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Conformational effects and stereocontrol in synthesis studies of medium-ring dolabellane carbocycles

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Dedicated to Harry H. Wasserman, scientist, artist and friend

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ABSTRACT

Stereoselective reactions are described which lead to functionalization of the dolabellane skeleton. The stereoselectivity is attributed to conformational effects imposed by the eleven-membered ring. An efficient pathway provides for the stereocontrolled synthesis of nonracemic 6(*S*)-hydroxy-4(*E*)-dolabellene-3-one **12** and related derivatives.

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Introduction

The dolabellanes are a significant family of diterpene natural products which exhibit a common [9.3.0] cyclotetradecane framework as shown in **1** (Fig. 1). Metabolites isolated from the digestive glands of the sea hare, *Dolabella californica*, were first described as dolabellanes by Faulkner, Clardy, and coworkers in 1976.[1] Subsequent studies have shown that dolabellanes are widely distributed among various species in the marine habitat, and are also found as secondary metabolites of fungi, liverwort, and higher plants.[2] In many cases, the eleven-membered carbocycle of **1** is elaborated by oxidation processes leading to the incorporation of carbonyl and hydroxyl functionality as well as epoxides and bridging ethers. In addition, the dolabellanes occupy a key biosynthetic branch point leading to the 5-7-6 dolastanes and the 5-8-5 tricyclic fusicoccanes.[3] Prior studies have described noteworthy strategies for the synthesis of representative metabolites featuring the eleven-membered carbocycle.[4] However, little information is known regarding the tactical efforts for reactions leading to regio- and stereocontrolled functionalization of the bicyclic [9.3.0] skeleton. Herein, we communicate studies which result in the stereoselective introduction of hydroxy substitution in the eleven-membered dolabellane system. Our findings indicate a substantial conformational bias in these [9.3.0] cyclotetradecanes which is exploited for the synthesis of nonracemic 6(*S*)-hydroxy-4(*E*)-dolabellene-3-one and related derivatives.

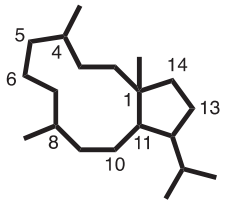

Figure 1. Dolabellane skeleton (**1**).

Results and discussion

We have previously demonstrated the direct formation of the eleven-membered ring of **2** (Scheme 1) via the intramolecular condensation of a reactive α-sulfonylcarbanion with a tethered α,β-unsaturated aldehyde.[5] Subsequent oxidation of the β-hydroxy sulfone **2** has provided enone **3** for further studies. General methodology for oxidative desulfonylation of **3** using the Davis oxaziridine **4** and KO^{t}Bu in THF yields the α-diketone **5** (86%),[6] and reduction with $LiBH_4$ leads to the diol **6** as a single diastereomer. Proton NMR data indicates H_A of **6** as a doublet at δ 4.18 (d, J = 8.2 Hz), but this information is insufficient for the unambiguous assignment of diol stereochemistry. Conversion to the acetonide **7** proceeds uneventfully, and the NMR spectrum of **7** is characterized by H_A (δ 4.56 (d, J = 6.2 Hz)) for the *trans*-fused dioxolane system.

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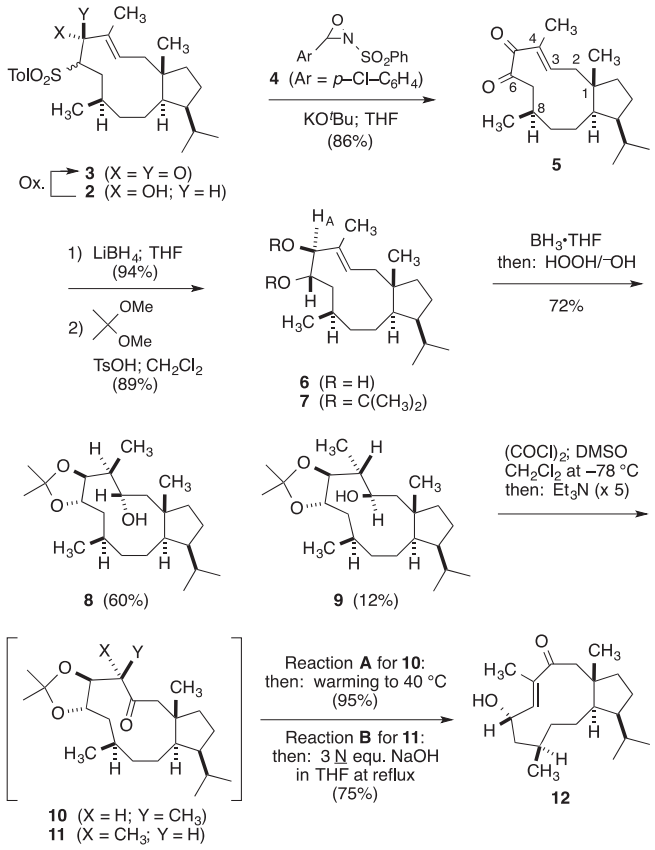


Scheme 1. Synthesis of the γ-hydroxy enone **12**.

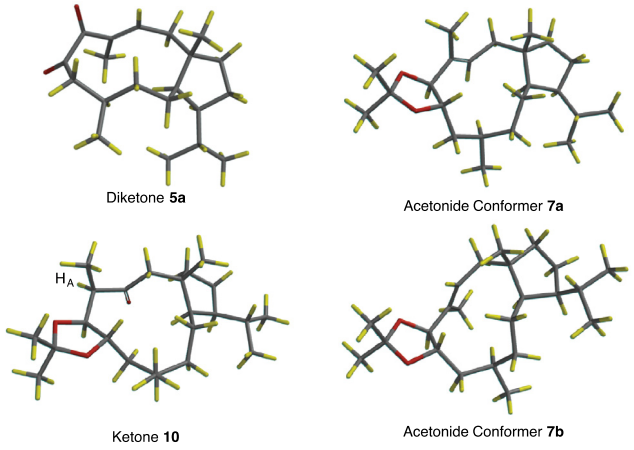


Figure 2. Conformations of substituted dolabellanes.

An evaluation of the NMR data of our reaction products requires the examination of conformations of the eleven-membered system.[7] Analysis of these conformational states also provides important insights, which support a rationale for several unanticipated experimental observations. For example, our modeling study[8] of diketone **5** indicates that an initial lithium borohydride reduction of the nonconjugated carbonyl in conformer **5a** (Fig. 2) results in an alkoxyborohydride species which internally delivers a second hydride to produce the *trans*-diol. Acetonide **7** is characterized by two interconverting rotamers **7a** and **7b** (Fig. 2) which individually expose each face of the C=C double bond for electrophilic attack from the exterior of the ring system.

Thus, hydroboration of **7** results in a separable mixture of alcohol diastereomers **8** and **9** (ratio 5:1) as shown in Scheme 1.[9] Subsequent oxidation to the corresponding ketones reveals a marked difference in the observed reactivity of these products toward further β-elimination. The conformation of the ketone derived from **8**, as illustrated in **10** (Fig. 2), permits the alignment of the α-hydrogen (H_A) for deprotonation and for the formation of the *Z*(O) enolate. Furthermore, the C—O bond of the leaving group at the β position can achieve a perpendicular orientation to the plane of the enolate resulting in the observed (*E*)-γ-hydroxy enone **12** of Scheme 1 in 95% yield. The epimeric ketone **11** as derived from alcohol **9** is surprisingly stable. In fact, our modeling indicates that H_A in **11a** (Fig. 3) is not available for deprotonation due to an unfavorable dihedral angle H_A—C—C—O (∠172°). However, the acidity (pK_a) of H_A is restored by rotation to the less stable conformation of **11b** which may lead to the formation of the *E*(O)-enolate. This enolate cannot undergo β-elimination because the C—O bond lies approximately within the plane of the enolate (∠180°). As a result, the *E*(O)-enolate provides for C-3 epimerization leading to **10** for the conversion to a single γ-hydroxy enone **12**. This elimination requires an additional step of heating the stable ketone **11** with 3 N aqueous NaOH in THF for 3 h at reflux.

Swern oxidation of **12** affords the *E*-enedione **13** (Scheme 2) as characterized by the appearance of a vinyl hydrogen singlet at $\delta = 6.91$ (s, 1H) in the NMR spectrum. The *E*-C=C geometry is supported by the absence of an NOE enhancement upon irradiation of the neighboring methyl group ($\delta = 1.98$ (s, 3H)). However, repeated attempts fail to form an enolate of **13** as indicated by the recovery of starting material without evidence of deuterium incorporation. Prolonged exposure of **13** to excess LDA in THF at 22 °C produces the alcohol **12** by an unusual hydride transfer in a similar fashion to the Meerwein–Pondorf–Verley reduction.[10] Reactions of enedi-

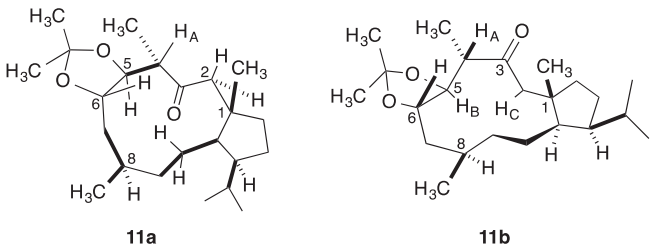
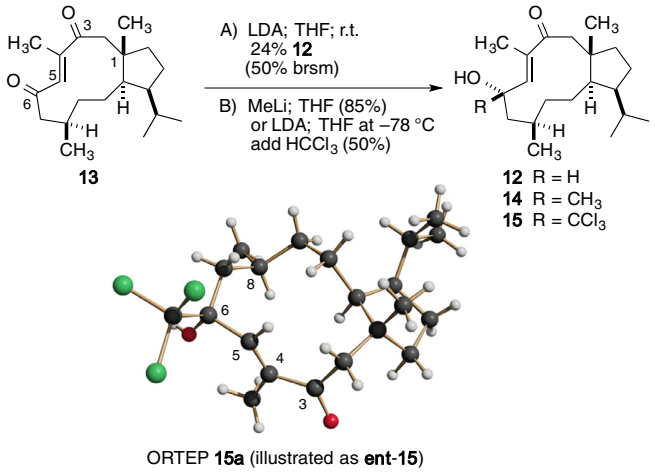


Figure 3. Conformation effects in ketone **11**.



Scheme 2. Reactions of *E*-4-dolabellene-3,6-dione **13**.

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