TOTAL SYNTHESIS OF (+)-cis-, trans-CEMBRANOLIDES AND (+)-SARCOPHYTONIN B FROM GERANYLGERANIOL

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Abstract - (+)-cis-Cembranolide (I) was synthesized via Cr(II) mediated intramolecular macrocyclization of α-formyl-β-methoxycarbonylallyl halides (6a and b), which were prepared starting from geranylgeraniol. The stereo-selective 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, and some of them possess interesting physiological properties. Some efforts have been made to synthesize cembranolides in recent years. The unnamed cis- and trans-cembranolides (I and II) were isolated from Sinularia mayi by Uchio et al., and also from Lobophyrum michaelae by Coll et al. Sarcophytonin B (III) was isolated from Sarcophyton sp. by Kobayashi et al. Several syntheses of the cembranolides (I and II) had been reported.

We recently described a facile synthesis of (+)-I via Cr(II) mediated macrocyclization of the α-formyl-β-methoxycarbonylallyl halide (6), derived from geraniol, and subsequent lactonization reaction. 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 α-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% H2O-THF). The bromohydrin (2) was treated with K2CO3 followed by HClO4 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. Conversion of the aldehyde into α-formylallyl halides (6a and 6b) had already been reported by us. 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). Treatment of the methyl ester (7) with NaH in THF gave the carboxylic acid (8), which was then treated with N,N-dimethylformamide dineopentylacetal via Walden inversion to give (±)-trans-cembranolide (II), mp 53.5-54.5 °C in 70% yield. The 1H- and 13C-nmr spectra were coincident with those of the natural (-)-trans-cembranolide.

Scheme 1

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\begin{align*}
\text{Geranylgeraniol; } R=\text{H} & \quad \xrightarrow{\text{a}} \quad \text{2} \quad \xrightarrow{\text{b}} \quad \text{3} \quad \xrightarrow{\text{c}} \\
\text{Geranylgeraniol; } R=\text{THP} & \quad \text{CHO} \quad \xrightarrow{\text{d}} \quad \text{4} \quad \xrightarrow{\text{e}} \quad \text{6a, b}
\end{align*}
\]

Scheme 2

\[
\begin{align*}
\text{6a, b} & \quad \xrightarrow{\text{a}} \quad \text{7} \quad \text{8} \quad \xrightarrow{\text{b}} \quad \text{I} \quad \xrightarrow{\text{d}} \quad \text{III} \quad \xrightarrow{\text{c}} \quad \text{II}
\end{align*}
\]

Scheme 1

a) NBS/THF-H2O (61%), b) K2CO3/McOH, 2) HClO4/THF-H2O (86%), c) Pb(OAc)4, K2CO3/benzene (94%), d) LDA, THF, -78°C (56%, conversion 70%), e) See reference 8 and note 10.

Scheme 2

a) 5.5 eq CrCl3/DMF(0.02M), room temperature (79-81%), b) p-TsOH/benzene, room temperature 10 min (87%), c) 1) NaH/THF, room temperature, 2) Me2NCH(O-neopentyl)/toluene, reflux (70%), d) RhCl3/EtOH-H2O, reflux (66%)
Isomerization of the \textit{exo}-cyclic double bond of \textit{cis}-cembranolide (I) into the \textit{endo}-cyclic one was effected with rhodium chloride.\textsuperscript{15} An aqueous ethanol solution of I and \textit{RhCl}_3 was heated for 7 h to afford (\pm)-sarcophytonin B (III) in 66\% yield. The \textit{1H}-nmr spectrum and other spectral properties were identical with those of the natural (+)-sarcophytonin B.\textsuperscript{16}

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\textbf{REFERENCES AND NOTES}

1. This paper forms "Studies on the Terpenoids and Related Alicyclic Compounds XLV". Part XLIV: reference 8.
11. The allylic bromide (6b) was synthesized by the same methods as described for 6a except bromination step (CBr_4 was used instead of CCl_4).
14. Spectra of the natural \textit{cis}- and \textit{trans}-cembranolides were kindly provided by Prof. M. Nakayama and Prof. Y. Uchio to whom we are grateful.
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