TOTAL SYNTHESIS OF (±)-CEMBRANOLIDE VIA Cr(II) MEDIATED INTRAMOLECULAR MACROCYCLIZATION OF β-ALKOXYCARBONYLALLYL HALIDE[1]

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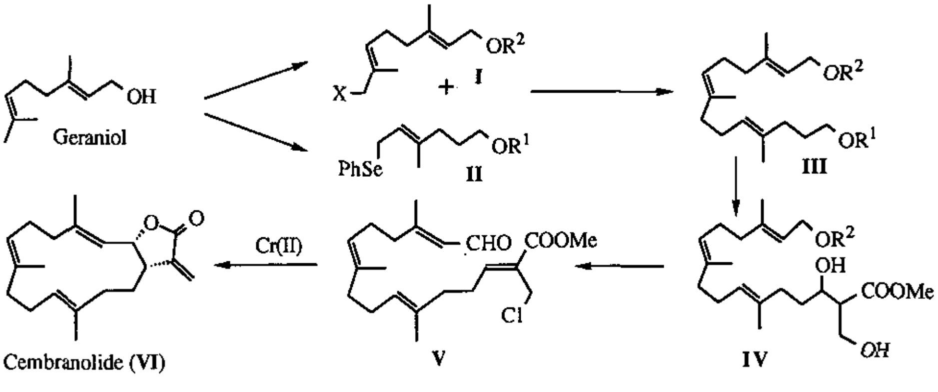
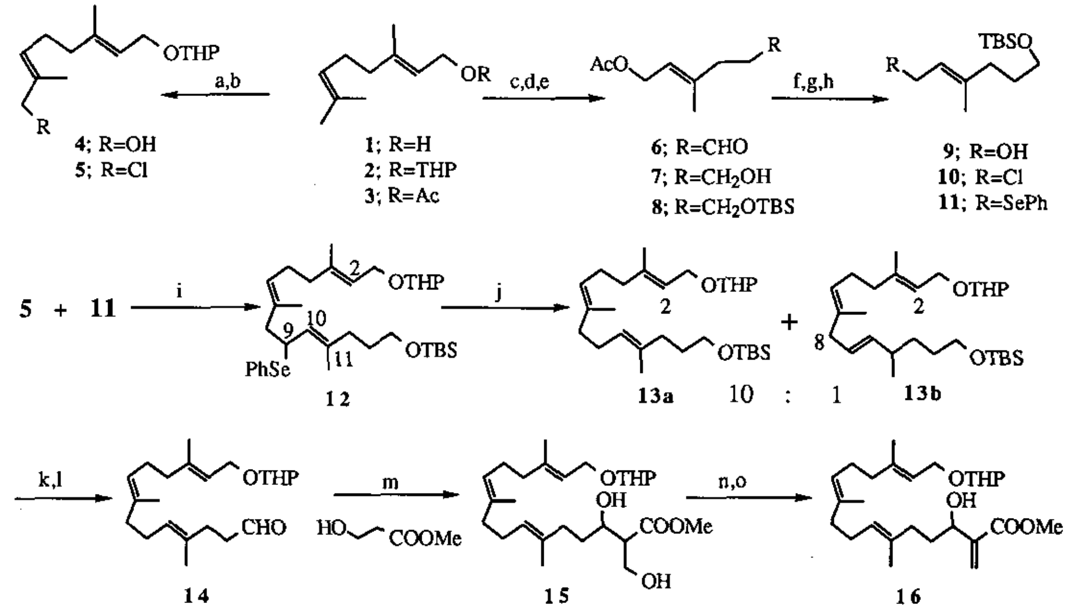
Abstract - The ω-formyl-β-methoxycarbonylallyl halide (**20**), prepared from geraniol and methyl β-hydroxypropionate, was cyclized efficiently and with high stereoselectivity to 14-membered *cis*-cycloalkenol (**21**) by $CrCl_2$ in DMF. The cycloalkenol was treated with *p*-TsOH to give an excellent yield of (±)-*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.

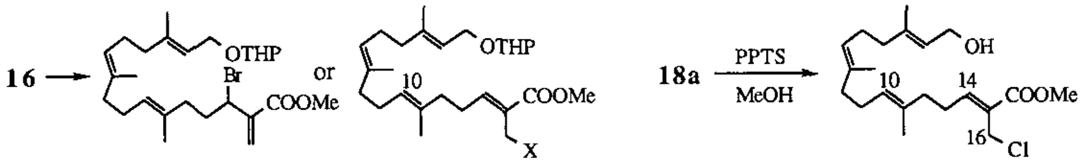


We would like to report a more facile synthesis of (±)-**VI**, by using macrocyclization followed by lactonization reaction. We had described the macrocyclization of ω-formyl-β-methoxycarbonylallyl halide into the α-methylene-γ-lactones fused to 12- and 14-membered carbocycles by Cr(II) reagent.[8-10] 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 oxidation[11] followed by chlorination[12] gave the first segment (**5**). The second segment (**II**) was prepared from geranyl acetate (**3**). Regioselective ozonolysis[13] followed by reduction gave an alcohol (**7**), which was protected with TBSCl to give **8**. Conversion to allylic alcohol (**9**) and chlorination and then phenylselenylation[14] gave the allylic selenide (**11**).

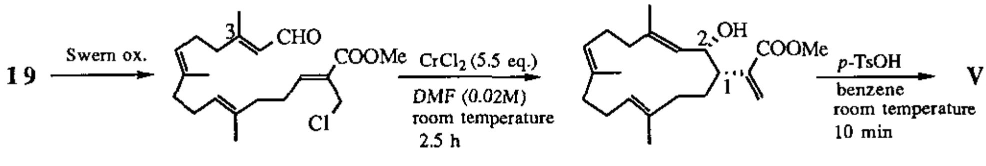


a) SeO_2,TBHP, CH_2Cl_2 (35%), b) LiCl , MsCl, *s*-collidine, DMF (87%), c) O_3, pyridine, CH_2Cl_2, -78°C then Me_2S (88%), d) $NaBH_4$, EtOH (80%), e) TBSCl, imidazole, DMF (93%), f) $LiAlH_4$, Et_2O (99%), g) LiCl, MsCl, *s*-collidine, DMF (97%), h) $(PhSe)_2$, $NaBH_4$, EtOH (97%), i) LDA, THF, -78°C (86%), j) W-2 Raney Ni, EtOH (93%), k) Bu_4NF, THF (91%),.
l) Swern ox. (87%), m) LDA, THF, -78°C (56%, conversion 70%), n) *p*-TsCl, pyridine (96%), o) DBU, Et_2O, 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 Et_2O 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/Me$_2$S[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_N 2 reaction in 67% yield. Other brominating reagent, CBr$_4$/Ph$_3$P,[18] also yielded the secondary bromide, however, CCl$_4$/tri-*n*-octylphosphine[19] 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%).



17 **18a**; X=Cl, **18b**; X=Br **19**



20 **21**

Macrocyclization of **20** was performed with 5.5 eq of CrCl$_2$ (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 ^{1}H-nmr spectrum and other spectral properties[22] as the unnamed *cis*-cembranolide isolated by Uchio *et al.* from the soft coral *Sinularia mayi*.[4]

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