TOTAL SYNTHESIS OF (±)-*cis*-, *trans*-CEMBRANOLIDES AND (±)-SARCOPHYTONIN B FROM GERANYLGERANIOL[1]

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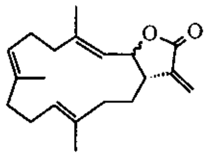
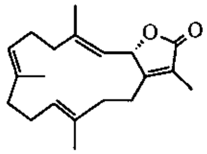
Abstract - (±)-*cis*-Cembranolide (**I**) was synthesized *via* Cr(II) mediated intramolecular macrocyclization of ω-formyl-β-methoxycarbonylallyl halides (**6a** and **b**), which were prepared starting from geranylgeraniol. The stereoselective synthesis of (±)-*trans*-cembranolide (**II**) was achieved by lactonization of 14-membered *cis*-intermediate (**7**) with inversion of the stereochemistry at C-2. (±)-Sarcophytonin B (**III**) was also synthesized from (±)-*cis*-cembranolide (**I**) *via* isomerization of the *exo*-cyclic double bond.

Many cembranolides, 14-membered diterpenoid lactones, have been found as marine natural products,[2] and some of them possess interesting physiological properties.[3] Some efforts have been made to synthesize cembranolides in recent years.[4] The unnamed *cis*- and *trans*-cembranolides (**I** and **II**) were isolated from *Sinularia mayi* by Uchio *et al.*,[5] and also from *Lobophytum michaelae* by Coll *et al.*[6] Sarcophytonin B (**III**) was isolated from *Sarcophyton* sp. by Kobayashi *et al.*[7] Several syntheses of the cembranolides (**I** and **II**) had been reported.[8]



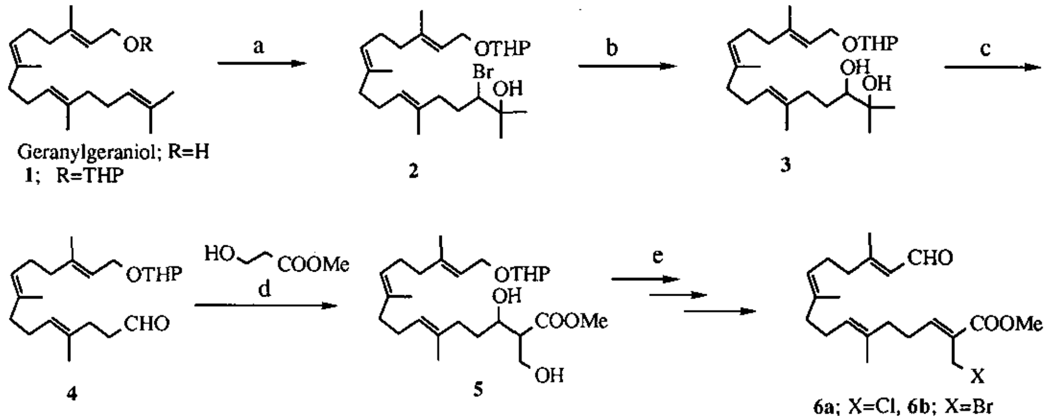
cis-Cembranolide (**I**)
trans-Cembranolide (**II**)



Sarcophytonin B (**III**)

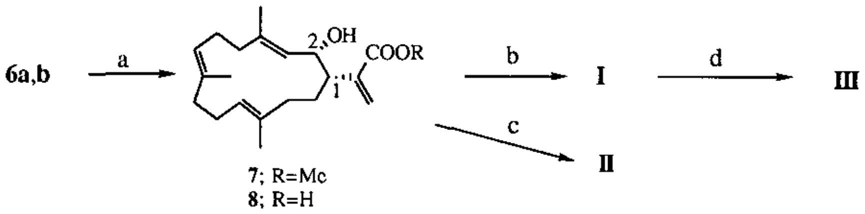
We recently described a facile synthesis of (±)-**I** *via* Cr(II) mediated macrocyclization of the ω-formyl-β-methoxycarbonylallyl halide (**6**), derived from geraniol, and subsequent lactonization reaction.[9] We now describe another more facile synthesis of (±)-**I** starting from geranylgeraniol. We also report the synthesis of (±)-*trans*-cembranolide (**II**), and (±)-sarcophytonin B (**III**) using this intramolecular macrocyclization method.

Preparation of the ω-formylallyl halide (**6**) starting from geranylgeraniol was as follows. The regioselective hydroxy bromination of the terminal double bond of the THP ether of geranylgeraniol (**1**) was performed by the method of van Tamelen *et al.* (NBS in 40% H_2O-THF).[10] The bromohydrin (**2**) was treated with K_2CO_3 followed by $HClO_4$ to give the diol (**3**), which was then converted into the aldehyde (**4**) with lead tetraacetate in good yield. The aldehyde was identified by the comparison with the authentic sample synthesized from geraniol.[9] Conversion of the aldehyde into ω-formylallyl halides (**6a** and **6b**) had already been reported by us.[9,11] Macrocyclization of the aldehydes (**6a** and **b**) selectively affords the *cis*-cyclized product (**7**) in good yields, and subsequent lactonization with *p*-TsOH gave (±)-*cis*-cembranolide (**I**).[9] Treatment of the methyl ester (**7**) with NaH in THF[12] gave the carboxylic acid (**8**), which was then treated with *N,N*-dimethylformamide dineopentylacetal *via* Walden inversion[12,13] to give (±)-*trans*-cembranolide (**II**), mp 53.5-54.5 °C in 70% yield. The ^1H- and ^{13}C-nmr spectra were coincident with those of the natural (-)-*trans*-cembranolide.[14]



Scheme 1

a) NBS/THF-H_2O (61%), b) 1) K_2CO_3/MeOH, 2) $HClO_4$/THF-H_2O (86%), c) $Pb(OAc)_4$, K_2CO_3/benzene (94%), d) LDA, THF, -78°C (56%, conversion 70%), e) See reference 8 and note 10.



Scheme 2

a) 5.5 eq $CrCl_2$/DMF(0.02M), room temperature (79~81%), b) *p*-TsOH/benzene, room temperature 10 min (87%), c) 1) NaH/THF, room temperature, 2) $Me_2NCH(O\text{-neopentyl})_2$/toluene, reflux (70%), d) $RhCl_3$/EtOH-H_2O, reflux (66%)

Isomerization of the *exo*-cyclic double bond of *cis*-cembranolide (**I**) into the *endo*-cyclic one was effected with rhodium chloride.[15] An aqueous ethanol solution of I and $RhCl_3$ was heated for 7 h to afford (±)-sarcophytonin B (**III**) in 66 % yield. The ^{1}H-nmr spectrum and other spectral properties were identical with those of the natural (+)-sarcophytonin B.[16]

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