanoate results in the formation of only a trace of the combined C–H activation/Cope rearrangement product **6**. The major products are the diastereomeric cyclopropanes **7** and **13** (as racemic mixtures). In contrast, the reaction catalyzed by $[Rh_2(R\text{-dosp})_4]$ is truly exceptional and results in a 1:1 mixture of the combined C–H activation product **6** and the cyclopropane **7** with just a trace of the diastereomer **13**. Furthermore, **6** was formed in 90% *ee*.

The synthesis of (+)-erogorgiaene (**1**) was readily completed as illustrated in Scheme 6. Owing to the tendency of **6**



Scheme 6. Total synthesis of (+)-erogorgiaene (**1**). PCC = pyridinium chlorochromate.

to undergo a retro-Cope rearrangement, the combined mixture of **6** and **7** was globally hydrogenated, and the ester was reduced to the alcohol **14**, which was isolated in 31% overall yield from the dihydronapthalene (±)-**4** (62% yield from the matched enantiomer (*R*)-**4**). Oxidation of **14** to the aldehyde with pyridinium chlorochromate (PCC) followed by a Wittig reaction completed the total synthesis of (+)-erogorgiaene (**1**).

In summary, we have demonstrated that the combined C–H activation/Cope rearrangement protocol is an exceptional method for the construction of the three stereogenic centers common to the numerous diterpenes isolated from *Pseudopterogorgia elisabethae*. The synthetic potential of this chemistry was demonstrated by means of a very direct synthesis of erogorgiaene. Further studies are in progress to apply this methodology to other members of this class of diterpenes.

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