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

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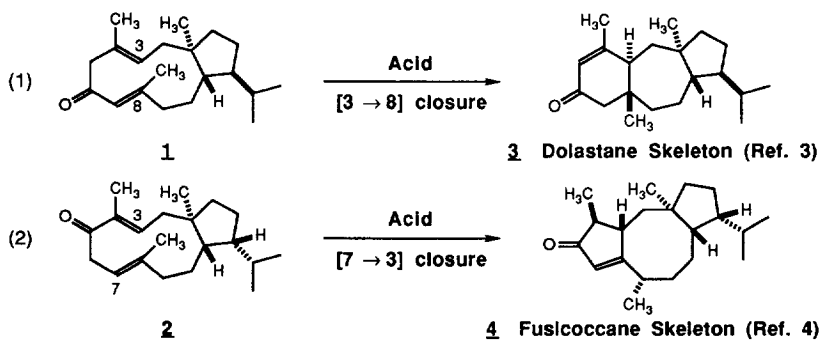
Abstract: *Eleven-membered dolabelladiene carbocycles have been transformed into several tricyclic ring systems via efficient, stereocontrolled, transannular olefin-enone cyclizations. Ring contractions of the [9.3.0]cyclotetradecane nucleus have provided 5-7-6 dolastane and 5-8-5 fusicoccane carbocycles.*

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 C_{20}-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.

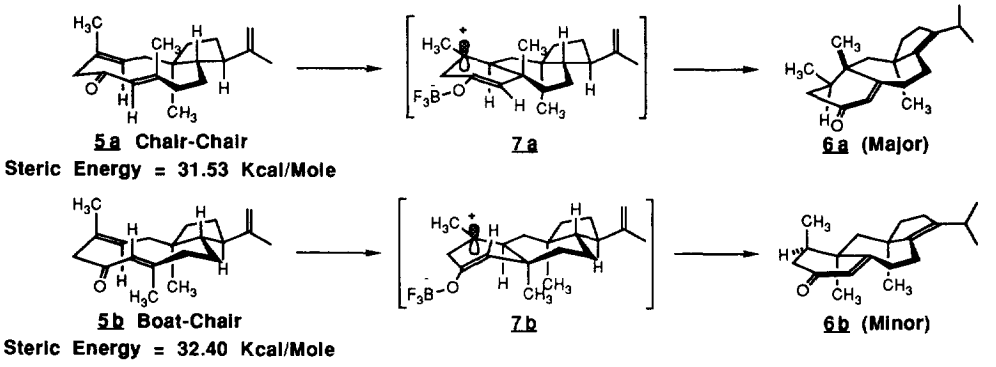
Scheme 1



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 (-)-3α,4β-dihydroxyclavulara-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.

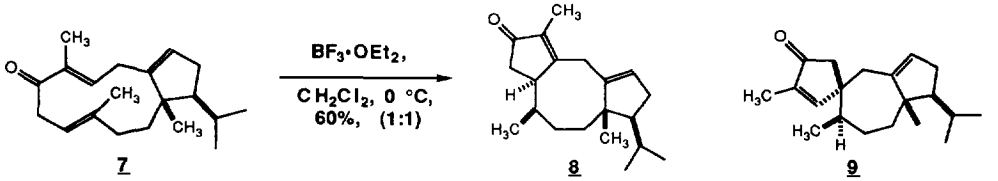
Formation of the dolastane skeleton (3) was investigated using the previously prepared dolabelladienone 5.[7a] Treatment of this enone (Scheme 2) with BF_3•OEt_2 led to the generation of a more polar, tricyclic product 6. In fact, ^1H NMR analysis of the cyclization product indicated a mixture (6:1) of two isomers 6a and 6b. Formation of the tricyclic species, 6a/6b, occurred via initial transannular bond formation [$C_3 \rightarrow C_8$] 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



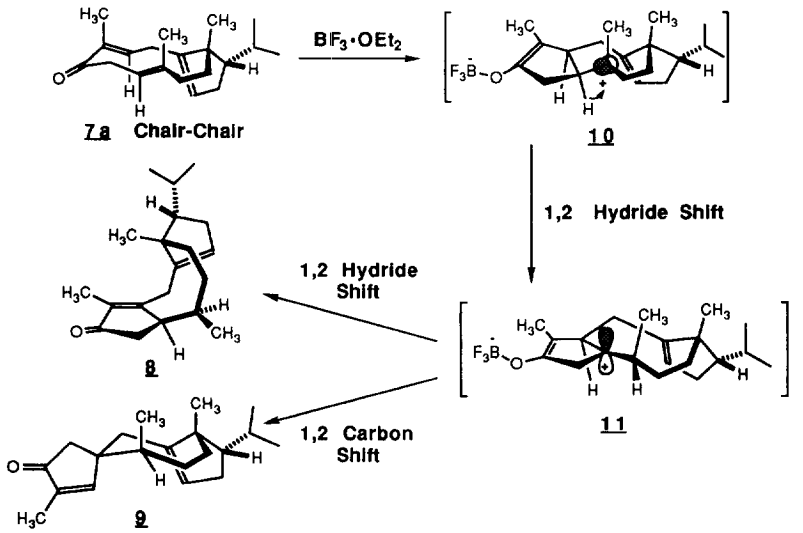
Conditions: BF_3•OEt_2, CH_2Cl_2, 0 ° → 22 °C, 18 h, 83%, 6:1 ratio

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 BF_3•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.

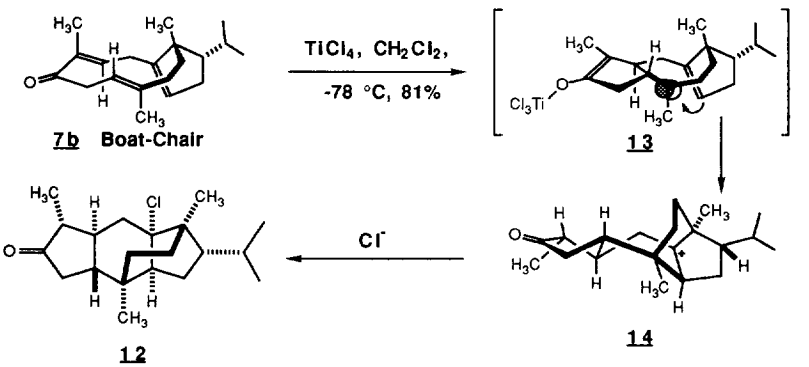
Scheme 3



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 BF_3•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]

Scheme 4



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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12. Crystallographic data for 12 are available from Indiana University Library. Request Molecular Structure Center Report 94132.

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