

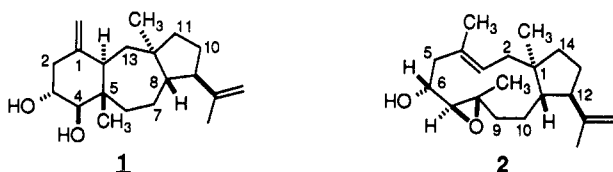
Synthesis Strategies for Marine Diterpenes. Total Synthesis of the Clavularanes

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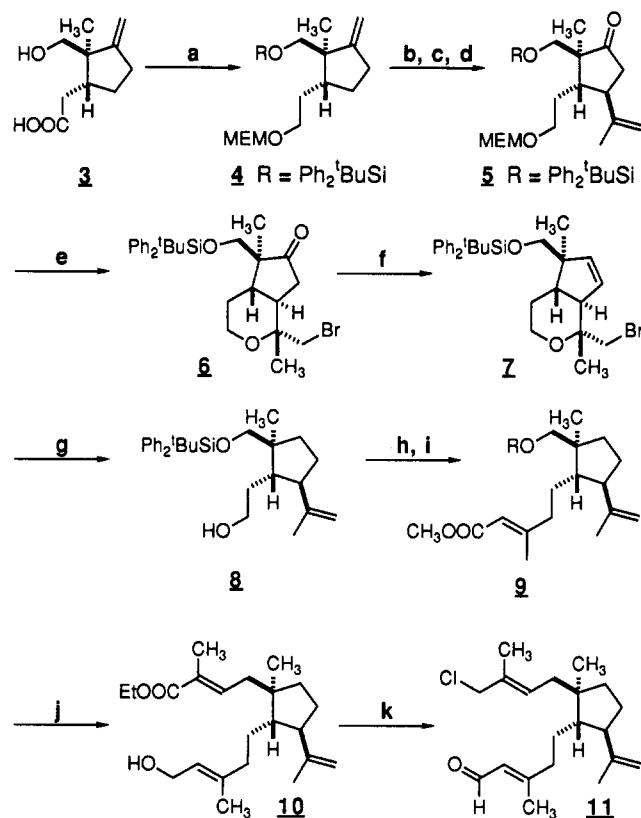
Octocorals have proven to be a rich source of novel diterpenes. In 1978, the clavularanes (**1**) were first reported as unique 5-7-6 tricyclic metabolites of *Clavularia inflata*.¹ Clavularanes and related dolastanes are postulated products of stereocontrolled transannular events of [9.3.0] cyclotetradecanes known as dolabellanes.² The dolabellanes are important constituents chiefly produced by the brown algae of *Dictyota*.³ It is assumed that the wide distribution of dolabellanes and tricyclic 5-7-6 terpenes among marine invertebrates is the result of dietary intake and further metabolism.⁴ Several dolabellanes have been isolated from the soft corals of *Clavularia*.⁵ Herein we report the first total synthesis of the clavularanes by preparation of (-)-3 α ,4 β -dihydroxylavulara-1(15),17-diene (**1**) via a biomimetic cyclization of its proposed dolabellane progenitor (**2**). Our efforts establish the absolute configurations of these natural products.



A stereocontrolled scheme for synthesis of **1** was designed to establish three contiguous asymmetric centers of a cyclopentane nucleus (C₈, C₉, and C₁₂ of **1**), in which the absolute configuration of the quaternary carbon (C₁₂) was incorporated from a chiral pool precursor.⁶ This was feasible via hydroxide treatment of (+)-9,10-dibromocamphor to afford the known carboxylic acid **3**.⁷ Bis-silylation and hydride reduction of the intermediate silyl ester gave a primary alcohol, which was protected as its (β -methoxyethoxy)methyl ether **4**.⁸ Oxidative cleavage of the exocyclic methylene of **4** and application of the Saegusa procedure⁹ provided an enone without evidence of γ -epimerization. Conjugate addition exclusively afforded ketone **5** in 92% yield (Scheme I).

Efforts for direct reduction of the hindered ketone **5** to its corresponding cyclopentane derivative were unsatisfactory. Hydride reduction of **5** yielded the β -alcohol. However, deoxygenation procedures gave side reactions which involved participation of the terminal alkene. Thus, the MEM ether was transformed

Scheme I



^a (a) (1) Ph₂^tBuSiCl (2.2 equiv), Et₃N, AgNO₃, DMF; (2) LiAlH₄, CH₂Cl₂, 0 °C; (3) MEMCl, *i*-Pr₂NEt, CH₂Cl₂, 0 °C, 87%; (b) O₃, CH₂Cl₂, -78 °C, then Ph₃P, 80%; (c) NaN(TMS)₂, THF, TMSCl, -15 °C, then Pd(OAc)₂, CH₃CN, 22 °C, 89%; (d) H₃CC(Br)=CH₂, *n*-BuLi (1.1 equiv), THF, CuBr·DMS, -78 °C, 92%; (e) NBS, THF, 0 → 22 °C, 88%; (f) (1) DIBAL, CH₂Cl₂, -78 °C, 88%; (2) Imd₃C=S, 1,2-dichlorobenzene, DMAP (catalytic amount), 22 → 180 °C, 85%; (g) (1) TsNHNH₂, NaOAc, THF/H₂O, 75 °C, 99%; (2) Zn, EtOH, NH₄Cl, reflux, 92%; (h) (1) TsCl, Et₃N, CH₂Cl₂, DMAP, 0 → 22 °C, 94%; (2) LiC≡CH (EDA complex), DMSO/Et₂O, 22 °C, 80%; (3) *n*-Bu₄NF/THF; (4) TsCl, pyr, DMAP, 22 °C, 74%; (i) (1) *n*-BuLi, THF, -78 °C, ClCO₂Me, 70%; (2) PhSH, NaOCH₃/CH₃OH; then CH₃MgBr, CuI, THF, -78 °C, 95%; (j) (1) DIBAL, CH₂Cl₂, -78 °C, 100%; (2) *n*-Bu₄N⁺CN⁻, CH₃CN, 80 °C, 86%; (3) DIBAL (2.5 equiv), CH₂Cl₂, -20 °C, 99%; (4) EtOCC(CH₃)=PPh₃, THF, 22 °C, 99%; (k) (1) Me₂^tBuSiCl, Et₃N, CH₂Cl₂; then DIBAL, -78 °C, 99%; (2) MeSO₂Cl, LiCl, Et₃N, DMF/CH₂Cl₂, 0 °C, 96%; (3) *n*-Bu₄NF/THF, 0 °C; then C₆H₄CO₂I(OAc)₃, CH₂Cl₂, 95%.

into a suitable protecting unit for the neighboring olefin via treatment of ketone **5** with recrystallized *N*-bromosuccinimide, affording a single tetrahydropyran **6**.¹⁰ Carbonyl reduction gave exclusively the β -alcohol of **6**, and subsequent acylation of this sterically hindered hydroxyl with (thiocarbonyl)diimidazole quantitatively led to a facile syn elimination.¹¹ Finally, the cyclopentene **7** was reduced in 97% yield with diimide, as generated *in situ* from *p*-toluenesulfonylhydrazide.¹² Deprotection with zinc powder in refluxing ethanol gave primary alcohol **8**, and elaboration of the C₆ → C₁₀ chain (see dolabellane **2** numbering) was accomplished with stereospecific preparation of the trisubstituted olefin **9**.¹³

(10) Irradiation of the axial methyl located at C₁ of the THP ring of **6** (δ 1.21 ppm) provided an 8% NOE enhancement of neighboring axial H_A (at C₂; δ 2.02 ppm). The trans ring fusion was indicated by the large coupling constant J_{AB} = 12 Hz for methine hydrogen H_B (at C₂; δ 2.53 ppm).

(11) Although thiocarbonyl imidazolides have not been widely used for syn eliminations, these substrates offer clear advantages over the corresponding xanthates.

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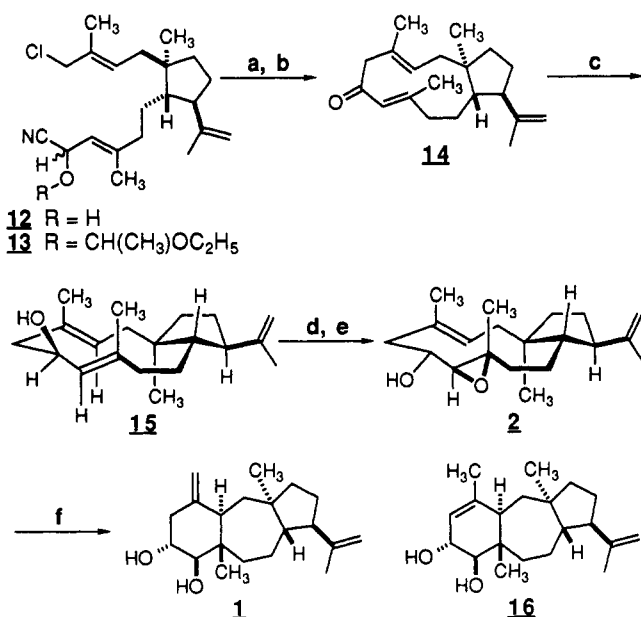
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Scheme II



* Conditions for **12**: Me₃SiCN, CH₂Cl₂, catalytic 18-crown-6, KCN (catalytic amount); then add aqueous HF, 96%. (a) EtOCH=CH₂, CH₂Cl₂, 22 °C, 97%; (b) NaN(TMS)₂, THF, 35 °C; then H₃O⁺; then aqueous NaOH, 85%; (c) DIBAL, CH₂Cl₂, -78 °C, 94%; (d) DEAD, PPh₃, THF, PhCOOH; then DIBAL, -78 °C, 65%; (e) VO(acac)₂, ^tBuOOH, CH₂Cl₂, 0 °C, 88%; (f) CSA, CH₂Cl₂, -78 → 22 °C.

Remaining carbons were introduced via hydride reduction of **9** to its corresponding allylic alcohol and cyanide displacement of the tosylate followed by DIBAL reduction to an intermediate aldehyde for Wittig olefination yielding **10**. Standard transformations led to the α,β -unsaturated aldehyde **11** in 83% overall yield from **10**.

Macrocyclization was effected via an intramolecular alkylation as shown in Scheme II. Thus, conversion of **11** to its corresponding cyanohydrin **12** by addition of trimethylsilyl cyanide and gentle hydrolysis was followed by formation of the ethoxyethyl ether **13**. Deprotonation with inverse addition of a solution of **13** (0.01 M THF) into a solution of sodium bis(trimethylsilyl)amide at 35 °C provided an acyl anion equivalent for efficient ring closure

to the 11-membered ketone **14** in 85% isolated yield.¹⁴ Hydride reduction of **14** predominantly yielded the axial alcohol **15** (10:1 ratio of β/α OH), exemplifying the stereoselectivity anticipated from considerations of the rigid crown conformation of 3(*E*),7-(*E*)-dolabelladienes.²

Biomimetic conversion to clavularane **1** was undertaken by Mitsunobu inversion of the allylic alcohol **15** and subsequent Sharpless oxidation to afford a labile dolabellene epoxide **2**. A stereocontrolled transannular cyclization was promoted by anhydrous camphorsulfonic acid at -78 °C producing a 77% yield of a mixture of alkenes. Olefin isomers were converted to their monobenzoates for efficient separation, and lithium hydroxide saponification provided **16** (12%) and pure **1** (38%), which was identical in all respects [excepting optical rotation; synthetic $[\alpha]^{25}_D$ -49.2 ($c = 0.12$, CHCl₃); natural $[\alpha]^{25}_D$ +51.0° ($c = 0.61$, CHCl₃)] to an authentic sample of the natural product.¹⁵

Thus the marine invertebrates of *Clavularia* must independently synthesize or selectively accumulate dolabellanes which are antipodal to those originating from the brown algae of certain Dictyotaceae.^{16,17} Further efforts for the enantioselective formation of marine diterpenes are underway.

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Supplementary Material Available: Data for **5–11**, **14**, **15**, **2**, and **1** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(15) We thank Professor Braekman, Laboratoire De Chimie Bio-organique, Universite Libre De Bruxelles, for a generous sample of naturally occurring 3 α ,4 β -dihydroxycavulara-1(15),17-diene.

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