

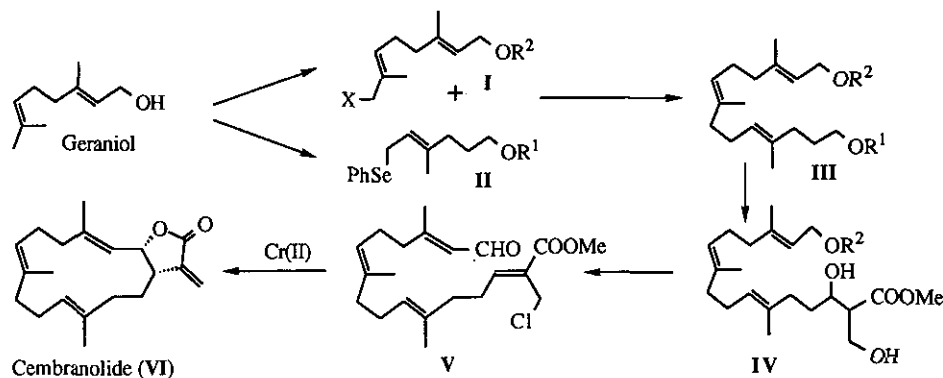
**TOTAL SYNTHESIS OF ($\pm$)-CEMBRANOLIDE VIA
Cr(II) MEDIATED INTRAMOLECULAR MACROCYCLIZATION
OF β -ALKOXYCARBONYLALLYL HALIDE¹**

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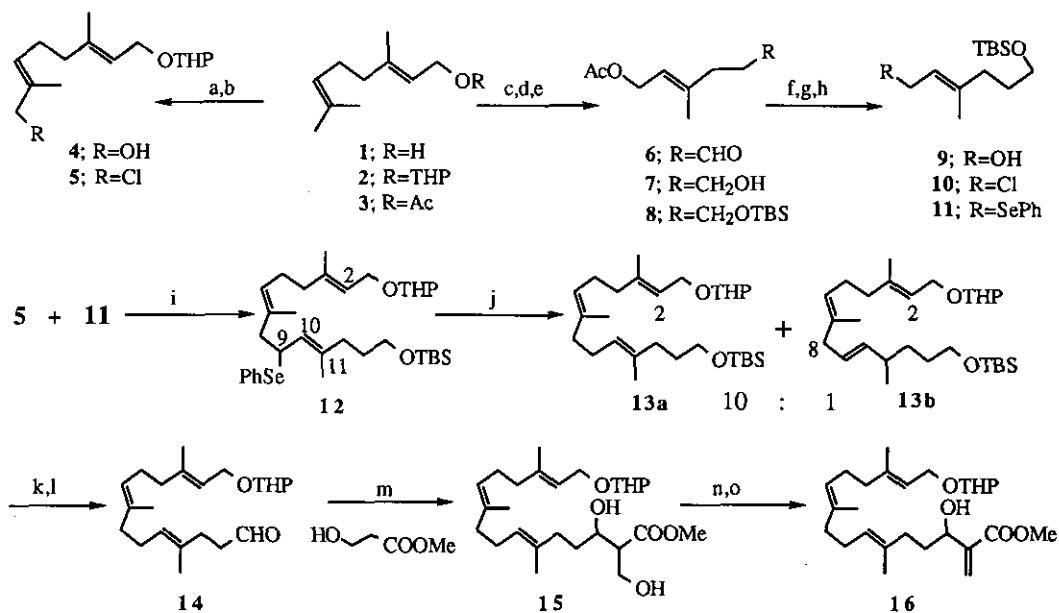
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Abstract - The ω -formyl- β -methoxycarbonylallyl halide (**20**), prepared from geraniol and methyl β -hydroxypropionate, was cyclized efficiently and with high stereoselectivity to 14-membered *cis*-cycloalkenol (**21**) by CrCl₂ in DMF. The cycloalkenol was treated with *p*-TsOH to give an excellent yield of ($\pm$)-*cis*-cembranolide (**VI**).

Cembranolides, 14-membered diterpene lactone, are a widely distributed class of marine natural products with interesting structural and biological properties.² Although there are a number of reports on the synthesis of cembranoids, some efforts have been made to synthesize cembranolides in recent years.³ The unnamed cembranolide (**VI**) was isolated from *Sinularia mayi* by Uchio *et al.*,⁴ and also from *Lobophytum michaelae* by Coll *et al.*⁵ The first synthesis of the cembranolide (**VI**) had been reported by Aoki *et al.*⁶ Marshall *et al.* have used an intramolecular addition of an allylic stannane to an aldehyde for their synthesis of the cembranolide.⁷ The Marshall's cyclization to 14-membered ring, a ynal-allylic stannane cyclization, gave a good result, however, there were some difficulties during the introduction of an α -methylene- γ -lactone moiety into the cycloalkenol.



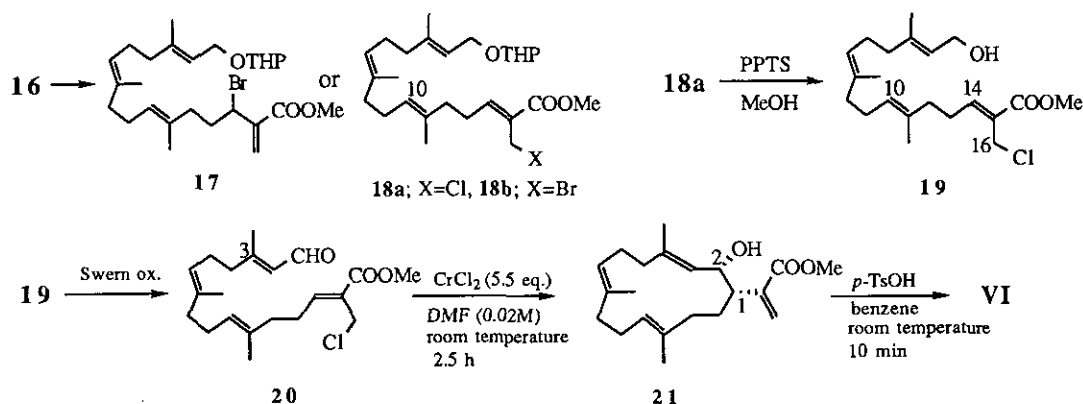
We would like to report a more facile synthesis of ($\pm$)-**VI**, by using macrocyclization followed by lactonization reaction. We had described the macrocyclization of ω -formyl- β -methoxycarbonylallyl halide into the α -methylene- γ -lactones fused to 12- and 14-membered carbocycles by Cr(II) reagent.⁸⁻¹⁰ We applied this methodology to geranylgeraniol derivative (**V**) for the synthesis of **VI**, having α -methylene- γ -lactone moiety. The two segments necessary for assembly of the cyclization precursor (**V**) were prepared from geraniol. Allyl chloride (**I**) was prepared from THP ether of geraniol (**2**). Allylic oxidation¹¹ followed by chlorination¹² gave the first segment (**5**). The second segment (**II**) was prepared from geranyl acetate (**3**). Regioselective ozonolysis¹³ followed by reduction gave an alcohol (**7**), which was protected with TBSCl to give **8**. Conversion to allylic alcohol (**9**) and chlorination and then phenylselenylation¹⁴ gave the allylic selenide (**11**).



a) SeO₂, TBHP, CH₂Cl₂ (35%), b) LiCl, MsCl, *s*-collidine, DMF (87%), c) O₃, pyridine, CH₂Cl₂, -78°C then Me₂S (88%), d) NaBH₄, EtOH (80%), e) TBSCl, imidazole, DMF (93%), f) LiAlH₄, Et₂O (99%), g) LiCl, MsCl, *s*-collidine, DMF (97%), h) (PhSe)₂, NaBH₄, EtOH (97%), i) LDA, THF, -78°C (86%), j) W-2 Raney Ni, EtOH (93%), k) Bu₄NF, THF (91%), l) Swern ox. (87%), m) LDA, THF, -78°C (56%, conversion 70%), n) *p*-TsCl, pyridine (96%), o) DBU, Et₂O, room temperature (83%)

Alkylation of the anion of **11** (LDA, THF, -78 °C, 30 min)¹⁵ with the chloride (**5**) at -78 °C for 10 min gave the coupled products (**12**) in 86% yield.¹⁶ Removal of the phenylseleno group with W2-Raney nickel in EtOH at -30 °C gave a 10:1 mixture of the desired trisubstituted olefin (**13a**) and isomerized disubstituted olefin (**13b**) in 93% yield.¹⁶ The mixture of the positional isomers of the olefins was converted to aldehyde (**14**) (TBAF, THF then Swern oxidation). The aldehyde was coupled with dianion of methyl β -hydroxypropionate to give diol (**15**), which was treated with *p*-TsCl in pyridine and then DBU in Et₂O to give α,β -unsaturated ester (**16**) in 80% yield. Usually, the β -hydroxy- α,β -unsaturated esters have been submitted to brominative allylic

rearrangement with NBS/Me₂S^{8,17} to give with allylic transposition and Z selectivity, (Z)-2-bromomethyl-2-alkenoic esters. Application of this method to the bromination of **16** did not give the rearranged bromide (**18b**), but unexpected secondary bromide (**17**) with S_N2 reaction in 67% yield. Other brominating reagent, CBr₄/Ph₃P,¹⁸ also yielded the secondary bromide, however, CCl₄/tri-*n*-octylphosphine¹⁹ gave with Z selectivity, the primary allylic chloride (**18a**) in 71% yield after purification by hplc. Deprotection of the THP ether (PPTS, MeOH) of **18a** gave 92% yield of the desired allyl chloride (**19**).²⁰ The final refunctionalization of **19** in preparation for macrocyclization consisted of conversion to the α,β-unsaturated aldehyde (**20**)²¹ by Swern oxidation (89%).



Macrocyclization of **20** was performed with 5.5 eq of CrCl₂ (Aldrich) in DMF (0.02M concentration) at room temperature for 2.5 h to give 14-membered *cis*-hydroxy ester (**21**), mp 85.5-86 °C, in 81% yield. Lactonization of **21** with *p*-TsOH in benzene at room temperature for 10 min, gave (±)-*cis*-lactone (**VI**), mp 82-83 °C, in 87% yield. The resulting α-methylene-γ-lactone (**VI**) was identified through direct comparison of ¹H-nmr spectrum and other spectral properties²² as the unnamed *cis*-cembranolide isolated by Uchio *et al.* from the soft coral *Sinularia mayi*.⁴

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