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An Efficient Synthesis of the Dolabellanes.

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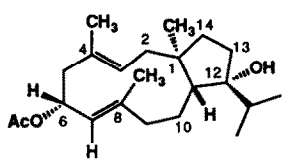
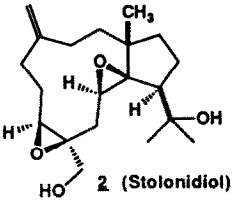
Key Words: Dolabellane synthesis; intramolecular Julia condensations

Abstract: *Eleven-membered carbocycles have been prepared by the intramolecular condensations of α-sulfonyl carbanions with α,β-unsaturated aldehydes Desulfonylation provides an efficient stereocontrolled synthesis of allylic alcohols featuring the [9.3.0] cyclotetradecane skeleton which characterizes the dolabellane diterpenes*

Marine diterpenes, exhibiting the bicyclic [9.3.0] skeleton, were first isolated from the opistobranch mollusk *Dolabella californica.*[1] In recent years, dolabellanes have been discovered in the brown seaweeds of Dictyotaceae,[2] the sea whips of *Eunicea*,[3] the liverwort *Odontoschisma denudatum*,[4] the mollusk *Aplysia dactylomela*,[5] and soft corals of *Clavularia.*[6a,b] Representative structures 1,[4] 2,[6a] and 3[6b] are illustrated.



1 (Acetoxyodontoschismenol)



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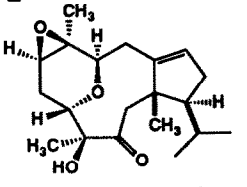


3 (Neodolabelline)

Nearly all of the dolabellanes exhibit antimicrobial activity against gram-positive and/or gram-negative bacteria. Many of these metabolites possess significant antitumor activity, and *in vivo* potency against influenza virus and adenovirus has been reported. Moreover, dolabelladienes (such as 1) certainly serve as direct biogenetic precursors of 5-7-6 tricyclic terpenes of the dolastane family,[7] many of which also display important antitumor activity. Herein we present our initial studies of a general synthesis pathway utilizing the intramolecular condensation of α-sulfonyl carbanions with remote aldehydes for preparation of fused [9.3.0] carbocycles. The ring closure process affords new allylic alcohols with high stereochemical control. These efforts have led to the efficient synthesis of two novel terpenes of the dolabellane class.

The installation of two appropriately functionalized alkyl chains on a preformed cyclopentane presents a common theme for our studies. A synthesis is illustrated in Scheme I for the specific case of the neodolabelladiene nucleus.[8] Thus, 2-methyl-2-cyclopentenone was efficiently transformed to racemic cyclopentanone 4.[9] Ketone 4 was converted into the corresponding vinylic iodide by treatment of its hydrazone with iodine and tetramethylguanidine at room temperature.[10] Desilylation and tosylation produced 5 in high yields. Elaboration of the $C_6 \rightarrow C_{10}$ side chain was accomplished with stereospecific preparation of the trisubstituted olefin.[11] Nucleophilic displacement of the primary sulfonate with lithium acetylide (ethylenediamine complex), and subsequent acylation gave an α,β-acetylenic ester for conjugate addition of benzenethiolate affording exclusively the *Z*-β-phenylthio-α,β-unsaturated ester. Copper (*I*)-catalyzed addition of methyl magnesium bromide produced 6 quantitatively with complete retention of alkene geometry. Hydride reduction of 6 and reaction with methanesulfonyl chloride in the presence of excess lithium chloride (2 equiv.) gave dihalogenated 7.

Scheme I. Formation of the Dolabellane Skeleton

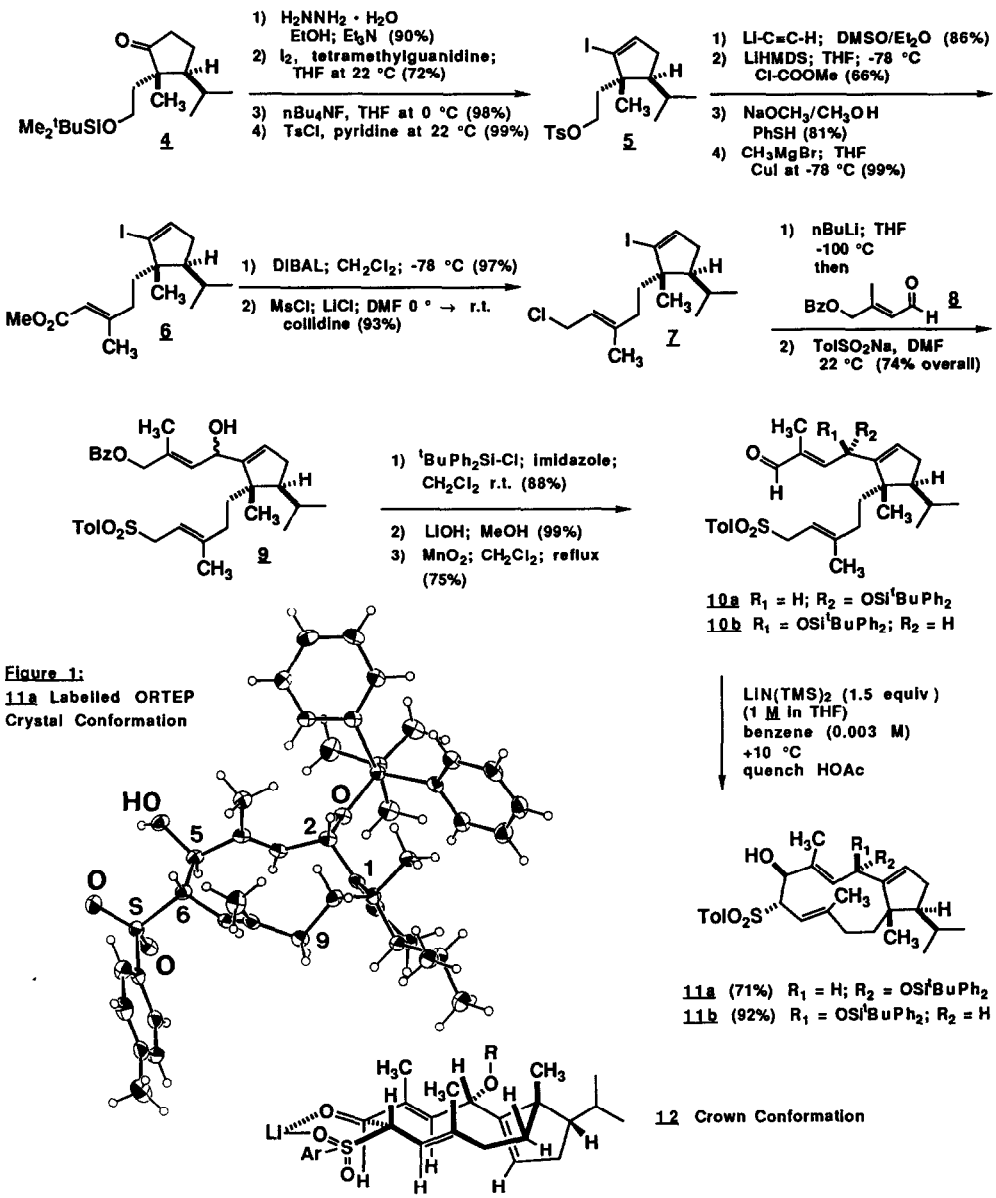
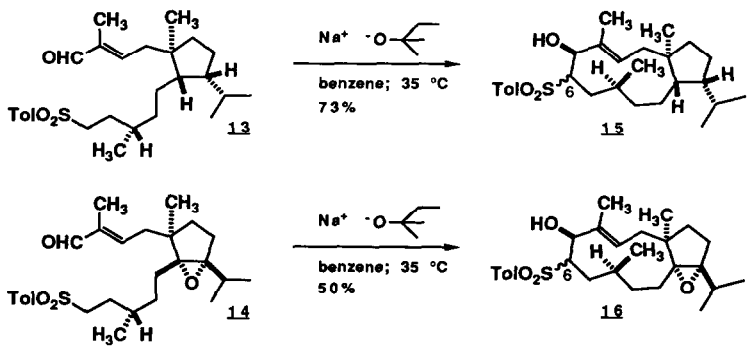


Figure 1:
11a Labelled ORTEP Crystal Conformation

Selective metal-halogen exchange of 7 with *n*-butyllithium at -100 °C was cleanly accomplished without adversely affecting the allylic chloride moiety. Trapping of the vinylic anion with aldehyde 8 provided a 1:1 ratio of diastereomeric alcohols. Crude reaction product was immediately treated with sodium sulfinate leading to purification of sulfones 9 in 74% overall yield for the two steps. Upon formation of their *tert*-butyldiphenylsilyl ethers, individual diastereomers were separated by flash chromatography, and saponification followed by MnO_2

oxidation gave the aldehydic sulfones 10a, b. Macrocyclizations of 10a, b were achieved upon addition of a slight excess of lithium bis(trimethylsilyl)amide (1.5 equiv.; 1 M in THF) into a benzene solution of 10a/10b at 10 °C. Reactions were immediately (within 5 min) quenched by addition of acetic acid, leading to a single new product 11a or 11b. Stereochemical assignments were achieved by ^{1}H-NMR decoupling studies and confirmed by X-ray diffraction analysis of one of our crystalline condensation products (Figure 1).[12,13] NOE studies have provided evidence of a rigid eleven-membered ring conformation not unlike the crystal structure.[2,3] Kinetic complexation of base with sulfone deprotonation could lead to an organized transition state 12. The diequatorial disposition of the β-hydroxysulfone also would suggest thermodynamic product development. No evidence for deprotonation and isomerization of the *bis*-allylic methine at C_2 was observed in traces of reisolated starting materials or crude reaction product.

Yoshii reported the first example of a Julia condensation as a strategy for macrocyclization in the synthesis of tetronolide.[14] Although Yoshii conditions were not successful for ring closure of 10a, b, we have utilized sodium *tert*-amylate for condensations of the saturated sulfone-aldehydes 13 and 14.[9] Thus, a benzene solution of aldehydic sulfone (1.27 g in 100 mL) was added (over 80 seconds) to a solution of base (10 equiv.) in benzene (180 mL at 35 °C) followed immediately by acetic acid quench (after 1 min.). Sulfone 13 gave two diastereomers 15 (ratios varied 3.5:1 to 1:1) in 73% yield, and 14 led to a 50% yield of 16 (ratio 1:1). All isomers were purified and characterized, demonstrating an epimeric stereorelationship at the carbon (C_6) bearing the sulfonyl unit. Pure products 15a and 15b were resubmitted to reaction conditions affording production of all four isomeric β-hydroxysulfones and regeneration of 13. However, considerable decomposition was observed in these experiments (1 hr).



Deployment of the Julia condensation strategy has efficiently provided dolabellanes as illustrated via sodium-amalgam desulfonylation of 11b with subsequent deprotection to yield 2(*S**),5(*R**)-dihydroxy-11(*S**),12(*S**)-neodolabell-3(*E*),7(*E*),14(1)-triene (17).[15] Alternatively, successive oxidations of 15a, b under Swern conditions at -78 °C followed by treatment with 2-[(p-chlorophenyl)sulfonyl]-3-(p-chlorophenyl)oxaziridine in the presence of *tert*-butoxide gave the $C_{5,6}$-diketone.[16] Reduction with $LiBH_4$ exclusively provided the *trans*-diol 19, [5(*R*),6(*R*)-dihydroxy-1(*S*),8(*S*),11(*R*),12(*S*)-dolabell-3(*E*)-ene].[17]

In conclusion, an intramolecular Julia condensation has yielded macrocyclization of [9.3.0] cyclotetradecanes with stereocontrol of a remote hydroxyl. Further studies of the dolabellanes are underway.

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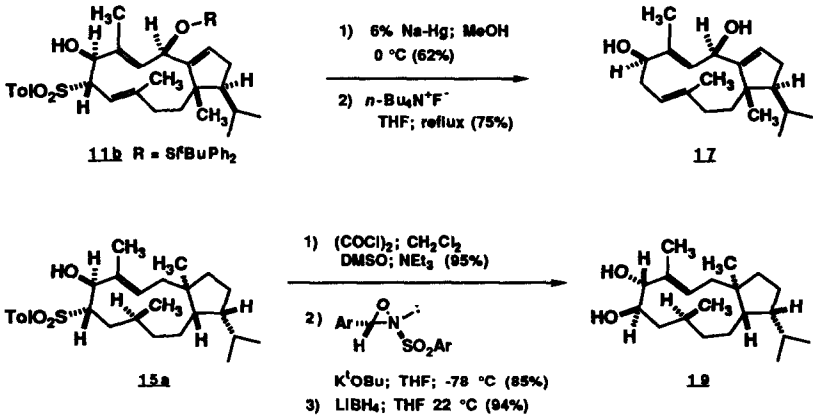

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12. Selected ^{1}H-NMR data for 11a: δ 6.07 (s, $C_{14}H$), 5.14 (d, J = 10 Hz, C_3H), 4.57 (d, J = 8.4 Hz, C_7H), 4.46 (d, J = 10 Hz, C_2H), 4.39 (d, J = 11.2 Hz, C_5H), 3.60 (dd, J = 8.4 Hz, J = 11.2 Hz, C_6H). For 11b : δ 5.22 (m, $C_{14}H$ and C_3H), 5.11 (d, J = 9.2 Hz, C_2H), 4.92 (d, J = 10 Hz, C_7H), 4.36 (d, J = 9.6 Hz, C_5H), 3.60 (dd, J = 9.6 Hz, J = 10 Hz, C_6H).
13. Structure determination of a colorless crystalline sample 11a (m.p. 147-149 °C; Hex/EtOAc) was established by X-ray diffraction at -175 °C. All atoms, including hydrogens, were refined by full-matrix least-squares to final residuals of R(F) = 0.0400 and R_W(F) = 0.0438. Crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 91260.
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17. The *trans* diol was characterized as its acetonide with a vicinal ^{1}H coupling of $J_{5,6}$ = 6.2 Hz. The C_6 stereochemistry was subsequently proven via an X-ray diffraction study of the γ-hydroxy-α,β-unsaturated ketone obtained from the acetonide of 19 via hydroboration-oxidation; Swern oxidation; and base-induced β-elimination. Details will be available in the full account.

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