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Enantioselective Syntheses of Authentic Sclerophytin A, Sclerophytin B, and Cladiell-11-ene-3,6,7-triol

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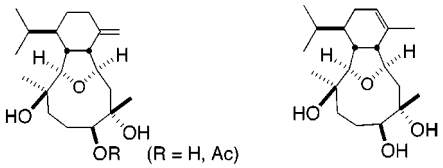
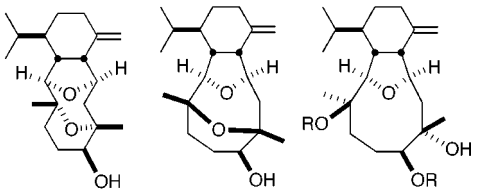
ABSTRACT



Two distinctively different total syntheses of natural sclerophytin A in its revised structural formulation are reported. The first proceeds from (*S*)-carvone via a cladiellene triol and involves photoisomerization of the double bond. The second route makes use of (5*S*)-5-(*d*-menthyloxy)-2(5*H*)-furanone, which is subjected to cycloaddition, Claisen ring expansion, and regiocontrolled dihydroxylation tactics.

In 1988, Sharma and Alam documented their isolation of the antineoplastic marine diterpene sclerophytin A, which was formulated as **1**.[1] The ambiguities resident in this



structural assignment proved sufficient to lead our groups independently to conclude that revision to the significantly less strained arrangement of the two oxygen bridges as in **2** was in order. Subsequent targeted synthesis of **2** at Ohio State[2] and at UC Irvine[3] established unequivocally that **2** is indeed not sclerophytin A. Detailed spectroscopic reevaluation of sclerophytin B, the monoacetate of the A factor, demonstrated the strong likelihood that these substances lack the second ether bridge and should be construed to be **3** and **4**.[4] Herein is described two synthetic strategies that have culminated in the synthesis of **3** and unequivocally confirmed the more recent tricyclic formulation for this cytotoxic soft coral metabolite. The closely related cladiell-11-ene-3,6,7-triol (**5**)[5] has also been accessed. The acetylation of **3** to produce **4**, although incorrectly formulated earlier, has previously been reported.[1b]

In the Overman group, the route to **3** and **5** commenced with tricyclic alcohol **6**, which is available in 17 steps and ca. 6% overall yield from (*S*)-carvone[3,6] (Scheme 1). Hy-

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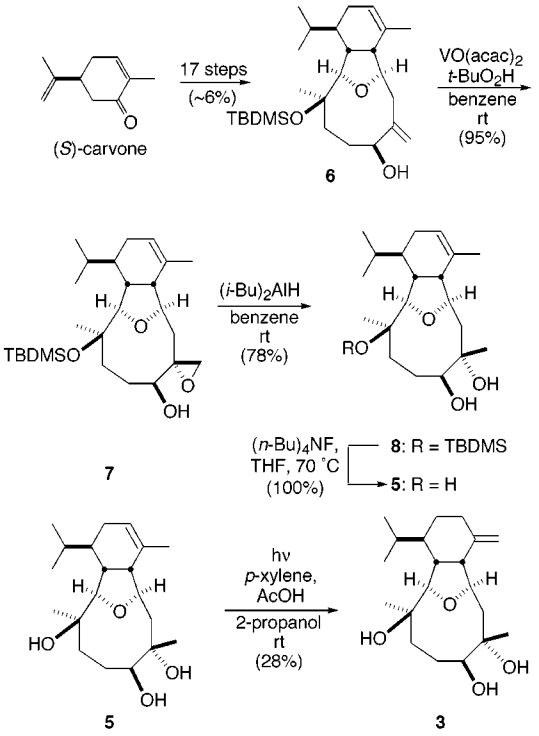
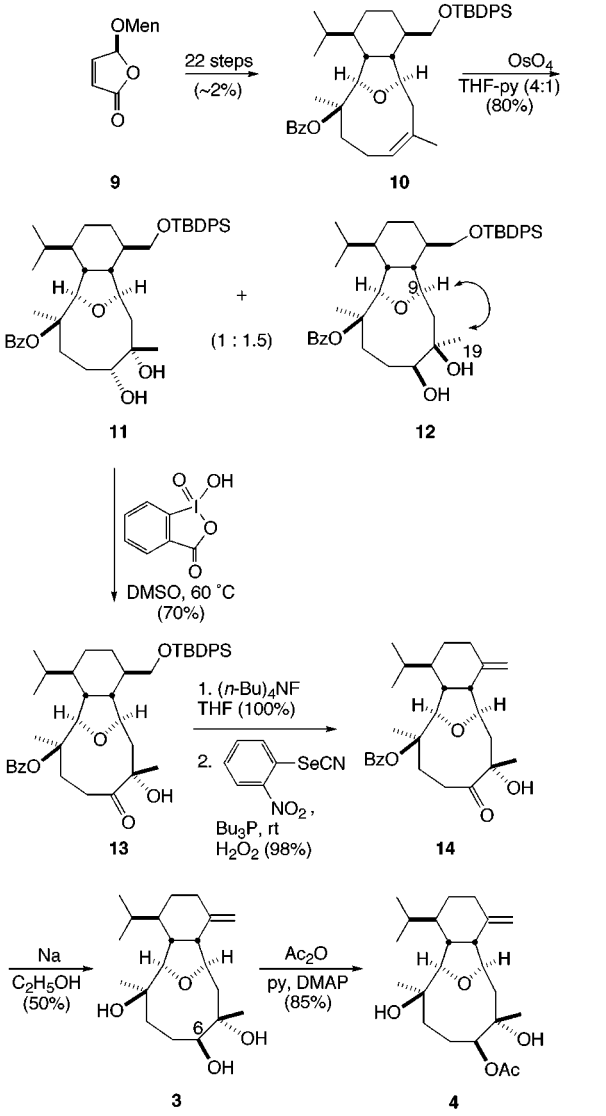
Scheme 1. Irvine Total Synthesis of Cladiellene Triol **5** and Sclerophytin A (**3**)



droxyl-directed epoxidation[7] of **6** with $VO(acac)_2/t\text{-}BuO_2H$ occurred with exquisite facial selectivity to deliver the lone epoxy alcohol **7** in excellent yield. Regioselective reduction[8] of **7** with $(i\text{-}Bu)_2AlH$ provided diol **8**, which upon treatment with $(n\text{-}Bu)_4NF$ gave rise to triol **5**.[9] Uchio, Fukazawa, and co-workers had earlier isolated this substance from extracts of a soft coral *Cladiella* species (Octocorallia, Alcyonacea) collected at Ishigaki Island, Okinawa, and confirmed its structure by single-crystal X-ray analysis.[5] The conversion of **5** to sclerophytin A (**3**) was accomplished by photochemical isomerization using a medium-pressure Hg lamp (450 W) fitted with a Vycor filter.[10]

The Paquette group advanced on sclerophytins A and B from the direction of **10**, a substantially functionalized cyclodecene obtained in 22 steps and ca. 2% yield from **9**,[2] a known enantiopure dienophilic lactone[11] (Scheme 2).

Scheme 2. Columbus Total Synthesis of Sclerophytin A (**3**) and Sclerophytin B (**4**)



Conventional dihydroxylation of **10** proceeded with little π-facial discrimination to deliver **11** and **12** in a 1:1.5 ratio. These readily separated stereoisomeric diols were easily distinguished by NOE methods. The strong correlation between H9 and H19 exhibited by **12**, but absent in **11**, is particularly noteworthy. Oxidation of **11** with *o*-iodoxybenzoic acid (IBX) in DMSO at 60 °C[12] proceeded without evidence of glycol C−C bond cleavage and furnished **13**. At this point, the exocyclic double bond was introduced by sequential desilylation and elimination via the *o*-nitroselenocyanate.[13]

The reduction of **14** with either $(i\text{-}Bu)_2AlH$ or $LiAlH_4$ proceeded smoothly but gave rise only to the triol with an α-hydroxyl substituent at C-6. Since recourse to kinetic control was met with exclusive hydride delivery from the β

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(9) Mp 205−206 °C, lit.[5] 205.5−206.0 °C; $[\alpha]^{23}_D$ −12.3 (*c* 0.4 or 1.0, $CHCl_3$). An identical rotation was measured in our hands for a sample of the natural product, while a rotation of $[\alpha]_D$ −16.1 (*c* 0.75, $CHCl_3$) was reported in the original disclosure.
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surface, we turned to sodium in ethanol in order to capitalize on thermodynamic factors.[14] The use of these conditions led cleanly to sclerophytin A (**3**) and made possible subsequent acetylation to generate sclerophytin B (**4**).

The samples of **3**−**5** generated in the present investigation were spectroscopically identical to the natural isolates (^{1}H NMR, ^{13}C NMR, IR, HRMS, and TLC). In addition, the optical rotation recorded for synthetic **3**, $[\alpha]^{20}_D$ −2.7 (*c* 0.11, $CHCl_3$), compares favorably with that of the authentic diterpenoid, $[\alpha]^{20}_D$ −6.9 (*c* 0.087, $CHCl_3$).[15]

In summary, the dual approach to sclerophytin A described herein fully corroborates the revised structural assignment recently advanced.[4] Consequently, there exists at present few known examples of octocoral-derived 2,11-cyclized cembranoids that contain two oxygen bridges within their cyclodecanol B ring.[16]

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Supporting Information Available: Relevant comparison spectra of natural and synthetic sclerophytin A. This material is available free of charge via the Internet at http://pubs.acs.org.

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