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Total Synthesis of Marine Diterpene Fuscol

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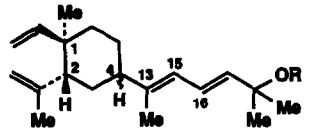
Key Words: total synthesis; marine diterpene; fuscol; prenylated elemane skeleton; sequential Michael reaction.

Abstract: *Marine diterpene fuscol was synthesized stereoselectively from D-mannitol via bicyclo[2.2.2]octane derivative 4, and its complete structure was established.*

Fuscol (**1**), isolated from the gorgonian *Eunicea fusca* by Schmitz *et al.*,[1] is the first diterpene shown to possess a unique prenylated elemane skeleton (lobane skeleton[2]). Recently, fuscol arabinose glycoside, fuscoside B (**2**), was isolated from *E. fusca* by Fenical *et al.*, and **2** was shown to selectively inhibit the synthesis of leukotriene and to possibly be an important lead compound for new antiinflammatory agents.[3] The structures of **1** and **2** were elucidated by NMR analysis. However, the relative configuration of C-4 and absolute structures have yet to be determined. Nearly ten fuscol-related diterpenes have been isolated from marine animals,[1-3] but their absolute structures remain to be determined. This paper reports the first total synthesis of fuscol in an optically active form. The synthesis involves the formation of bicyclo[2.2.2]octane derivative **4** for construction of the key asymmetric center C-1, oxidative cleavage of the double bond in **7** to give pentasubstituted cyclohexane **8**, removal of the 1,3-dioxolane moiety of **9**, and elongation of the side chain. The present result defined the complete structure of fuscol to be **14**.

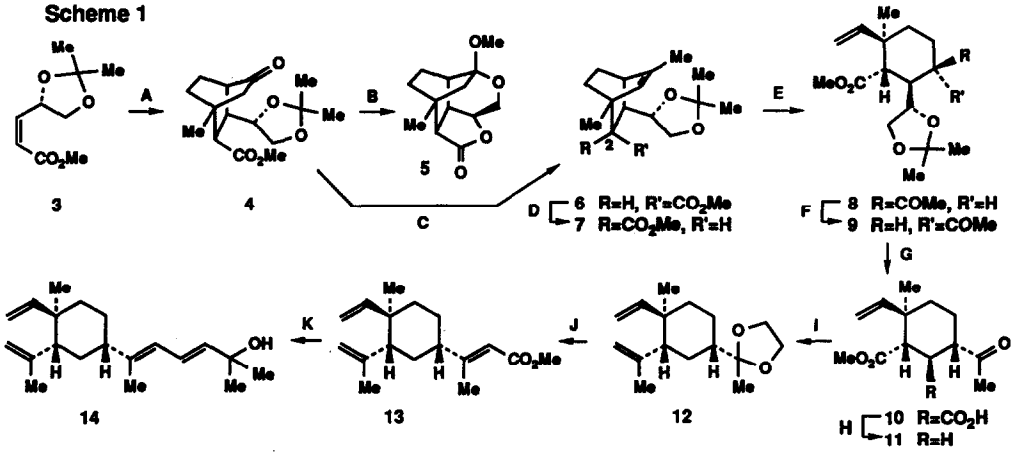


1 R=H
2 R=arabinose

Compound **14** was chosen as the target molecule, since elemane-type sesquiterpenes have a C-2, 4 *cis* configuration.[4] Sequential Michael reaction of the kinetic enolate of 3-methyl-2-cyclohexenone with α,β-unsaturated ester **3**,[5] prepared from D-mannitol, afforded exclusively bicyclo[2.2.2]octane derivative **4**,[6] $[\alpha]_D$ -28.0° (c 2.48, $CHCl_3$), in high yield (Scheme 1).[7] The configuration of **4** was confirmed by the formation of **5** on treatment of the former with a catalytic amount of (±)-10-camphorsulfonic acid in methanol. Keto ester **4** was converted to olefin **6** via methylation of the corresponding enol phosphate with methylmagnesium iodide in the presence of a catalytic amount of nickel acetylacetonate.[8] Epimerization at the C-2[4] position in **6** was carried out by treatment with potassium *t*-butoxide to give thermodynamically stable isomer **7**. Ozonolysis of **7** in MeOH-CH_2Cl_2 (2:1) containing 0.2 equiv of pyridine followed by selective methylenation of aldehyde with diiodomethane in the presence of zinc and a catalytic amount of trimethylaluminum[9] gave **8**. The C-4 position of **8** was isomerized with sodium methoxide to give **9** bearing the desired chiral centers at the C-1, C-2 and C-4 corresponding to those of **14**. The 1,3-dioxolane moiety for the induction of these asymmetric centers was then removed to give **11** via decarboxylation of **10** according to Bartons method.[10] After protecting the ketone in **11**

as ketal, the carbomethoxy group was converted to the isopropenyl group in three steps: i) hydrolysis of ester, ii) methylation with methyllithium and iii) treatment with Lombardo reagent[11] to give **12**. Finally, the side chain moiety with 13(15)*E*, 16*E* configurations was constructed to conduct the synthesis of **14**. Removal of ketal in **12**, followed by Reformatsky reaction during the irradiation of ultrasonic waves and subsequent dehydration gave (*E*)-α,β-unsaturated ester **13** along with *Z* isomer (*E*:*Z*=4.6:1). Following their separation, **13** was transformed to the corresponding α,β-unsaturated aldehyde which was then successively treated with Horner-Emons reagent and methyllithium to give **14**, $[\alpha]_D$ +17.4° (c 0.16, $CHCl_3$). The spectral data of synthesized **14** and reported data of natural fuscol, $[\alpha]_D$ +17.6° (c 0.9, $CHCl_3$),[3] were identical including the sign of optical rotation. This synthesis indicated the absolute configurations of fuscol to be 1*R*, 2*R*, 4*S*.

Scheme 1



Reagents: A. 3-methyl-2-cyclohexenone, LDA, THF, -78°C, 1 h, -40°C, 10 h, 93%; B. MeOH, CSA, 50°C, 91%; C. i) LDA, THF then $(EtO)_2POCl$, -78°C to -20°C, 98%; ii) MeMgI, $Ni(acac)_2$, THF, 0°C, 73%; D. *t*-BuOK, THF-DMSO, 23°C, 99%; E. i) O_3, pyridine (0.2 equiv), MeOH-CH_2Cl_2 (2:1), -78°C then Me_2S, 96%; ii) CH_2I_2, Zn, Me_3Al, THF, 20°C, 79%; F. MeONa, MeOH, 50°C, 83%; G. i) 80% AcOH, 23°C; ii) $NaIO_4$, silica gel, CH_2Cl_2-H_2O, 78% (2 steps); iii) $NaClO_2$, NaH_2PO_4, $MeCH{=}CMe_2$, *t*-BuOH-H_2O, 23°C, 78%; H. i) $(COCl)_2$, pyridine, PhH, 5°C; ii) N-hydroxypyridine-2-thione sodium salt, DMAP, PhH, 5°C to 25°C then Bu_3SnH, AIBN, 50°C, 71% (from **10**); I. i) $HOCH_2CH_2OH$, TsOH, PhH, 80°C, 89%; ii) 20% KOH, DMSO, 40°C, 93%; iii) MeLi, THF, 0° to 24°C, 98%; iv) CH_2Br_2-Zn-$TiCl_4$, THF-CH_2Cl_2, 25°C, 84%; J. i) 80% AcOH, 26°C, 93%; ii) $BrCH_2CO_2Me$, Zn, 1,3-dioxane, 40°C, US; iii) AcCl, $PhNMe_2$, $CHCl_3$, 60°C, 60% (2 steps); iv) DBU, PhH, 80°C, 93% (*E*:*Z*=4.6:1); K. i) DIBAL, CH_2Cl_2, -78°C, ii) PDC, 4Å MS, 26°C, 92% (2 steps); iii) $(i\text{-PrO})_2P(O)CHCO_2Me$, *t*-BuOK, THF, -78° to 0°C, 95%; iv) MeLi, Et_2O, -30°C, 86%.

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