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Synthesis of 1,3-Diyne Derivatives of Lembehyne B with Antitumor and Neuritogenic Activity †

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Abstract: The report presents data from our studies on obtaining lembehyne B derivatives with cytotoxic and neuritogenic activity. The methods and approaches to the synthesis of the above-mentioned lembehynes presented in the report are based on the use of the catalytic cross-cyclomagnesiation of 1,2-dienes (the Dzhemilev reaction) at the key stage of the synthesis.

Keywords: lembehyne B; 1Z,5Z-dienes; cross-cyclomagnesiation; anti-cancer; neuritogenic activity

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1. Introduction

Natural polyacetylenes are compounds containing two or more carbon–carbon triple bonds in their structure. Naturally occurring polyacetylenes have a wide range of structural diversity and are widely distributed in plants, fungi, marine invertebrates, etc. Acetylene metabolites exhibit a wide range of biological activities, including antifungal, antimicrobial and antitumor activities, inhibition of HIV reverse transcriptase, which makes them interesting for medicine, pharmacology, medicinal chemistry, and the pharmaceutical industry [1–3].

Some secondary metabolites identified in various sponge species have antitumor activity. Sea sponges are leaders in their content of biologically active substances in comparison with other marine invertebrates. Some compounds isolated from sponges have complex structures and exhibit biological activity at very low doses [4,5].

The polyacetylenic compounds halicynones A **(1)** and B **(2)** were isolated from the marine sponge *Haliclona* sp., possessing antifungal activities against *Candida glabrata* and a high cytotoxicity against human colon tumor cells (HCT). Additionally, pellynols A **(3)** and B **(4)** showed strong cytotoxicity against some melanoma and ovarian cancer cells [6–8]. Acetylene alcohols, strongylodiols A **(5)**, and C **(6)** were obtained from the Okinawan marine sponge belonging to the genus *Strongylophora* (Figure 1). Each of these compounds was a mixture of enantiomers in different ratios and exhibited cytotoxic activity against human T-lymphocytic leukemia (MOLT-4) cells [9].

Lembehynes A–C **(7–9)**, long chain acetylenic alcohols, were isolated from the Indonesian marine sponge *Haliclona* sp. Lembehyne A **(7)** induces bipolar neuritogenesis of Neuro 2A cells, and also enhances the activity of Neuro2A acetylcholinesterase. Lembehynes B **(8)** and C **(9)** also exhibit neuritogenic activity against the Neuro 2A neuroblastoma cell line [10–12] (Figure 2).

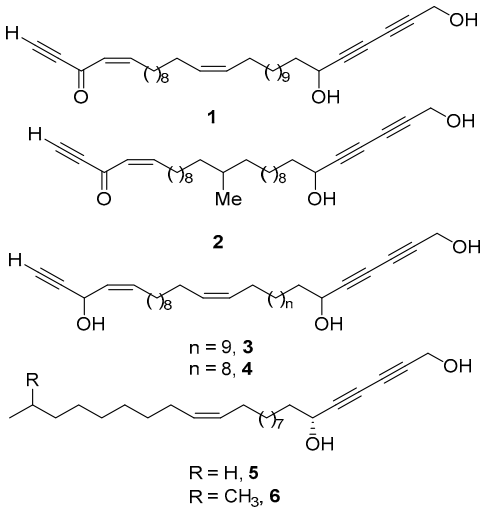


Figure 1. Natural polyacetylene compounds.

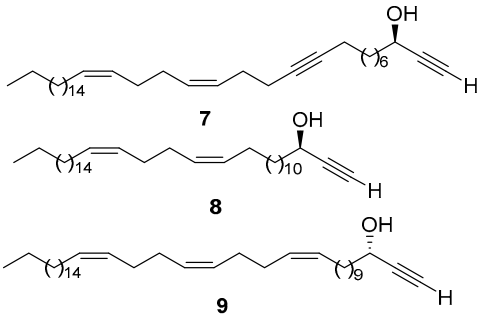
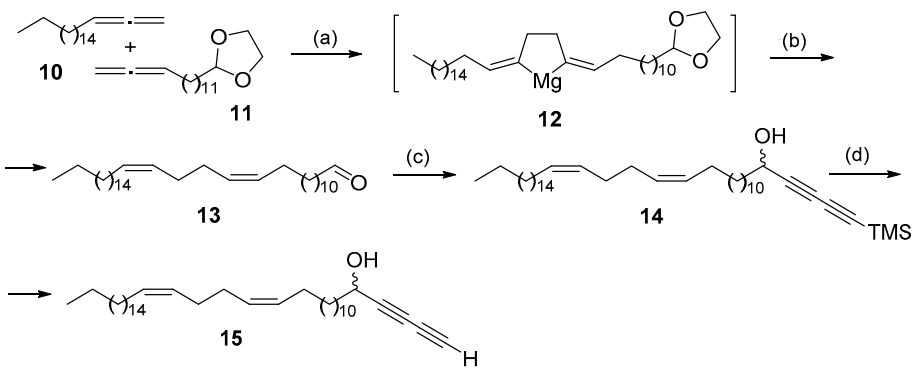


Figure 2. Lembehynes A–C.

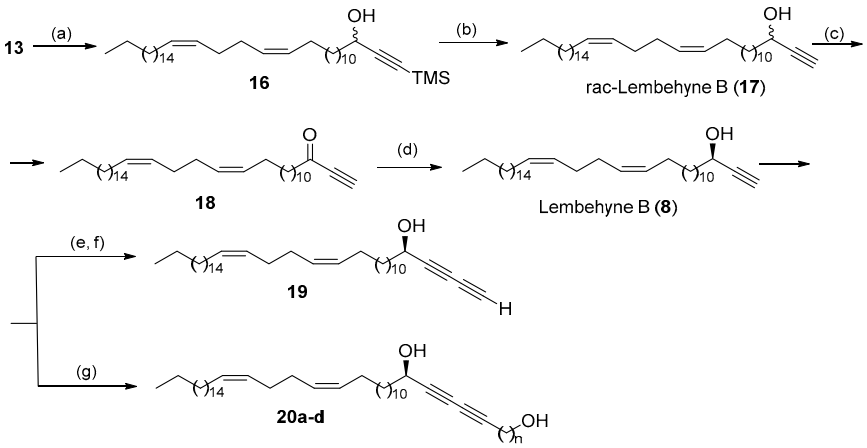
2. Results and Discussion

We have synthesized new 1,3-diyne derivatives of lembehyne B using the catalytic cross-cyclomagnesiation of O-containing and aliphatic allenes at the key stage [13–32]. At the first stage, (13Z,17Z)-tetraconta-13,17-dienal **(4)** was obtained by the reaction of cross-cyclomagnesiation of 1,2-nonadecadiene **(10)** and 2-tetradec-12,13-dien-1-yl-1,3-dioxolane **(11)** with EtMgBr in the presence of metallic Mg and catalytic amounts of Cp_2TiCl_2 (10 mol.%) (**10**:**11**:EtMgBr:Mg:[Ti] = 12:10:30:20:0.1, Et_2O, 20–22 °C, 7 h), giving a 79% yield (Scheme 1). At the second stage, successive reactions of aldehyde **(13)** with preliminarily obtained 1-lithium-4-trimethylsilyl-1,3-butadiine and removal of the trimethylsilyl group with trimethylbutylammonium fluoride (TBAF) in THF gave the target 1,3-diyne analogue of rac-lembehyne B **(15)** with a ~66% yield (Scheme 1).



Scheme 1. Synthesis of the new 1,3-diyne derivatives of lembehyne B. (a) EtMgBr, Mg, Cp_2TiCl_2, Et_2O, rt; (b) H^+; (c) 1-lithium-4-trimethylsilyl-1,3-butadiine, THF, rt, 85%; (d) TBAF, THF, rt, 99%.

In order to elucidate the influence of the stereoconfiguration of the hydroxyl group in the acetylenic derivatives of lembehyne B, we developed an original method for the synthesis of the latter, with the R-configuration of the hydroxyl group, by adding the corresponding 1-bromoalkynes directly to the molecule of lembehyne B synthesized from aldehyde **(13)** (Scheme 2).



Scheme 2. Synthesis of the new 1,3-diyne analogs of lembehyne B. (a) Lithium trimethylsilylacetylenide, THF, rt, 90%; (b) TBAF, THF, rt, 99%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 86%; (d) B-3-pinanyl-9-borabicyclo[3.3.1]nonane, THF, rt, 84% (95% ee); (e) 1-bromo-2-trimethylsilylacetylene, CuCl, NH_2OH, n-$BuNH_2$, H_2O, rt,; (f) TBAF, THF, rt, 97%; (g) 1-bromo-2-(ω-hydroxyalkyl)acetylene, CuCl, NH_2OH, n-$BuNH_2$, H_2O, rt, 99%; n = 1–3.

Thus, according to the developed scheme, we carried out the synthesis of racemic **(17)** and natural lembehyne B **(8)** by successive reactions of the addition of lithium trimethylsilylacetylenide to aldehyde **(13)**, deprotection of the resulting alkyne **(16)**, oxidation of alcohol **(17)**, and stereoselective reduction of ketone **(18)** at the final stage of synthesis. Reactions of natural lembehyne B **(8)** with 1-bromo-2-trimethylsilylacetylene or 1-bromo-2-(ω-hydroxyalkyl)acetylenes under the action of CuCl led to the synthesis of the target 1,3-diyne analogs of lembehyne B **(19)** and **(20a–d)** in high yields (50–67%). For the synthesized 1,3-diyne derivatives of lembehynes B, apoptosis-inducing activity against five tumor cell lines Jurkat, K562, U937, HeLa, and HEK293 and neuritogenic activity against PC12, PC9, and Neuro2A cell cultures were studied in detail.

Experimental Section

^1H and ^{13}C NMR spectra and the general procedure for all the synthesized compounds are presented in previously published articles [22–28].

3. Conclusions

Thus, we have synthesized, for the first time, 1,3-diyne analogues of lembehyne B containing a Z,Z-diene group using the cross-cyclomagnesiation reaction of aliphatic and O-containing 1,2-dienes catalyzed by Cp_2TiCl_2 at the key stage of the synthesis, and also studied their antitumor activity using modern methods of flow cytometry and multiplex analysis.

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