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Studies on the Dolabellanes: Stereoselective Transannular Cyclizations of Dolabelladiene Macrocycles.

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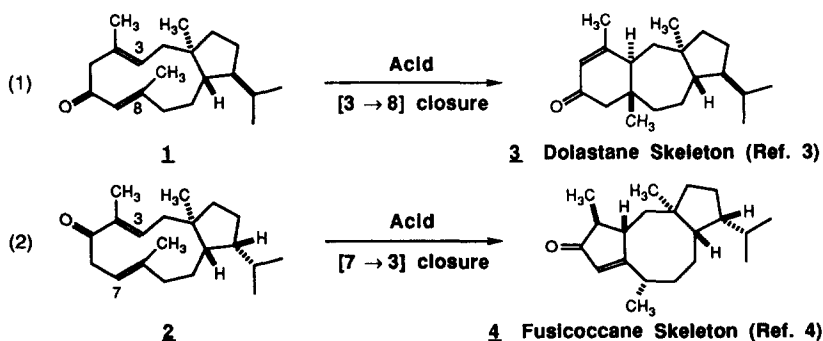
Key Words: Transannular cyclization, Michael conjugate additions

Abstract: Eleven-membered dolabelladiene carbocycles have been transformed into several tricyclic ring systems via efficient, stereocontrolled, transannular olefin-enone cyclizations. Ring contractions of the [9.3.0]cyclotetradecane nucleus have provided 5-7-6 dolastane and 5-8-5 fusicoccane carbocycles.

The dolabellanes are a diverse class of marine natural products characterized by a common bicyclic [9.3.0] cyclotetradecane skeleton.¹ Many of these compounds exhibit a range of biological properties including antimicrobial activity, antitumor activity, and antiviral action.² The dolabelladienes **1** and **2** may be important precursors to families of C₂₀-diterpenes which have fused 5-7-6 dolastane (**3**)³ and 5-8-5 fusicoccane (**4**)⁴ tricyclic structures. It is proposed that the tricyclic dolastanes are biosynthetically generated by cyclization from the dolabelladiene precursors.⁵

We have envisioned stereoselective construction of **3** and **4** via complementary transannular olefin-enone cyclizations of the 1,5-diene systems of **1** and **2** in conformationally controlled processes.

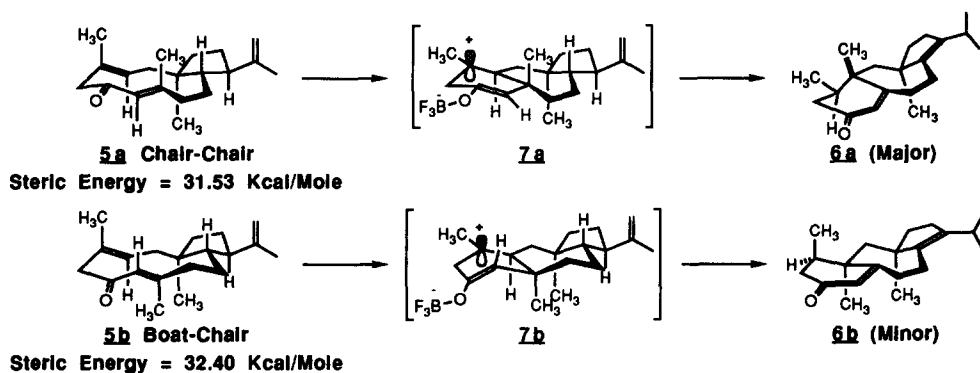
Scheme 1



Recently an intramolecular Julia condensation strategy was used to prepare the eleven-membered carbocycle of the dolabellanes.⁶ The rigid conformational properties of these macrocycles were demonstrated in a biomimetic synthesis of (-)-3 α ,4 β -dihydroxycyclavulara-1(15),17-diene in which a stereoselective transannular epoxy-olefin cyclization was used to generate the 5-7-6 tricyclic diterpene.⁷ Herein we report new findings of our preliminary investigations of the transannular olefin cyclization chemistry of the dolabelladienes. Stereoselective syntheses of several polycyclic systems are presented in which olefin-enone cyclizations of the dolabelladienes give rise to novel, ring-contracted products.

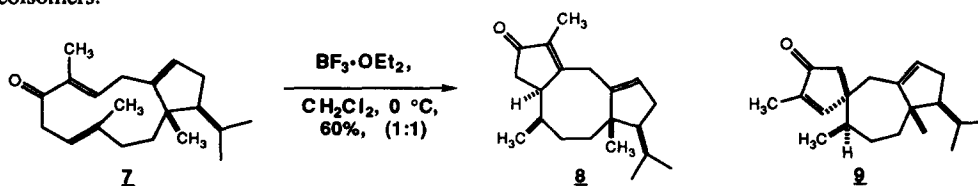
Formation of the dolastane skeleton (**3**) was investigated using the previously prepared dolabelladienone **5**.^{7a} Treatment of this enone (Scheme 2) with $\text{BF}_3 \cdot \text{OEt}_2$ led to the generation of a more polar, tricyclic product **6**. In fact, ^1H NMR analysis of the cyclization product indicated a mixture (6:1) of two isomers **6a** and **6b**. Formation of the tricyclic species, **6a/6b**, occurred via initial transannular bond formation [$\text{C}_3 \rightarrow \text{C}_8$] of the dolabelladiene **5** to give the boron enolates **7a/7b**. Successive suprafacial 1,2-hydrogen and 1,2-carbon migrations provided new tertiary carbocation intermediates for regeneration of the α,β -unsaturated system. Isomerization of the terminal olefin in **5** to the fully-substituted endocyclic position yielded the dolastane species **6a** and **6b**. Preparative thin-layer chromatography led to the purification of **6a** (mp 77-79 °C from Et_2O) for complete characterization.⁸ Molecular mechanics calculations (GMMX, Version 1.0)⁹ of **5** indicated two low energy conformations **5a/5b**, in which the chair-chair conformer is more stable by 0.9 kcal/mole. The observed stereochemistry of products **6a/6b**, as well as the product ratio is well correlated with this ground state analysis.

Scheme 2



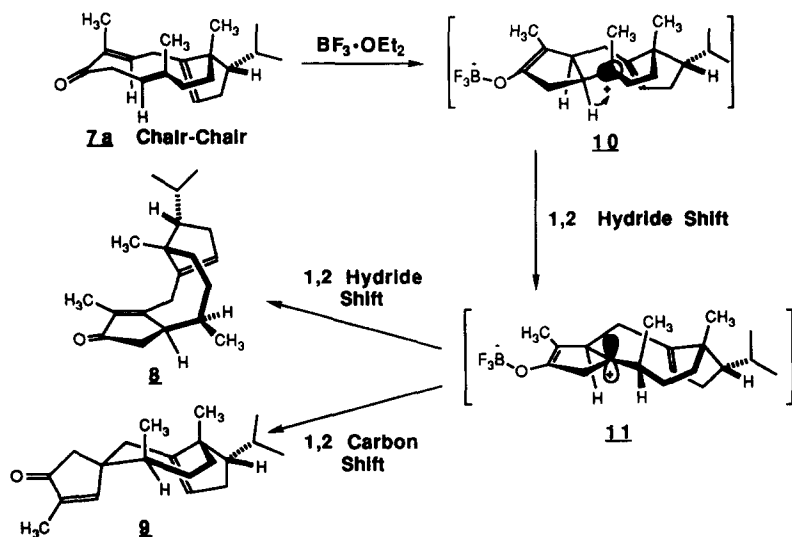
Conditions: $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , $0^\circ \rightarrow 22^\circ \text{C}$, 18 h, 83%, 6:1 ratio

To examine the reactivity of the isomeric enone system presented by **2**, our investigations have made use of dolabelladienone **7**.¹⁰ Treatment of **7** with freshly distilled $\text{BF}_3 \cdot \text{OEt}_2$ led to the rapid formation of two new crystalline products **8** and **9**. Spectral analysis indicated that these tricyclic species were produced as single stereoisomers.



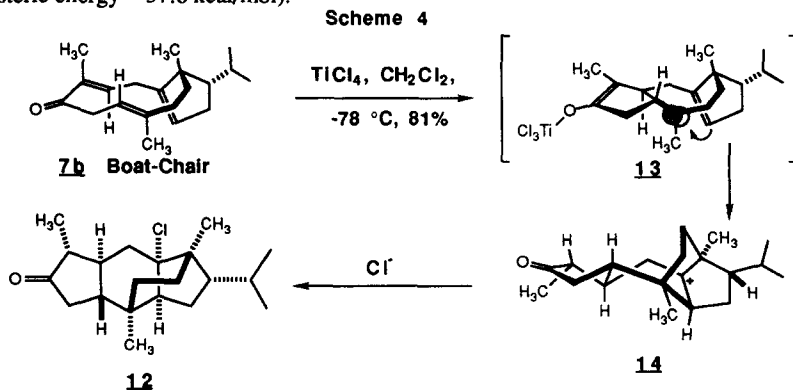
The structural assignments for **8** and **9** were firmly established by X-ray diffraction analyses.¹¹ The less polar ketone **8** (mp 74-78 °C) possessed the desired 5-8-5 fusicoccane skeleton. Constituent **9** (mp 81-83 °C) presented the spiroannulation of a cyclopentenone unit fused to a bicyclic 5-7 system. Both cyclization products **8** and **9** can be rationalized beginning with a single, chair-chair conformer **7a** of the dolabelladiene **7** (Scheme 3). Stereoselective formation of the 5-8-5 cyclization product **8** was rationalized by initial formation of the tricyclic boron enolate **10**.

Scheme 3



Two successive 1,2-hydride shifts followed by regeneration of the conjugated enone system provided **8** as single stereoisomer. Alternatively, formation of the spirocyclic product **9** occurred via a 1,2-carbon shift of the common carbocation **11**.

Employing titanium tetrachloride in place of $\text{BF}_3 \cdot \text{OEt}_2$ in the transannular cyclization of enone **7** resulted in the isolation of a new, crystalline product **12** (mp 123-125 °C), which had no olefinic carbons by ^{13}C NMR and presented a parent molecular ion ($M^+ + 1 = 323.2233$) which suggested incorporation of chloride. X-ray diffraction analysis afforded unambiguous assignment of the tetracyclic species **12**.¹² Formation of the bridged polycyclic system is proposed via transannular cyclization of the boat-chair conformer **7b** (Scheme 4) to give the transient cation **13**. In a second transannular cyclization, participation of the π -system of the C_{14} - C_1 olefin generates a new bridgehead carbocation **14**, followed by nucleophilic capture with chloride. Ground state molecular mechanics calculations performed on the dolabelladiene macrocycle **7** indicated that the boat-chair conformation **7b** was stabilized to a greater extent than the chair-chair conformer **7a** (**7a**, steric energy = 40.8 kcal/mol; **7b**, steric energy = 37.6 kcal/mol).⁹



In summary, our initial studies on the transannular reactivity of the dolabelladienones have demonstrated the suitability of these substrates for transformation into more complex, polycyclic systems. A high degree of stereoselectivity has been observed in these cyclizations which is attributable to conformational preferences of the eleven-membered ring. As a strategy for construction of polycyclic diterpenes, the ring contractions of dolabelladiene macrocycles offer significant opportunities for natural product synthesis.

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8. ¹H NMR data for **6g**: (400 MHz, C₆D₆) δ 5.93 (s, 1H), 2.52-2.44 (m, 2H), 2.30 (dd, *J* = 12.9, 3.2 Hz, 1H), 2.21-2.04 (m, 4H), 1.99 (ddd, *J* = 12.0, 5.5, 2.7 Hz, 1H), 1.83 (dt, *J* = 12.3, 2.4 Hz, 1H), 1.69-1.58 (m, 2H), 1.51-1.40 (m, 2H), 1.27 (d, *J* = 12.0 Hz, 1H), 0.94 (d, *J* = 5.5 Hz, 3H), 0.88 (d, *J* = 5.5 Hz, 3H), 0.83 (s, 3H), 0.66 (d, *J* = 5.4 Hz, 3H), 0.65 (s, 3H) ppm.
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10. For preparation of **7**, see the preceding communication: Williams, D.R.; Coleman, P.J. *Tetrahedron Lett.* **1994** this issue.
11. Crystallographic data for **8** and **9** are available from Indiana University Library. Request Molecular Structure Center Reports 94150 and 94128.
12. Crystallographic data for **12** are available from Indiana University Library. Request Molecular Structure Center Report 94132.

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