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Olefin Cross-Metathesis as a Tool in Natural Product Degradation. The Stereochemistry of (+)-Falcarindiol

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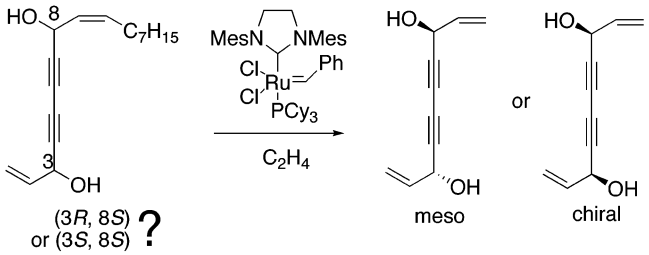
ABSTRACT



There are conflicting reports in the literature concerning the absolute sterochemistry at C-3 of the common plant polyacetylene oxylipin (+)-falcarindiol. We have employed olefin cross-metathesis using Grubbs' second generation catalyst and ethylene gas to degrade falcarindiol to the symmetrical 1,9-decadiene-4,6-diyne-3,8-diol. The reaction is completely selective for net removal of the aliphatic side chain. Degradation of (+)-falcarindiol from *Tetraplasandra hawaiiensis* yields a meso product as shown by chiral HPLC. Hence, (+)-falcarindiol from this source has a (3*R*,8*S*)-configuration.

As part of an ongoing research program on the discovery of new antitumor agents, we examined the organic extract of the Hawaiian endemic plant *Tetraplasandra hawaiiensis*. Bioassay-guided fractionation using a cytotoxicity assay led us to a group of oxylipins of which falcarindiol (+)-**1** was the major constituent.

During our efforts to determine the stereochemistry of the minor oxylipins from this extract we also reviewed the information available regarding (+)-falcarindiol. The absolute configuration of (+)-**1** from *Peucedanum oreoselinum* (entry 1, Table 1) had first been assigned as 3*R*,8*S* by Lemmich in 1981 on the basis of chemical correlation studies.[1] However, in 1996, a group from the NCI proposed a (3*S*,8*S*)-configuration for a similarly strongly dextrorotatory sample of (+)-**1** isolated from *Dendropanax arboreus* (entry 2, Table 1).[2] The assignment of the stereochemistry of the latter sample was based on an application of the advanced Mosher method.[3] It should be noted, however, that the analysis of chemical shift changes in bis-MTPA esters of 1,*n*-diols may be fraught with problems as demonstrated by Riguera.[4] In addition, in the case of (+)-**1**, one has to rely on the analysis of $\Delta\delta$-values from resonances for protons on only one side of the MTPA-plane, a practice that the developers of the method and also Riguera have cautioned against.[3,5]

Table 1. Optical Rotations and Assigned Configurations of Falcarindiol

entry	$[\alpha]_D$	assigned configuration	ref
1	+284[a]	3*R*,8*S*	ref 1
2	+300[b]	3*S*,8*S*	ref 2
3	+219.4[c]	3*R*,8*S*	refs 6 and 7
4	+302[a]	3*R*,8*S*	this work
5	+276[b]	3*R*,8*S*	this work
6	+250[c]	3*R*,8*S*	this work

[a] (*c* 1.0, ether). [b] (*c* 0.14, ether). [c] (*c* 4.6, $CHCl_3$).

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Without reference to the report from the NCI, in 1999 Cai et al. published a chemical synthesis of (+)-(3*R*,8*S*)-falcarindiol.[6] The stereocenters were introduced by transformations of L-tartaric acid and D-xylose. The former gave rise to the C-8 stereochemistry, while the latter was used to generate the absolute configuration at C-3. The synthetic product had an optical rotation and other spectroscopic data reportedly matching those of falcarindiol isolated from *Glehnia littoralis* (entry 3, Table 1).[7]

The sample of **1** that we had isolated from *T. hawaiiensis* showed optical rotations (entries 4−6, Table 1) matching (within experimental error) all of the literature values reported for either of the diastereomers of **1** for which an absolute configuration had been proposed. Hence an unambiguous assignment of the absolute configuration of our sample could not be made on the basis of the chiroptical data available in the literature. We therefore decided to pursue a determination by an independent method. We reasoned that a confirmation of either of the proposed absolute configurations might be obtained if it were possible to modify the C-1/C-2 and C-9/C-10 double bonds present in falcarindiol in such a way that a symmetrical compound is formed. The degradation product would either be meso or chiral if (+)-**1** possesses a (3*R*,8*S*)- or (3*S*,8*S*)-configuration, respectively. However, all attempts to reduce this idea to practice using oxidative methods on TBS-protected **1** failed, as no tractable products could be isolated.[8,9]

At this point we considered the use of olefin cross-metathesis on **1** as an alternative to oxidative degradation (Figure 1).[10]

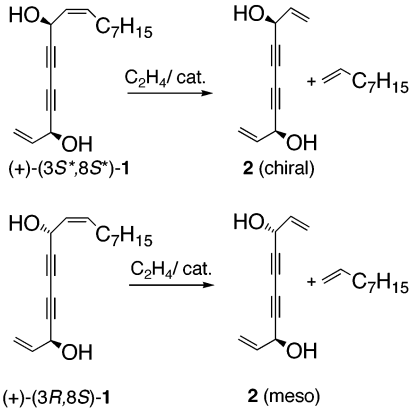
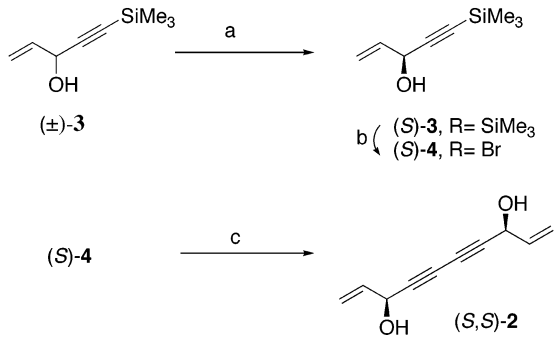


Figure 1. Hypothetical stereochemical consequences of the degradation of diasteroisomers of (+)-**1** by cross-metathesis.

In the simplest implementation of this approach, ethylene gas would serve as the second olefin in a reaction catalyzed by one of Grubbs' ruthenium carbenes. A review of the available literature did not reassure us that removal of the C-11 to C-17 chain, the desired reaction, would prevail over potential competing ones such as intermolecular enyne metathesis in the multifunctional environment of **1**.[11] However, side reactions proved to be much less of a problem than we had anticipated. Using the second-generation Grubbs catalyst (10 mol %, DCM, 16 h, room temperature, ethylene-filled double balloon, 1 mM (+)-**1**),[12] we observed a quantitative conversion (^{1}H NMR, TLC) of **1** to a single, slightly more polar compound. The product was isolated in 81% yield by careful chromatography and shown to be **2** (see Supporting Information). We deemed chromatography to be necessary due to the large specific rotation of **1**. Potential contamination of **2** by small amounts of **1** not detectable by ^{1}H NMR or TLC might induce a measurable optical rotation in samples of **2** and hence might lead to an erroneous conclusion as to its configuration. In the event, the crystalline sample of **2** isolated from the cross-metathesis reaction possessed marginal optically activity $[\alpha]_D$ +5 (*c* 3.8, $CHCl_3$), which was suspiciously low when compared to that of (+)-**1**.

For comparison purposes, we therefore prepared a synthetic sample of (*S*,*S*)-**2** shown in Scheme 1. Thus, 5-tri-

Scheme 1. Synthesis of (*S*,*S*)-1,9-Decadiene-4,6-diyne-3,8-diol[a]



[a] Reaction conditions: (a) lipase from *Pseudomonas fluorescens*, vinyl acetate, 4 Å MS, hexanes, room temperature, 20 h, 35%; (b) NBS, cat. $AgNO_3$, acetone, 3 h, 55%; (c) CuCl, $NH_2OH{\cdot}H_2O$, ethylamine, aqueous MeOH, room temperature, 16 h, 80%.

methylsilylpent-1-en-4-yne-3-ol (±)-**3** was resolved using lipase from *Pseudomonas*.[13] The remaining nonacylated (*S*)-**3**

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($[\alpha]_D$ +38 (*c* 2.0, $CHCl_3$), ≥95% ee) was desilylated and converted to bromide (*S*)-**4** using Isobe's convenient one-pot procedure.[14] Dimerization of (*S*)-**4** under Cadiot−Chodkiewicz conditions yielded (*S*,*S*)-**2** ($[\alpha]_D$ +102 (*c* 3.8, $CHCl_3$)).

The assignment of an (*S*)-configuration to the nonacylated (+)-enantiomer of **3**, and hence to (+)-**2**, rests on two lines of evidence. First, the results of an application of the advanced Mosher method to (+)-**3** are in accord with this assignment (see Supporting Information).[3] Compound **3** was chosen for the analysis because it bears the TMS group, which yielded one data point on the right side of the MTPA plane. Second, in resolutions of similarly substituted propargylic alcohols, the remaining starting material was shown to have an (*S*)-configuration.[13,15]

The low optical rotation of the sample of **2** from the degradation could be indicative of meso stereochemistry. However, a stereorandom sample of low or null optical activity might also result from epimerization of **1** or of **2** during the cross-metathesis by a variant of the hydride shift mechanism first proposed by Hoye.[16] To investigate this possibility we resorted to analytical HPLC on a chiral stationary phase.

Upon chromatography on a Chiralcel OD column, a sample of symmetrical diol **2** derived from (±)-**4** yielded three well-resolved peaks in a 1:2:1 ratio. This result, albeit not necessarily in that elution order, is to be expected in a successful separation and resolution of a statistical mixture of meso and chiral diastereomers. Synthetic (+)-(*S*,*S*)-**2** from dimerization of (+)-**4** showed only one peak, which coincided with the last-eluting peak from the stereorandom sample of **2**. Last, **2** obtained from degradation of (+)-**1** from *T. hawaiiensis* gave rise to only one peak, which eluted at the same retention time as the large peak due to the meso diastereomer of **2** in the synthetic sample (see Supporting Information). This result suggests that epimerization does not accompany cross-metathesis when (+)-**1** is being degraded to **2** because the product is the pure meso isomer. It is important to note that the same meso isomer is also found exclusively if the crude degradation reaction mixture is analyzed directly by chiral HPLC without prior purification and crystallization of **2**. In an additional control experiment, (+)-**2** was subjected to the cross-metathesis conditions used for degradation of (+)-**1**. This did not result in any noticeable change in optical purity of (+)-**2** as shown by chiral HPLC analysis of the crude reaction mixture and by polarimetry.

The present results prove unambiguously that (+)-**1** from *T. hawaiiensis* has the same (3*R*,8*S*)-stereochemistry as the material obtained by Cai et al. through total synthesis. Upon cross-metathesis with ethylene, a sample of this configuration is expected to yield the meso isomer of **2**, as is observed experimentally.

Having established the absolute stereochemistry of (+)-**1** from *T. hawaiiensis* unambiguously, we were then able to validate the advanced Mosher method for application in such diyne−diol systems. The result of an analysis of the $\Delta\delta(\delta_S - \delta_R)$ values of the bis-MTPA esters according to the established model was in accordance with (3*R*,8*S*)-stereochemistry of this sample. The resonances for protons H-9, H-10, and H-11 all showed positive $\Delta\delta$ values, while those of the resonances for H-1_E, H-1_Z, and H-2 were all negative. The sample of (+)-**1** from *D. arboreus* (entry 2, Table 1) had shown all negative $\Delta\delta$ values, which had been interpreted as indicating a (3*S*,8*S*)-configuration.[2] Our results, being clearly different, indirectly support this assignment. Unfortunately, we were not able to obtain a sample of this material for degradation by our method for a rigorous confirmation. However, it appears that Nature does indeed elaborate two diastereomeric forms of (+)-**1**, which cannot be distinguished by polarimetry. Hence, all assignments of stereochemistry to samples of **1** and analogous compounds using this latter method must be regarded as suspect.

In conclusion, we have demonstrated that olefin cross-metathesis using ethylene can be a viable alternative to the classical oxidative degradation procedures for natural products containing double bonds. Olefin metathesis has revolutionized synthetic organic chemistry. This is a consequence of the outstanding functional group tolerance of Grubbs' and Schrock's metathesis catalysts, which are all commercially available.[17,18] Our results suggest that natural product chemists interested in structure elucidation may derive a similar benefit especially from the use of the robust and easy-to-handle Ru-based catalysts.

It is worth noting that our earlier attempts to perform the metathesis reaction on TBS-protected **1** were unsuccessful. Furthermore, in the present circumstance, the use of ethylene as the donor olefin proved to be preferable over the more nucleophilic allyltrimethylsilane because the latter yielded an inseparable mixture of olefin geometrical isomers.[19]

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Supporting Information Available: Experimental procedures for the preparation of (+)-**2**, ^{1}H NMR data for configuration analysis and optical purity determination of (+)-**3**, chiral HPLC chromatograms of **2**, Mosher analysis of (+)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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