Synthesis Strategies for Marine Diterpenes. Total Synthesis of the Clavularanes

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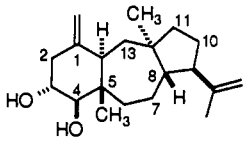
Octocorals have proven to be a rich source of novel diterpenes. In 1978, the clavularanes (**1**) were first reported as unique 5-7-6 tricyclic metabolites of *Clavularia inflata*.[1] Clavularanes and related dolastanes are postulated products of stereocontrolled transannular events of [9.3.0] cyclotetradecanes 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 (−)-3α,4β-dihydroxyclavulara-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.



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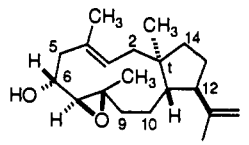

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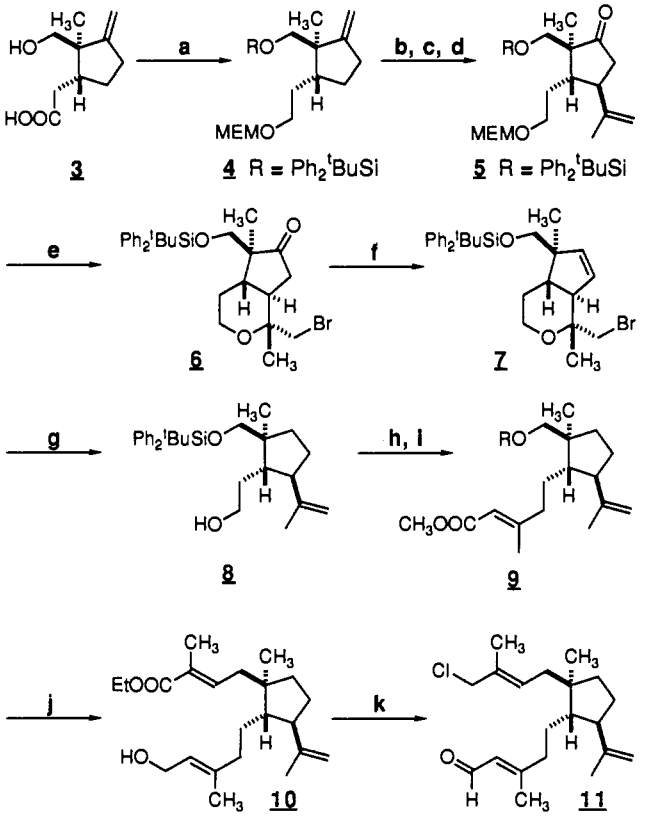
A stereocontrolled scheme for synthesis of **1** was designed to establish three contiguous asymmetric centers of a cyclopentane nucleus (C_8, C_9, and C_{12} of **1**), in which the absolute configuration of the quaternary carbon (C_{12}) was incorporated from a chiral pool precursor.[6] This was feasible 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 procedure[9] 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 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*-toluenesulfonohydrazide.[12] Deprotection with zinc powder in refluxing ethanol gave primary alcohol **8**, and elaboration of the $C_6 \rightarrow C_{10}$ chain (see dolabellane **2** numbering) was accomplished with stereospecific preparation of the trisubstituted olefin **9**.[13]

Scheme I



[a] (a) (1) $Ph_2{}^tBuSiCl$ (2.2 equiv), Et_3N, $AgNO_3$, DMF; (2) $LiAlH_4$, CH_2Cl_2, 0 °C; (3) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 87%; (b) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 80%; (c) $NaN(TMS)_2$, THF, TMSCl, −15 °C, then $Pd(OAc)_2$, CH_3CN, 22 °C, 89%; (d) $H_3CC(Br)=CH_2$, *n*-BuLi (1.1 equiv), THF, CuBr·DMS, −78 °C, 92%; (e) NBS, THF, 0 → 22 °C, 88%; (f) (1) DIBAL, CH_2Cl_2, −78 °C, 88%; (2) $Imd_2C=S$, 1,2-dichlorobenzene, DMAP (catalytic amount), 22 → 180 °C, 85%; (g) (1) $TsNHNH_2$, NaOAc, THF/H_2O, 75 °C, 99%; (2) Zn, EtOH, NH_4Cl, reflux, 92%; (h) (1) TsCl, Et_3N, CH_2Cl_2, DMAP, 0 → 22 °C, 94%; (2) LiC≡CH (EDA complex), DMSO/Et_2O, 22 °C, 80%; (3) *n*-Bu_4NF/THF; (4) TsCl, pyr, DMAP, 22 °C, 74%; (i) (1) *n*-BuLi, THF, −78 °C, $ClCO_2Me$, 70%; (2) PhSH, $NaOCH_3/CH_3OH$; then CH_3MgBr, CuI, THF, −78 °C, 95%; (j) (1) DIBAL, CH_2Cl_2, −78 °C, 100%; (2) *n*-$Bu_4N^+CN^-$, CH_3CN, 80 °C, 86%; (3) DIBAL (2.5 equiv), CH_2Cl_2, −20 °C, 99%; (4) $EtOOCC(CH_3)=PPh_3$, THF, 22 °C, 99%; (k) (1) $Me_2{}^tBuSiCl$, Et_3N, CH_2Cl_2; then DIBAL, −78 °C, 99%; (2) $MeSO_2Cl$, LiCl, Et_3N, DMF/CH_2Cl_2, 0 °C, 96%; (3) *n*-Bu_4NF/ THF, 0 °C; then $C_6H_4CO_2I(OAc)_3$, CH_2Cl_2, 95%.

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(10) Irradiation of the axial methyl located at C_1 of the THP ring of **6** (δ 1.21 ppm) provided an 8% NOE enhancement of neighboring axial H_A (at C_3; 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 C_2; 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.
(12) Diimide modification as described in the following: Hart, D. J.; Hung, N.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4664.
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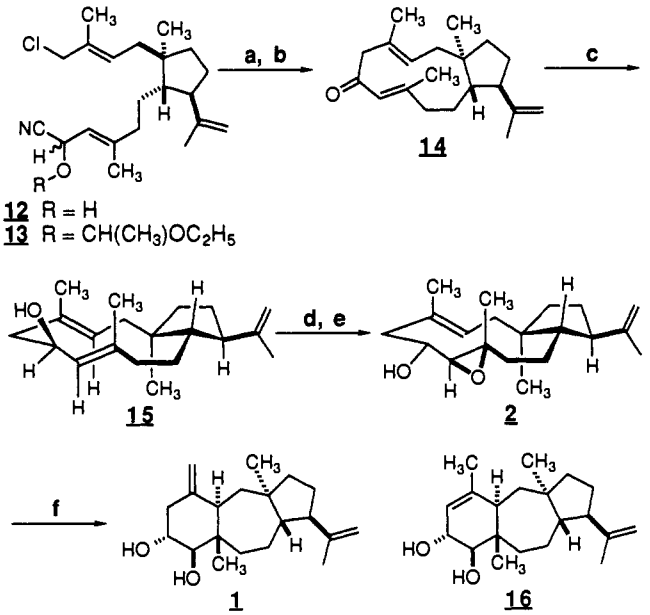
Scheme II



[a] Conditions for **12**: Me_3SiCN, CH_2Cl_2, catalytic 18-crown-6, KCN (catalytic amount); then add aqueous HF, 96%. (a) $EtOCH{=}CH_2$, CH_2Cl_2, 22 °C, 97%; (b) $NaN(TMS)_2$, THF, 35 °C; then H_3O^+; then aqueous NaOH, 85%; (c) DIBAL, CH_2Cl_2, −78 °C, 94%; (d) DEAD, PPh_3, THF, PhCOOH; then DIBAL, −78 °C, 65%; (e) $VO(acac)_2$, ^tBuOOH, CH_2Cl_2, 0 °C, 88%; (f) CSA, CH_2Cl_2, −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, $CHCl_3$); natural $[\alpha]^{25}_D$ +51.0° (c = 0.61, $CHCl_3$)] 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.

Acknowledgment. Financial assistance was provided by the National Institutes of Health (GM42897).

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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