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# Dialkoxycarbenes in (4 + 1) Cycloadditions: Application to the Synthesis of Carotol

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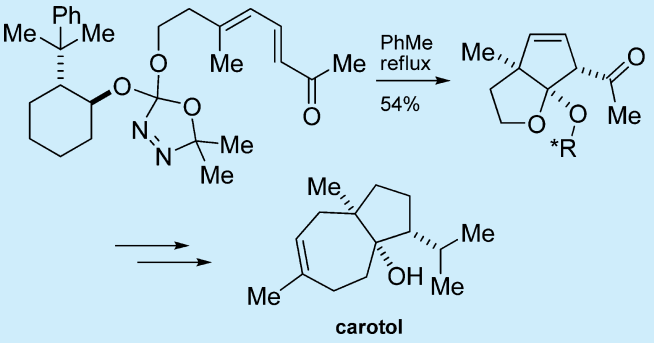
Supporting Information

**ABSTRACT:** Dialkoxycarbenes are more reactive than NHCs and participate in many reactions including a formal (4 + 1) cycloaddition with electron-deficient dienes. We have learned to control the relative stereochemistry of the newly created chiral carbons in this process and now report that, combined with a chiral auxiliary, it has been used successfully in a short and efficient synthesis of the sesquiterpene carotol.




Dialkoxycarbenes[1] (DACs) are the more reactive counterparts of the better known N-heterocyclic carbenes (NHCs)[2] and acyclic diaminocarbenes (ADCs).[3] Dialkoxycarbenes participate as nucleophilic species in reactions with carbonyls, alkenes, alkynes,[1] isocyanates,[4] and vinyl isocyanates.[5] We have ourselves described their reaction with electron-deficient dienes to give (4 + 1) cycloadducts.[6] The reaction takes place via a concerted (4 + 1) cycloaddition or a concerted cyclopropanation/vinylcyclopropane rearrangement, depending on the substrate structure.

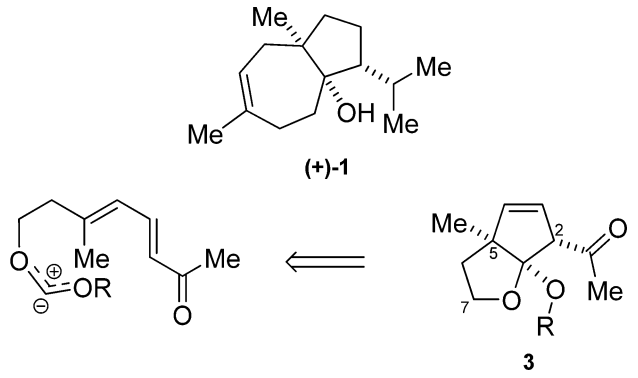
Dialkoxycarbenes can be generated easily using Warkentin's oxadiazoline method, but despite this fact, relatively few applications of DACs to the synthesis of natural products have been reported.[7] We wish to report a short and efficient synthesis of carotol and thus showcase the convenience of oxadiazolines as DAC precursors and the effectiveness of the (4 + 1) cycloaddition between DACs and dienes to construct natural products.

(+)-Carotol (**1**) is a daucane-type sesquiterpene found in the seeds and roots of many plants of the Apiaceae (carrots) and Zingiberaceae (ginger) families.[8] Controversy existed around its structure for a while,[9] but it was eventually proven by Šorm in 1959.[10] It has strong larvicidal[11] and antimicrobial[12] activities and acts as a potent olfactive attractant to the black bean aphid (*Aphis fabae*).[13]

We are aware of only one synthesis of (+)-carotol in very low yield from (+)-daucene by Levisalles and co-workers in 1972.[14] Approaches to the daucane skeleton have been reported, however.[15]

The diastereocontrol exerted over the C2−C5 relative stereochemistry by the length of the tether connecting the carbene to the diene in intermediate **2** is a key feature of our strategy (Scheme 1). When the tether is composed of three atoms, the formal (4 + 1) cycloaddition of carbene **2** will generate a 5−5 cis-fused ring system **3** having the C2−C5 relative stereochemistry as shown.[6] If the tether had been four or five atoms long, the C2−C5 stereochemistry of the corresponding oxabicyclic cycloadducts would have been the opposite of that shown for product **3**. For many synthetic targets, the length of the tether is of little consequence after the cyclic acetal has been opened. The three-atom tether supplies the right number of carbons to efficiently complete the syntheses of members of this family of sesquiterpenes.

**Scheme 1. Retrosynthetic Analysis for Carotol**




First, the carbene precursor **8a** was prepared starting from 3-butyn-1-ol (**4**), which was subjected to Negishi's carboalumination protocol to give vinyl iodide **5** (Scheme 2). The latter was efficiently coupled to methyl vinyl ketone via a Heck reaction to give diene **6** as a single *E,E* geometrical isomer. Submitting alcohol **6** to a catalytic amount of camphorsulfonic

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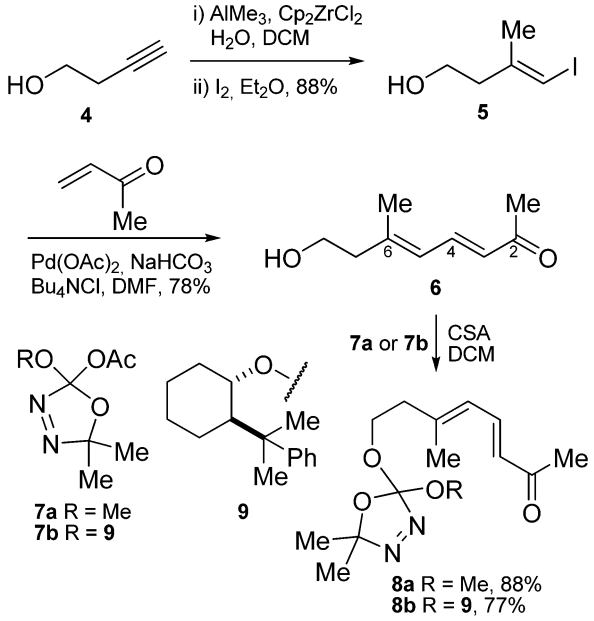
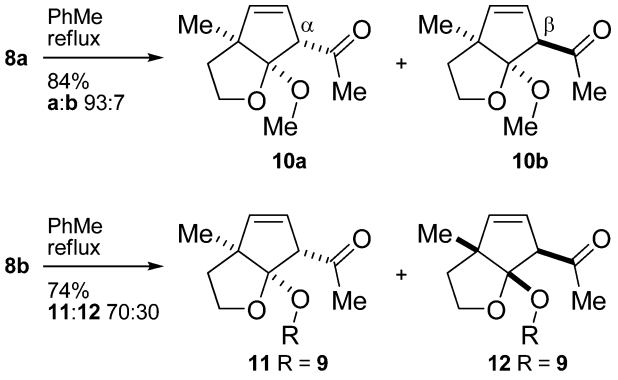
**Scheme 2. Preparation of the DAC Precursors 8a and 8b**




acid and Warkentin's oxadiazoline **7a** gave an excellent yield of the DAC precursor **8a**.

Heating a toluene solution of oxadiazoline **8a** to reflux temperature afforded an 84% yield of an expected 93:7 mixture of oxabicyclo[3.3.0]octenes **10a** and **10b**, which are easily separable by normal column chromatography (Scheme 3).

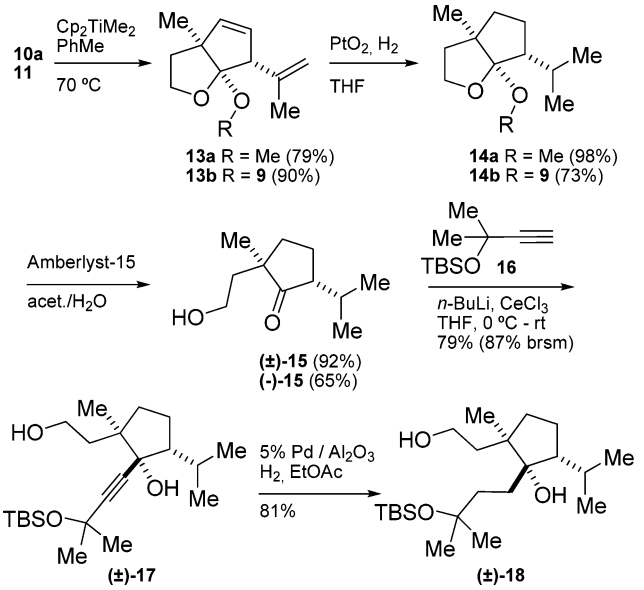
**Scheme 3. Key (4 + 1) Cycloadditions**




Their relative stereochemistries were assigned by NOESY experiments (see the Supporting Information). Then the chiral alcohol corresponding to structure **9** was transformed into the corresponding oxadiazoline **7b** following Warkentin's procedure (Scheme 2; see the Supporting Information for details). The exchange of acetate in **7b** for alcohol **6** was efficient, and the resulting chiral carbene precursor **8b** underwent the formal (4 + 1) cycloaddition with success in 74% yield (Scheme 3). The C2−C5 relative stereochemistry was unaffected by the chirality of the auxiliary, remaining >93:7. After separation, a 55% yield of optically pure oxabicycle **11** was isolated from a 70:30 ratio of diastereomers **11** and **12** in the crude mixture.

Converting the methyl ketone in **10a** or **11** to the isopropyl unit in **13a** or **13b**, respectively, was uneventful: the missing carbon was added using the Petasis reagent, and both double bonds were hydrogenated over platinum oxide (Scheme 4). Hydrolysis of the acetal in racemic **14a** or optically pure **14b**

**Scheme 4. Synthesis and Alkynylation of Ketones 15**




was best achieved with Amberlyst-15 resin and gave good yields of the corresponding keto alcohols (±)-**15** or (−)-**15**. In the latter case, the commercial chiral auxiliary (alcohol) could be recovered in 89% yield and reused. A very small amount of epimerization occurred, but the C2 epimer could easily be separated from (−)-**15**. Keto alcohol (−)-**15** had been made by Srikrishna and co-workers in eight steps from (+)-limonene.[16] We have made it in seven steps from 3-butyn-1-ol.

The optical rotation of (−)-**15** was compared with the one obtained by Srikrishna, and we thus could infer that the major diastereomer formed in the formal (4 + 1) cycloaddition was compound **11**.[17] The absolute stereochemistry of natural (+)-carotol was established in 1964.[18] In addition, the minor diastereomer **12** was also transformed into the corresponding diastereomer of **14b** (not shown), and X-ray diffraction analysis of a single crystal confirmed the assignation. The mechanism of the reaction proceeds via the formation of a cyclopropane,[6] which is the stereodetermining step, followed by rearrangement. Following our model,[6] we believe that the average of conformers **A** and **B**, lacking the steric interaction between the R group and the rest of the molecule, is favored over the average of conformers **C** and **D**, in which the R group is directed toward the forming ring (conformation D), leading to the preferred formation of **11** (Figure 1).

We then completed the synthesis of carotol using racemic alcohol **15**. We tried to add $sp^3$- or $sp^2$-hybridized carbon nucleophiles to ketone **15**, but all of our efforts were in vain (Scheme 4).[19] Only alkynylmetals successfully added to this rather hindered ketone. We tried several different ones and reaction conditions and opted for the cerium derivative of TBS-protected 2-methylbut-3-yn-2-ol (**16**).[20] The TBS protecting group also helps avoid inopportune hydrogenolysis of the adjacent C−O bond during the subsequent hydrogenation of the triple bond. This was best accomplished with Pd on alumina to give compound **18** in excellent yield.

The primary alcohol was oxidized with IBX, and the resulting aldehyde underwent a Wittig olefination to give product **19** (Scheme 5). After deprotection, the tertiary alcohol was submitted to Martin's sulfurane reagent to give the elimination product **20** with the terminal double bond as the major



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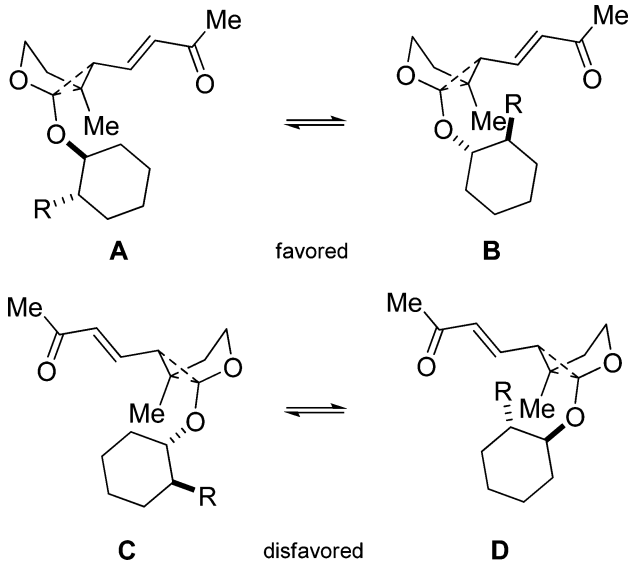
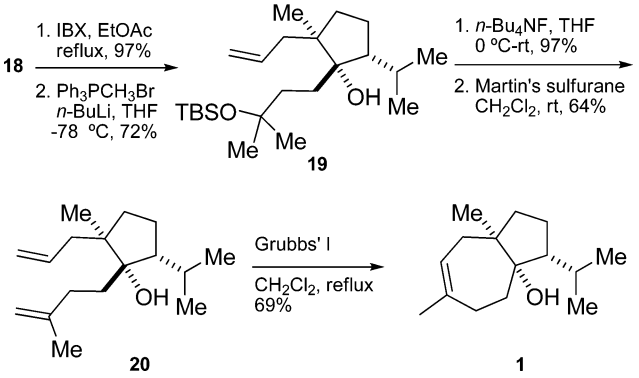



**Figure 1.** Suggested model for the diastereoselectivity.

**Scheme 5. Completion of the Synthesis of Carotol**




product. A ring-closing metathesis[21] gave pure racemic carotol in 69% yield from the mixture of alkene isomers (the corrected yield of the desired RCM product is 86%). Since we have in hand optically pure (−)-**15**, we have also achieved a formal synthesis of (+)-carotol. The synthesis has a total of 14 steps from the structurally very simple 3-butyn-1-ol, a global yield of 5.6% (counting the nonracemic route), and an average of 82% yield per step.

With this short synthesis of carotol, we have demonstrated the power of DACs as partners in (4 + 1) cycloadditions. It is noteworthy that an *all-carbon quaternary center* was thus created with control over its relative and absolute stereochemistry. Ketone **15** is a central fragment for many terpenoids of this type.[15]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02023.

Characterization data and copies of NMR spectra for new compounds and an ORTEP of compound **14b** (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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