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Total Synthesis of Cladocorans A and B: A Structural Revision

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Cladocorans A and B, isolated from the Mediterranean coral *Cladocora cespitosa*, are novel sesterterpenoids whose structures were initially proposed as **1** and **2**, respectively. These designations, however, subsequently came under doubt. In the present study, the synthesis of compounds **5** and **6** was undertaken. The physical properties of **5** and **6** were found to be identical to those of natural cladocorans A and B, whose structures were thus concluded to be **5** and **6**, respectively. Cladocoran B is thus clearly shown to be an olefinic regioisomer of dysidiolide and cladocoran A as its acetate.

Cladocorans A and B, isolated from the Mediterranean coral *Cladocora cespitosa* by Fontana et al. in 1998, are novel sesterterpenoids each with a unique carbon skeleton (Figure 1).[1] Cladocorans A and B are regarded as analogues of dysidiolide, a natural inhibitor of protein phosphatase cdc25A that is essential for cell proliferation.[2] The biological activity of cladocoran has not been reported, but the compound may likely be an inhibitor of protein phosphatase and phospholipase A_2 in consideration of its structural characteristics.[3−6] The relative configuration (C-7, C-12, C-15 and C-16) of the decalin ring system in cladocoran A was determined on the basis of coupling constants and NOEs of a derivative compound obtained from cladocoran A. The absolute configuration of the secondary hydroxy group at C-18 was determined by the modified Mosher method,[7] though the relative configurations of the hydroxy group at C-18 and decalin ring remain to be elucidated. Fontana et al. have presented the structural formulas **1** and **2** for cladocorans A and B, respectively.

Numerous attempts have been made to conduct the total synthesis of dysidiolide, prompted by its unique structure features and potential biological significance.[8−17] The total synthesis of dysidiolide was previously carried out by the authors using intramolecular Diels−Alder reaction as the key reaction.[11] But the total synthesis of cladocoran has not yet been reported. The total synthesis of cladocorans A and B was thus conducted in the present study so as to clarify their structures and establish a method for synthesis.

Recently, Marcos et al. reported the chemical conversion of *ent*-halimic acid to compounds **1** and **2** proposed by Fontana et al., but the physical properties of the synthesized compounds did not match those of natural cladocorans.[18] It was thus apparent that the structures of cladocorans A and B should be revised. We considered the absolute configurations at the C-7 and C-16 positions of cladocorans to be identical with those of dysidiolide, in that these compounds bear close connection with biogenesis, and their structures were consequently assumed to be **3** and **4**. The authors synthesized compounds **3** and **4** whose physical properties were clearly found to differ with those of natural cladocorans. It was then anticipated that actual structures of cladocorans A and B would be **5** and **6**, both epimers at C-15 of **3** and **4**, based on analysis of NMR data of natural cladocorans **3**

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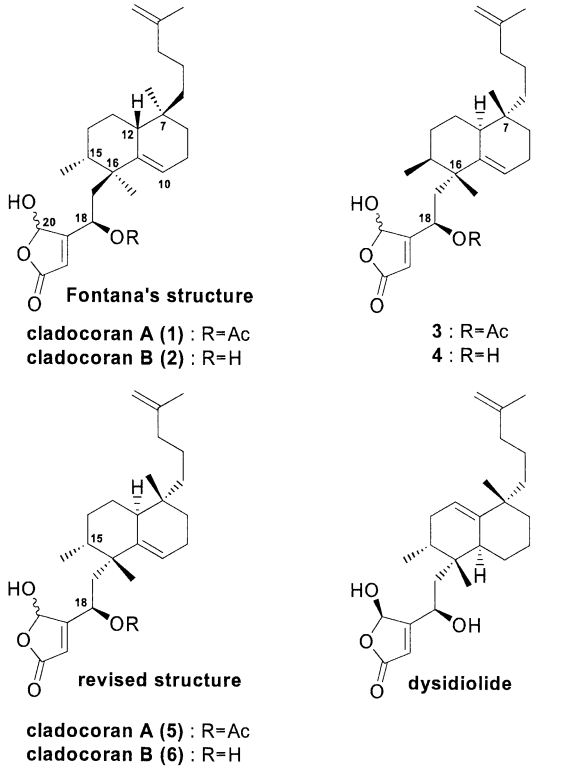
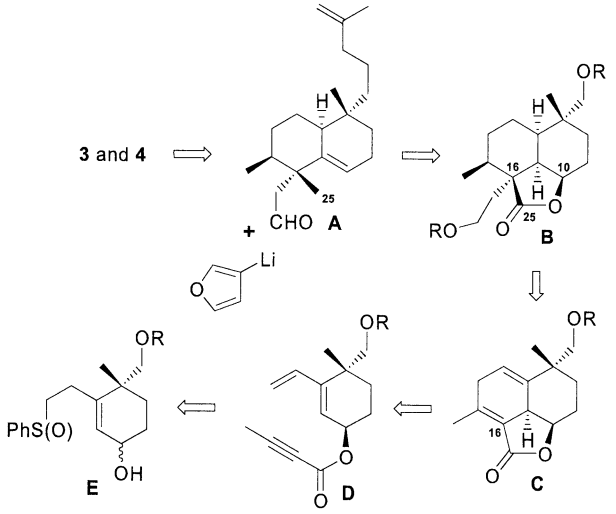


FIGURE 1. Chemical structures proposed for cladocorans and that of dysidiolide.

SCHEME 1. Synthetic Strategy for Compounds 3 and 4



and **4**. The synthesis of compounds **5** and **6** was carried out and their physical properties were seen to be identical with those of natural cladocorans. The structures of cladocorans A and B were thus revised as **5** and **6**. This paper reports in detail the total synthesis of cladocorans A and B and the structural revision is presented.

The synthetic strategy for compounds **3** and **4** as cladocorans A and B is presented in Scheme 1. The method of synthesis may be considered essentially the same as that for synthesis of dysidiolide, as previously reported.[11] Optically active allylic alcohol **E**, the synthetic intermediate for dysidiolide, was used as starting material. The decalin framework, the core structure of cladocoran, was constructed in such a way that lactone **C** would be produced by intramolecular Diels−Alder reaction of diene ester **D** obtained from allylic alcohol **E** via esterification. It was considered that stereoselective hydrogenation and alkylation at C-16[19] of lactone **C** would take place so as to provide lactone **B**, knowing the α-face of lactone **C** to be the less hindered side. Lactone **B** would undergo conversion to aldehyde **A** by elimination of the oxygenated functional group at C-10, deoxygenation at C-25, and elongation of the side chain. The highly functional γ-hydroxybutenolide would be obtained by addition of 3-lithiofuran to aldehyde **A** and photochemical oxidation of the furan moiety to give compounds **3** and **4**.

The synthesis of compounds **3** and **4** was initiated from optically active allylic alcohols **7a**[11b] and **7b**,[11b] both synthetic intermediates for dysidiolide (Scheme 2). The secondary hydroxy group of sulfoxide **7a** was acylated with 2-butynoic acid, DCC, and DMAP in toluene to afford ester **8**. Allylic alcohol **7b** was converted to ester **8** via Mitsunobu reaction[20] using 2-butynoic acid, DEAD, and Ph_3P. A solution of ester **8** in toluene was refluxed in the presence of ethyl propiolate and pyridine to construct the diene by elimination of phenyl sulfoxide. Subsequent intramolecular Diels−Alder reaction gave decalin **9** corresponding to lactone **C** in the synthetic strategy as the sole product. In the absence of ethyl propiolate, there were many byproducts, and decalin **9** was obtained in only low yield. The relative configuration of **9** was confirmed on the basis of the NOESY spectrum. NOESY correlations were noted between the methine proton at C-11 and one of the methylene protons at C-6 and between the olefinic proton at C-13 and the methyl protons at C-23. The relative configuration of **9** is thus that shown in Scheme 2.

Stereoselective hydrogenation of two carbon−carbon double bonds in lactone **9** was carried out in the presence of PtO_2 and acetic acid at medium pressure of H_2 (4.0 atm) to afford 15β-methyl lactone. Removal of the TBDMS group with tetrabutylammonium fluoride (TBAF) provided alcohol **10** as the sole product. The relative configurations of C-12, C-15, and C-16 in **10** were determined from NOESY correlations between both methylene protons at C-6 and the methine proton at C-12, between the methine proton at C-10 and the methine proton at C-16, and between the methine proton at C-12 and methine proton at C-15. Stereoselectivety of hydrogenation in **9** may possibly be due to approach of the hydrogenation catalyst from the convex face.

The hydroxy group in lactone **10** was converted to the phenylsulfanyl group by treatment with *N*-phenylthiosuccinimide, Bu_3P, and pyridine. Stereoselective alkylation at C-16 was carried out by treatment with LDA and then 1-iodo-2-(tetrahydro-2-pyranyloxy)ethane[11] in the presence of HMPA to give lactone **11**, corresponding to lactone **B** in the synthetic strategy, as the sole product. The relative configuration at C-16 in **11** was determined from the NOESY spectrum of alcohol **11′**, prepared from **11** by acid catalytic methanolysis of the THP group with PPTS. NOESY correlations were evident between the

(19) Numbering of compounds is in accordance with that for cladocoran in this paper.

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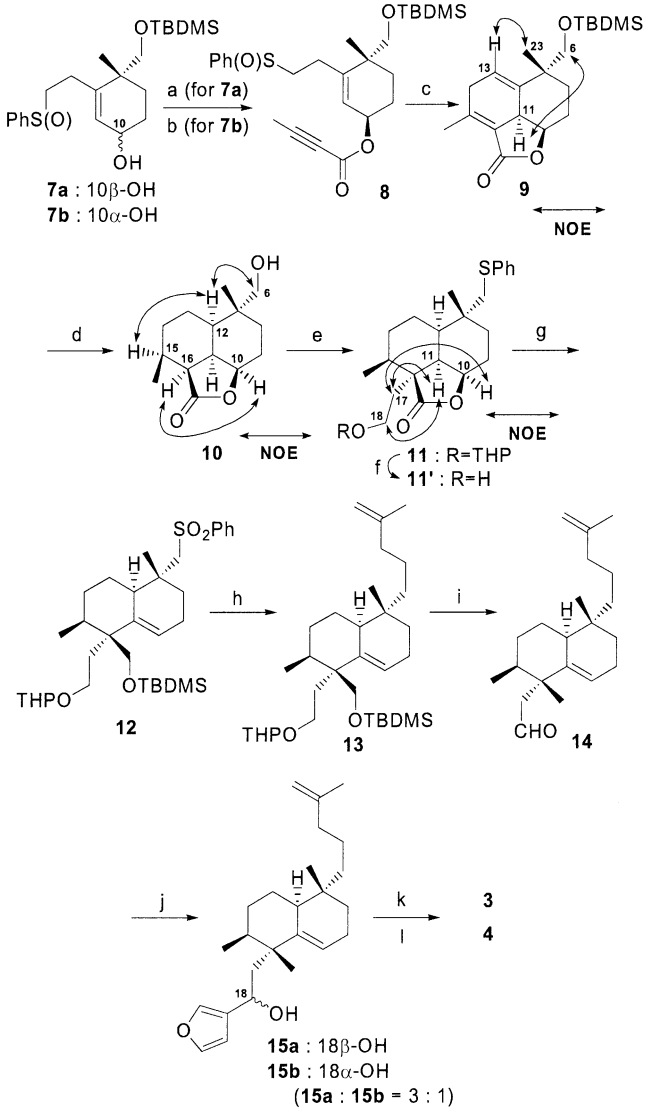
SCHEME 2[a]

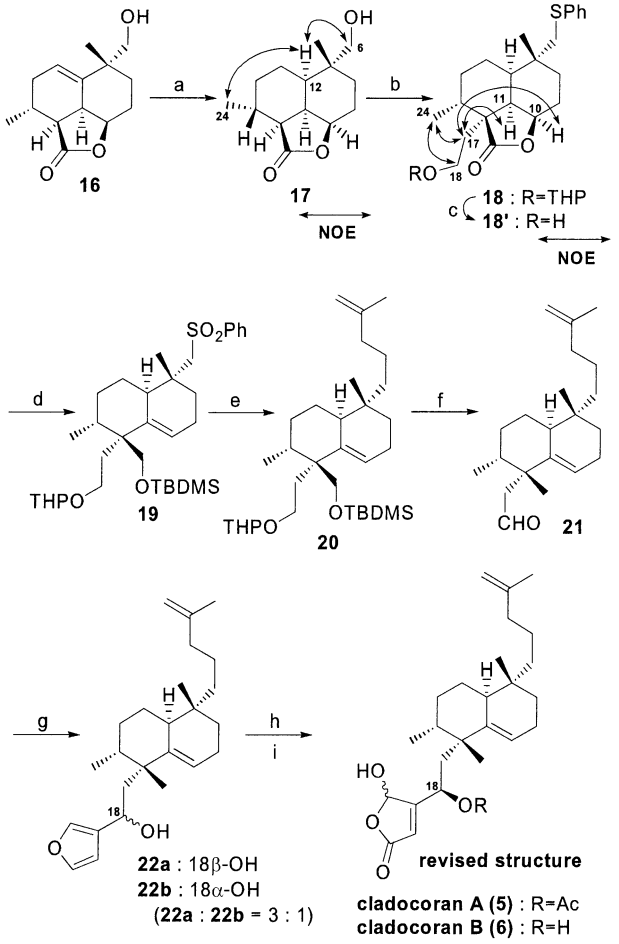


[a] Reagents and conditions: (a) 2-butynoic acid, DCC, DMAP, toluene, rt, 93%; (b) 2-butynoic acid, DEAD, Ph_3P, THF, rt, 91%; (c) pyridine, ethyl propiolate, toluene, reflux, 84%; (d) (i) H_2 (4.0 atm), PtO_2, AcOH, rt, (ii) TBAF, THF, rt, 92% (two steps); (e) (i) *N*-phenylthiosuccinimide, Bu_3P, pyridine, 60 °C, 79%, (ii) LDA, HMPA, $THPOCH_2CH_2I$, THF, 0 °C, 97%; (f) PPTS, MeOH, rt, 77%; (g) (i) DIBALH, toluene, −78 °C, (ii) $LiBH_4$, THF, 40 °C, quant (two steps), (iii) TBDMSCl, imidazole, DMF, rt, 92%, (iv) $SOCl_2$, pyridine, 0 °C, 97%, (v) TPAP, NMO, CH_2Cl_2, 95%; (h) (i) BuLi, 4-iodo-2-methyl-1-butene, THF, 50 °C, 94%, (ii) Na−Hg, Na_2HPO_4, MeOH, rt, 86%; (i) (i) TBAF, THF, 50 °C, 92%, (ii) TPAP, NMO, CH_2Cl_2, rt, 72%, (iii) H_2NNH_2, KOH, diethylene glycol, 200 °C, 71%, (iv) PPTS, MeOH, rt, 92%, (v) TPAP, NMO, CH_2Cl_2, rt, 91%; (j) 3-bromofuran, BuLi, THF, −78 °C, 89%; (k) for **3**: (i) Ac_2O, pyridine, rt, 91%, (ii) O_2, *hν*, Rose Bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 37%; (l) for **4**: O_2, *hν*, Rose Bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 68%.

methine proton at C-10 and one of the methylene protons at C-17, between the methine proton at C-11 and both methylene protons at C-17, and between the methine proton at C-11 and both methylene protons at C-18.

Following deoxygenation of the C-10 and C-25 positions, lactone **11** was reduced with DIBALH to give the hemiacetal, the reduction of which with $LiBH_4$ afforded the diol. The primary hydroxy group in the diol was

SCHEME 3[a]



[a] Reagents and conditions: (a) H_2 (4.4 atm), PtO_2, AcOH, rt, 89%; (b) (i) *N*-phenylthiosuccinimide, Bu_3P, pyridine, 60 °C, 86%, (ii) LDA, HMPA, $THPOCH_2CH_2I$, THF, 0 °C, 94%; (c) PPTS, MeOH, rt, 26%; (d) (i) DIBALH, toluene, −78 °C, (ii) $LiBH_4$, THF, 40 °C, 91% (two steps), (iii) TBDMSCl, imidazole, DMF, rt, quant, (iv) $SOCl_2$, pyridine, 0 °C, 93%, (v) TPAP, NMO, CH_2Cl_2, 98%; (e) (i) BuLi, 4-iodo-2-methyl-1-butene, THF, 50 °C, 89%, (ii) Na−Hg, Na_2HPO_4, MeOH, rt, 91%; (f) (i) TBAF, THF, 50 °C, 85%, (ii) TPAP, NMO, CH_2Cl_2, rt, 82%, (iii) H_2NNH_2, KOH, diethylene glycol, 200 °C, 70%, (iv) PPTS, MeOH, rt, 94%, (v) TPAP, NMO, CH_2Cl_2, rt, 80%; (g) 3-bromofuran, BuLi, THF, −78 °C, 95%; (h) for **5**: (i) Ac_2O, pyridine, rt, quant., (ii) O_2, *hν*, Rose Bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 83%; (i) O_2, *hν*, Rose Bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 83%.

protected by treatment with TBDMSCl and imidazole as TBDMS ether as the sole product. Elimination of the secondary hydroxy group was carried out by treatment with $SOCl_2$ in pyridine and oxidation of sulfide with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) produced sulfone **12**.

Elongation of the side chains and deoxygenation of the C-25 position were carried out to produce the compounds **3** and **4**. Reaction of the lithio derivative of sulfone **12** with 4-iodo-2-methyl-1-butene at 50 °C gave the coupling product and subsequent removal of the benzenesulfonyl group with Na−Hg in the presence of Na_2HPO_4 provided silyl ether **13**. Silyl ether **13** was converted to aldehyde **14**, corresponding to aldehyde **A** in the synthetic strategy, in five steps: (1) removal of the TBDMS group in **11** with TBAF, (2) TPAP-oxidation of the hydroxy group to provide aldehyde, (3) Wolff−Kishner reduction[21] of the

formyl group with H_2NNH_2 and KOH in diethylene glycol at 200 °C, (4) methanolysis of the THP group with PPTS to give alcohol, and (5) TPAP-oxidation of the primary hydroxy group with NMO. Treatment of aldehyde **14** with 3-lithiofuran, prepared from 3-bromofuran and BuLi, gave a mixture of β-alcohol **15a** and its epimer **15b** (**15a**/**15b** = 3:1), which was readily separatable by silica gel chromatography. The absolute configuration of the secondary hydroxy group in **15a** was determined to be the *R* configuration by the modified Mosher method.[7] Following acetylation of alcohol **15a**, photochemical oxidation[22] of the obtained acetate in the presence of excess *i*-Pr_2NEt afforded **3**, $[\alpha]^{26}_D = -17.9$ (*c* 0.56, $CHCl_3$). Photochemical oxidation[22] of **15a** in the presence of excess *i*-Pr_2NEt afforded **4**, $[\alpha]^{23}_D = -31.0$ (*c* 1.04, $CHCl_3$). Spectral data of synthesized **3** and **4** were not identical with those reported for natural cladocoran A, $[\alpha]^{20}_D = -25.8$ (*c* 0.4, $CHCl_3$),[1] and cladocoran B, $[\alpha]^{20}_D = -59.9$ (*c* 0.6, $CHCl_3$).[1] 18-*epi*-**3** (*ent*-**1**), $[\alpha]^{26}_D = -7.2$ (*c* 0.25, $CHCl_3$), and 18-epi-**4** (*ent*-**2**), $[\alpha]^{23}_D = -64.3$ (*c* 0.28, $CHCl_3$), were thus synthesized from α-alcohol **15b** in essentially the same way. None of spectral data for these compounds was identical to the data reported for natural cladocorans, and so consequently, structural revision of cladocorans A and B was considered necessary. The actual structures for cladocorans A and B may be concluded to be **5** and **6**, respectively, on the basis of the spectral data of natural cladocorans A and B, synthesized **3**, 18-*epi*-**3**, **4**, and 18-*epi*-**4**. The synthesis of **5** and **6** was subsequently carried out.

Compounds **5** and **6** were synthesized from lactone **16**,[11b] the intermediate synthesized by the authors for dysidiolide (Scheme 3). Stereoselective hydrogenation of olefin in lactone **16** was done in the presence of PtO_2 and acetic acid at medium pressure of H_2 (4.4 atm) to afford *cis*-decalin **17** as the sole product. The relative configuration of C-12 in **17** was determined from its NOESY correlations between the methylene proton at C-6 and methine proton at C-12 and between the methine proton at C-12 and the methyl proton at C-24. Lactone **17** was treated with *N*-phenylthiosuccinimide, Bu_3P, and pyridine to give phenyl sulfide and treatment with LDA, and then 1-iodo-2-(tetrahydro-2-pyranyloxy)ethane[11] in the presence of HMPA provided lactone **18** as the sole product. The relative configuration of C-16 in **18** was determined from the NOESY spectrum of alcohol **18′** prepared from **18** by methanolysis of the THP group. NOESY correlations were observed between the methine proton at C-10 and both methylene protons at C-17, between the methine proton at C-11 and both methylene protons at C-17, and between both methylene protons at C-18 and the methyl protons at C-24.

Lactone **18** was converted to aldehyde **21** via sulfone **19** and silyl ether **20** in a similar manner as above. Treatment of aldehyde **21** with 3-lithiofuran gave a mixture of β-alcohol **22a** and the epimer **22b** (**22a**/**22b** = 3:1). The absolute configuration of the secondary hydroxy group in **22a** was determined as the *R* configuration by the modified Mosher method.[7] Alcohols **22a** and **22b** were acetylated, and photochemical oxidation[22] of the acetates thus obtained afforded compounds **5**, $[\alpha]^{26}_D = -30.0$ (*c* 0.20, $CHCl_3$), and 18-*epi*-**5**, $[\alpha]^{26}_D = -34.5$ (*c* 0.29, $CHCl_3$). Photochemical oxidation[22] of **22a** and **22b** afforded compounds **6**, $[\alpha]^{26}_D = -63.8$ (*c* 0.26, $CHCl_3$), and 18-*epi*-**6**, $[\alpha]^{24}_D = -22.4$ (*c* 0.25, $CHCl_3$). Spectral data and signs of optical rotation of **5** and **6** were identical to those of reported natural cladocoran A, $[\alpha]^{20}_D = -25.8$ (*c* 0.4, $CHCl_3$) and cladocoran B, $[\alpha]^{20}_D = -59.9$ (*c* 0.6, $CHCl_3$), respectively.

From the present results, the structures of cladocorans A and B are clearly indicated to be those presented as **5** and **6**, respectively, and cladocoran B is thus clearly shown to be an olefinic regioisomer of dysidiolide and cladocoran A as its acetate.

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Supporting Information Available: Experimental procedures and product characterizations of all new compound synthesized. Copies of ^1H and ^{13}C NMR spectra for compounds **3**, 18-*epi*-**3**, **4**, 18-*epi*-**4**, **5**, 18-*epi*-**5**, **6**, 18-*epi*-**6**, **8**−**14**, **15a**,**b**, **17**−**21**, and **22a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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