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

Kiyoshi Nishitani, Toshihiko Konomi, Youji Mimaki, Takashi Tsunoda,
and Koji Yamakawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo,
Ichigaya-funagawara, Shinjuku-ku, Tokyo 162, Japan

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 (±)-cis-
embranolide (VI).

Cembranolides, 14-membered diterpene lactone, are a widely distributed class of marine natural products with
interesting structural and biological properties. Although there are a number of reports on the synthesis of
embranoloids, some efforts have been made to synthesize cembranolides in recent years. The unnamed
embranolide (VI) was isolated from Sinularia mayi by Uchio et al., and also from Lobophytum michaelae by
Coll et al. The first synthesis of the cembranolide (VI) had been reported by Aoki et al. Marshall et al. have
used an intramolecular addition of an allylic stannane to an aldehyde for their synthesis of the cembranolide.
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 α-formyl-β-methoxycarbonylallyl halide into the α-methylene-γ-lactones fused to 12- and 14-membered carbocycles by Cr(II) reagent. 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 followed by chlorination gave the first segment (5). The second segment (II) was prepared from geranyl acetate (3). Regioselective ozonolysis 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 gave the allylic selenide (11).

\[
\begin{align*}
4: R &= \text{OH} \\%
5: R &= \text{Cl} \\
1: R &= \text{H} \\
2: R &= \text{THP} \\
3: R &= \text{Ac} \\
6: R &= \text{CHO} \\
7: R &= \text{CH}_2\text{OH} \\
8: R &= \text{CH}_2\text{OTBS} \\
9: R &= \text{OH} \\
10: R &= \text{Cl} \\
11: R &= \text{SePh}
\end{align*}
\]

5 + 11 \rightarrow

\[
\begin{align*}
\text{PhSe} & \\
\text{OTBS} & \\
\text{OTB} &
\end{align*}
\]

\[
\begin{align*}
12 & \\
13a & \\
13b &
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \\
\text{OH} &
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \\
\text{MeO} &
\end{align*}
\]

a) SeO\textsubscript{2}:TBHP, CH\textsubscript{2}Cl\textsubscript{2} (35%), b) LiCl, MsCl, s-collidine, DMF (87%), c) O\textsubscript{3}, pyridine, CH\textsubscript{2}Cl\textsubscript{2}, -78°C then Me\textsubscript{2}S (88%), d) NaBH\textsubscript{4}, EtOH (80%), e) TBSCI, imidazole, DMF (93%), f) LiAlH\textsubscript{4}, Et\textsubscript{2}O (99%), g) LiCl, MsCl, s-collidine, DMF (97%), h) (PhSe)\textsubscript{2}, NaBH\textsubscript{4}, EtOH (97%), i) LDA, THF, -78°C (86%), j) W-2 Raney Ni, EtOH (93%), k) Bu\textsubscript{4}NF, THF (91%).

l) Swern ox. (87%), m) LDA, THF, -78°C (56%, conversion 70%), n) p-TsCl, pyridine (96%), o) DBU, Et\textsubscript{2}O, room temperature (83%) Alkylation of the anion of 11 (LDA, THF, -78°C, 30 min)\textsuperscript{15} with the chloride (5) at -78°C for 10 min gave the coupled products (12) in 86% yield.\textsuperscript{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.\textsuperscript{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\textsubscript{2}O 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/Me2S8,17 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 SN 2 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 refunctonalization 
of 19 in preparation for macrocyclization consisted of conversion to the α,β-unsaturated aldehyde (20)21 by 
Swern oxidation (89%).

![Chemical Structures]

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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natural cembranolide were kindly provided by Professor Nakayama and Professor Uchio to whom we are 
grateful.

REFERENCES AND NOTES
1. This paper forms "Studies on the Terpenoids and Related Alicyclic Compounds XLIV". Part XLIII: 
822.


10. Some Cr(II)-mediated macrocyclization of allyl halides, without β-alkoxycarbonyl function, to cembranoids have been reported. For example; C. M. Rayner, P. C. Astles, and L. A. Paquette, *J. Am. Chem. Soc.*, 1992, 114, 3926, and reference 15.


16. The ratio of the positional isomers was evidenced by $^1$H-nmr spectrum at 500 MHz ($^1$H, t, $J=7$ Hz, 2-H of 13a and b), $^1$H, d, $J=5.1$ Hz, 8-H of 13b).


20. The geometry of the allylic chloride (19) at C14-15 was deduced to be Z by its $^1$H-nmr spectrum, exhibiting a triplet signal due to 14-H at $^6$ 6.99. M. F. Semmelhack and E. S. C. Wu, *J. Am. Chem. Soc.*, 1976, 98, 3384. No regioisomer was observed in the $^{13}$C- and the $^1$H-nmr spectra.


22. The ir, $^{13}$C-nmr and mass spectral data were good agreement with those reported.

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