Graphical Abstract

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

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

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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**. 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

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

occupy a key biosynthetic branchpoint leading to the 5-7-6 dolastanes and the 5-8-5 tricyclic fusicocanes.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.

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^tBu in THF yields the α -diketone **5** (86%),⁶ and reduction with LiBH₄ 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.

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

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[†] Dedicated to Harry H. Wasserman, scientist, artist and friend.

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

modeling study⁸ of diketone **5** indicates that an initial lithium borohydride reduction of the nonconjugated carbonyl in conformer **5a** (Figure 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** (Figure 2) which individually expose each face of the $\text{C}=\text{C}$ 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** (Figure 2), permits the alignment of the α -hydrogen (H_A) for deprotonation and for the formation of the *Z*(O) enolate.

Figure 2. Conformations of substituted dolabellanes.

Furthermore, the $\text{C}-\text{O}$ 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** (Figure 3) is not available for deprotonation due to an unfavorable dihedral angle $\text{H}_\text{A}-\text{C}-\text{C}-\text{O}$ ($\angle 172^\circ$). However, the acidity ($\text{p}K_\text{a}$) of H_A is restored by rotation to the less stable conformation of **11b** which may lead to formation of the *E*(O)-enolate. This enolate cannot undergo β -elimination because the $\text{C}-\text{O}$ bond lies approximately within the plane of the enolate ($\angle 180^\circ$). 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 hours at reflux.

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

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*- $\text{C}=\text{C}$ 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 similar fashion to the Meerwein-Ponndorf-Verley reduction.¹⁰ Reactions of enedione **13** with methyl lithium in THF at -78°C result in a single tertiary alcohol. The assignment of stereochemistry of this product has proven to be challenging and derivatives of this hindered alcohol are difficult to prepare. This issue is resolved by the addition of the trichloromethyl anion as derived by the introduction of a small quantity of chloroform into LDA solutions of **13** at -78°C . X-ray analysis of the highly crystalline alcohol **15** has unambiguously established the stereochemistry of the newly formed chiral center as well as the *E*-double bond as displayed in the ORTEP **15a**.¹¹

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

Our studies have also explored oxidations of the conjugated diene **16** as a potential precursor to the isomeric Z-enedione **17** (Scheme 3).¹² Diene **16** is efficiently produced from the β -hydroxy sulfone **2** of Scheme 1 by mesylation and elimination ((a) MsCl; pyr; (b) then NaH in THF/DMF (2:1) at 22 °C (90% yield)). Photo-oxygenation of **16** leads to an interesting result as these reactions produce an Alder ene hydroperoxide. Direct reduction of this hydroperoxide with Al(Hg) in ether results in the formation of an allylic alcohol **18** with complete stereoselectivity (50% yield; 62.5% brsm). The assignment of stereochemistry is complicated by NMR studies that show unusual NOE enhancements of the vinylic hydrogens at δ 7.40 (H_D) and δ 5.61 (H_B) upon irradiation of the allylic methine hydrogen (H_A) at δ 4.44. The presence of the hydroxy moiety is confirmed by a facile Swern oxidation to yield the ketone **19** (75%). The stereochemical assignment of the alcohol **18** is resolved by X-ray crystallography (ORTEP **20**),¹³ which indicates that the *exo*-methylene is conformationally orthogonal to the plane of the α,β -unsaturated sulfone. This conformation of the eleven-membered ring places the three hydrogens H_A , H_B and H_D in close proximity as confirmed by the results of the NOE experiments.

Scheme 3. Oxidation of diene **16**.

Conclusion

In summary, our studies have demonstrated high stereoselectivity for several useful reactions which lead to functionalization of the intact dolabellane diterpene skeleton. Our investigations indicate that the eleven-membered carbocyclic system displays significant conformational bias. These qualities have led to surprising reactivity in some cases. Studies have described a stereocontrolled preparation as well as a preliminary assessment of reactivity of 6(*S*)-hydroxy-4(*E*)-dolabellene-3-one as an advanced intermediate for synthesis of complex members of the diterpene family.

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- Conformers of Figure 2 were generated using the Spartan '10 graphic user interface (version 1.1.0) (Wavefunction, Inc.; www.wavefun.com).
- Characterization data are provided for compounds of Scheme 1. *Trans*-diol **6**: $[\alpha]_D^{24}$ -0.07° (c 3.05, CHCl₃); FTIR 3415, 2960, 1450, 1380, 1215, 1005, 910 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.53 (m, 1H), 4.18 (br d, J = 8.2 Hz, 1H), 4.10 (m, 1H), 2.24 (t, J = 12.1 Hz, 1H), 2.10 (br m, 1H), 1.82 (s, 3H), 1.72–1.10 (m, 14H), 1.01 (s, 3H), 0.95 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 6.2 Hz, 3H), 0.84 (d, J = 6.2 Hz, 3H); HRMS (CI, NH₃) m/z calcd for C₂₀H₃₄O (M – H₂O)⁺ 290.2605, found 290.2611. Alkene **7**: mp 91–92 °C; $[\alpha]_D^{24}$ $+0.3^\circ$ (c 0.4, CHCl₃); FTIR 2950, 1455, 1370, 1250, 1215, 1025, 890 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.52 (dd, J = 11.0, 4.5 Hz, 1H), 4.55 (d, J = 6.5 Hz, 1H), 4.41 (m, 1H), 2.24 (m, 1H), 1.91 (dd, J = 13.0, 5.0 Hz, 1H), 1.77 (s, 3H), 1.74–1.58 (m, 4H), 1.55–1.48 (m, 3H), 1.4 (m, 2H), 1.53 (s, 3H), 1.36 (s, 3H), 1.34–1.19 (m, 4H), 1.06 (m, 1H), 0.94 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 132.97, 125.30, 107.76, 82.99, 77.98, 49.88, 45.01, 44.35, 43.56, 42.99, 36.67, 34.73, 27.56, 27.18, 26.62, 25.56, 25.19, 24.06, 23.32, 23.22, 22.17, 21.23, 14.76; HRMS m/z calcd for C₂₃H₄₁O₂ (M+H)⁺ 349.3108, found 349.3102. Alcohol **8**: $[\alpha]_D^{24}$ -0.5° (c 0.4, CHCl₃); FTIR 3490, 2940, 1460, 1370, 1255, 1210, 1060, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.36 (m, 1H), 4.13 (dd, J = 11.0, 7.0 Hz, 1H), 3.62 (td, J = 11.0, 5.5 Hz, 1H), 2.33 (m, 1H), 2.28 (dd, J = 10.0, 7.0 Hz, 1H), 2.05 (m, 1H), 1.93 (m, 1H), 1.86–1.74 (m, 3H), 1.76 (m, 1H), 1.70 (m, 1H), 1.51 (s, 3H), 1.50–1.26 (m, 8H), 1.37 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H); ¹³C NMR

- (500 MHz, CDCl₃) δ 108.44, 79.96, 77.91, 76.08, 55.32, 51.62, 47.14, 45.20, 42.68, 37.45, 36.61, 32.10, 27.02, 26.28, 26.14, 25.14, 23.74, 23.48, 22.89, 22.37, 21.57, 18.09; HRMS m/z calcd for C₂₂H₃₉O₃ (M – CH₃)⁺ 351.2901, found 351.2878. Alcohol **9**: $[\alpha]_D^{24}$ –2.0° (c 0.20, CHCl₃); FTIR 3480, 2940, 1455, 1375, 1260, 1210, 1005 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 4.44 (dd, J = 7.5, 7.0 Hz, 1H), 4.05 (dd, J = 7.0, 1.5 Hz, 2H), 2.09 (m, 2H), 1.74–1.55 (m, 5H), 1.49–1.36 (m, 5H), 1.50 (s, 3H), 1.34 (s, 3H), 1.30–1.18 (m, 5H), 1.03 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.75 (s, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 107.12, 83.49, 74.39, 66.13, 46.03, 45.27, 43.96, 40.86, 40.27, 37.62, 32.89, 28.37, 26.75, 25.13, 24.33, 24.02, 23.94, 23.81, 22.58, 20.51, 20.28, 12.69; HRMS m/z calcd for C₂₂H₃₉O₃ (M – CH₃)⁺ 351.2901, found 351.2895. Hydroxy enone **12**: $[\alpha]_D^{25}$ +1.0° (c 0.40, CHCl₃); FTIR 3440, 2950, 1700, 1645, 1450, 1380, 1210, 1035 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 6.73 (br d, J = 7.4 Hz, 1H), 4.86 (m, 1H), 2.75 (AB, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ = 227.8 Hz, 2H), 2.21–1.88 (m, 3H), 1.86–1.15 (m, 11H), 1.78 (s, 3H), 1.03 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.76 (s, 3H); HRMS (CI, NH₃) m/z calcd for C₂₀H₃₁O₂ (M + H)⁺ 307.2638, found 307.2634. Ene-dione **13**: $[\alpha]_D^{25}$ +0.5° (c 0.40 CHCl₃); FTIR 2950, 1695, 1670, 1620, 1460, 1380, 1375, 1270, 1215 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 6.90 (s, 1H), 2.97 (d, J = 12.5 Hz, 1H), 2.58 (m, 1H), 2.48 (d, J = 12.0 Hz, 1H), 2.33 (dd, J = 12.5, 4.0 Hz, 1H), 1.98 (s, 3H), 1.74–1.25 (m, 12H), 1.02 (d, J = 6.5 Hz, 3H), 0.96 (s, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 204.80, 203.48, 145.56, 134.07, 50.46, 49.90, 47.75, 46.59, 46.05, 39.35, 35.90, 30.37, 27.96, 24.32, 24.06, 23.53, 22.11, 20.61, 19.85, 13.22; HRMS m/z calcd for C₂₀H₃₂O₂ (M)⁺ 304.2404, found 304.2395. Enone **15**: $[\alpha]_D^{26}$ –3.0° (c 0.30 CHCl₃); FTIR 3450, 2970, 1665, 1460, 1380, 1220, 1160 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 6.64 (s, 1H), 3.09 (d, J = 12.0 Hz, 1H), 2.53 (s, 1H), 2.28 (d, J = 12.0 Hz, 1H), 2.20 (dd, J = 14.0, 4.5 Hz, 1H), 2.12 (s, 3H), 1.83 (dd, J = 15.0, 4.5 Hz, 2H), 1.78–1.31 (m, 11H), 1.06 (d, J = 6.5 Hz, 3H), 0.92 (s, 3H), 0.89 (d, J = 6.5 Hz, 6H); ¹³C NMR (500 MHz, CDCl₃) δ 204.22, 143.48, 134.94, 110.14, 107.35, 88.70, 48.06, 47.19, 45.26, 43.45, 38.10, 36.64, 27.56, 26.14, 24.92, 24.85, 24.38, 23.97, 21.36, 20.64, 12.12; HRMS m/z calcd for C₂₁H₃₄Cl₃O₂ (M+H)⁺ 423.1619, found 423.1602.
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 11. CCDC 1035384 contains the supplementary crystallographic data for compound **15**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
 12. Characterization data is provided for compounds of Scheme 3. Diene **16**: $[\alpha]_D^{24}$ –40.3° (c 0.30, CHCl₃); FTIR 2950, 1615, 1600, 1450, 1380, 1300, 1145, 810 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 5.58 (d, J = 12.0 Hz, 1H), 2.67 (d, J = 16.5 Hz, 1H), 2.44 (s, 3H), 2.26 (t, J = 13.0 Hz, 1H), 1.87 (m, 2H), 1.78–1.70 (m, 2H), 1.72 (s, 3H), 1.61–1.54 (m, 4H), 1.44–1.32 (m, 4H), 1.26–1.04 (m, 4H), 0.97 (s, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H), 0.59 (d, J = 7.0 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 144.12, 141.86, 141.04, 136.76, 131.55, 129.87, 128.98, 128.67, 48.15, 46.69, 44.64, 44.59, 43.07, 35.85, 30.67, 28.92, 26.58, 26.32, 24.73, 24.29, 21.77, 21.66, 21.43, 20.63, 16.75; HRMS (CI, NH₃) m/z calcd for C₂₇H₄₁O₂S (M + H)⁺ 429.2829, found 429.2826. Alcohol **18**: mp 162–163 °C; $[\alpha]_D^{24}$ –3.0° (c 0.65, CHCl₃); FTIR 3500, 2940, 1600, 1450, 1380, 1280, 1140, 1080, 1010, 810, 745 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.75 (d, J = 7.5 Hz, 2H), 7.40 (s, 1H), 7.32 (d, J = 7.5 Hz, 2H), 5.61 (s, 1H), 5.35 (s, 1H), 4.44 (m, 1H), 2.55 (dd, J = 15.5, 9.0 Hz, 1H), 2.44 (s, 3H), 2.31 (dd, J = 15.5, 5.0 Hz, 1H), 2.22 (m, 1H), 1.84 (m, 2H), 1.71 (m, 2H), 1.62–1.09 (m, 9H), 0.88 (s, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H); HRMS (CI, NH₃) m/z calcd for C₂₇H₄₀O₃S (M⁺) 444.2700, found 444.2710. Ketone **19** (unstable): FTIR 3020, 2950, 1670, 1600, 1450, 1380, 1300, 1140, 1080, 945, 810, 660 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (m, 2H), 7.55 (s, 1H), 7.34 (m, 2H), 6.20 (br s, 1H), 5.70 (d, J = 2.3 Hz, 1H), 2.65 (AB, J_{AB} = 12.9 Hz, $\Delta\nu_{AB}$ = 49.1 Hz, 2H), 2.44 (s, 3H), 2.25 (d, J = 7.4 Hz, 2H), 1.94 (m, 1H), 1.85–1.20 (m, 11H), 0.94 (s, 3H), 0.83 (d, J = 6.2 Hz, 3H), 0.82 (d, J = 5.8 Hz, 3H), 0.80 (d, J = 6.0 Hz, 3H); HRMS (CI, NH₃) m/z calcd for C₂₇H₃₉O₃S (M + H)⁺ 443.2614, found 443.2607.
 13. CCDC 1035383 contains the supplementary crystallographic data for compound **18**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.