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An Original Method for the Synthesis and Study of the Biological Activity of Natural Lembehyne B Aromatic Analogs †

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Abstract: In the development of earlier-initiated studies on the synthesis of natural and synthetic neuritogenic alkynols, lembehynes A–C—which simultaneously exhibit high antitumor activity—we developed a method for the synthesis of an analogue of natural lembehyne B containing a phenyl radical in its structure. It is shown that the synthesized aromatic analogue of lembehyne B exhibits higher antitumor activity in vitro than a number of tumor cell lines (Jurkat, K562 and U937).

Keywords: 1,2-dienes; cross-cyclomagnesiation; lembehyne B

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1. Introduction

Lembehynes are a unique class of natural compound that exhibit a wide range of biological activities and have neuritogenic, antitumor and antibacterial properties [1–10].

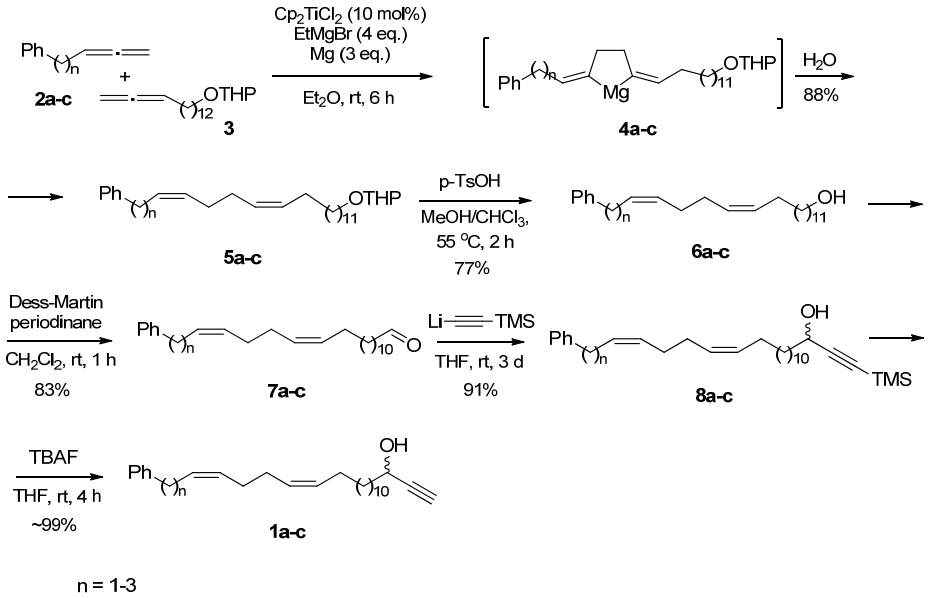
Earlier, we reported on the complete synthesis of natural lembehyne B, as well as the preparation of synthetic derivatives of lembehyne B containing a 1,3-diyne fragment in their structure. The synthesized lembehynes showed cytotoxicity toward tumor cells of the Jurkat, U937, K562, HeLa and Hek293 lines and neuritogenic activity toward Neuro 2A mouse neuroblastoma cells [11,12].

It is known that the π–π stacking interaction of aromatic radicals, which are biologically active compounds with nitrogenous bases of the DNA or RNA of tumor cells, can lead to disruption of the processes of transcription and replication, leading to apoptosis [13,14].

Based on the results obtained earlier, we have synthesized a number of aromatic derivatives of lembehyne B using terminal allenes at the key stage of the catalytic cross-cyclomagnesiation reaction (Dzhemilev reaction) [14–25].

2. Results and Discussion

Cross-cyclomagnesiation reactions of 1,2-dienes containing aromatic radicals **2(a–c)** and tetrahydropyran esters of 13,14-pentadecadienol **3** using EtMgBr in the presence of metallic Mg and a Cp_2TiCl_2 catalyst (10 mol%), through the stage of formation of magnesacyclopentanes **4(a–c)**, the hydrolysis of which gave tetrahydropyran ethers 13Z,17Z-dienes **5(a–c)** in 79–82% yields. Successive reactions of the removal of tetrahydropyranyl protection and the oxidation of unsaturated alcohols **6(a–c)** using Dess–Martin periodinane led to 13Z,17Z-diene aldehydes **7(a–c)** in ~78–82% yields. As a result of the reaction of pre-synthesized lithium (trimethylsilyl)acetylenide with aldehydes **7(a–c)** and the removal of the trimethylsilyl protection with TBAF, racemic lembehyne B **1(a–c)** derivatives were formed in ~80–84% yields (Scheme 1).



Scheme 1. Synthesis of aromatic derivatives of lembehyne B.

For the synthesized compounds, the in vitro antitumor activity was assessed on Jurkat, K562, HL-60, and U937 cell lines and fibroblasts, including the determination of IC50 using flow cytometry and multiplex analysis.

3. Conclusions

An effective method was developed for the preparation of aromatic derivatives of lembehyne B, using, at the key stage of synthesis, the reaction of catalytic cross-cyclomagnesiation of terminal 1,2-dienes (Dzhemilev reaction). Moreover, their antitumor activity was also studied using the modern methods of flow cytometry and multiplex analysis.

4. Experimental Part

Commercially available reagents (Sigma-Aldrich and Acros) were used. Reactions with organomagnesium compounds were carried out under a dried argon atmosphere. 1,2-dienes were prepared according to the known procedure. Reaction products were analyzed on a Carlo Erba chromatograph (a Hewlett Packard Ultra-1 glass capillary column, 25 m × 0.2 mm, flame ionization detector, operating temperature 50–170 °C, carrier gas helium). TLC was performed on Silufol UV-254 plates. The elemental composition of compounds was determined using a Carlo Erba-1106 instrument. Mass spectra were obtained using a Bruker MALDI-TOF/TOF Autoflex III instrument. The 1H and 13C NMR spectra were recorded on a Bruker Avance 400 spectrometer (100.62 MHz for 13C, and 400.13 MHz for 1H).

*Cross-cyclomagnesiation of 1,2-diene (**2(a–c)**) and 2-(pentadeca-13,14-dien-1-yloxy)tetrahydro-2H-pyran (**3**) with EtMgBr in the presence of Mg metal and Cp_2TiCl_2 catalyst was carried out, according known procedure [11]. 2-(((13Z,17Z)-19-phenylnonadeca-13,17-dien-1-yl)oxy)tetrahydro-2H-pyran (**5a**).* Yield, 79%; R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34-1.93 (28H, m, CH_2), 2.03-2.29 (8H, m, CH_2), 3.40-3.96 (4H, m, CH_2-O), 4.64 (1H, t, *J* = 6 Hz, CH-O), 5.42-5.68 (2H, m, CH=), 7.21-7.44 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 19.71, 25.63, 26.26, 27.36, 27.40, 27.53, 29.41–29.86, 30.84, 33.61, 62.17, 67.65, 98.76, 125.85, 128.36, 128.39, 128.49, 128.94, 130.26, 130.60, 141.08; MS (MALDI-TOF), *m/z*: 440 $[M]^+$; $C_{30}H_{48}O_2$; found (%): C, 81.61; H, 10.89; calc. for $C_{30}H_{48}O_2$ (%): C, 81.76; H, 10.97. *2-(((13Z,17Z)-20-phenylicosa-13,17-dien-1-yl)oxy)tetrahydro-2H-pyran (**5b**).* Yield, 78%; R_f = 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.91 (30H, m, CH_2), 2.00-2.29 (8H, m, CH_2), 3.41-3.96 (4H, m, CH_2-O), 4.63 (1H, t, *J* = 6 Hz, CH-O), 5.42-5.68 (2H, m, CH=), 7.21-7.45 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 19.70, 25.66, 26.26, 26.90, 27.36, 27.41, 27.53, 29.41–29.86, 30.84, 33.61, 62.17, 67.65, 98.76,

125.85, 128.36, 128.39, 128.49, 128.94, 130.26, 130.61, 141.08; MS (MALDI-TOF), *m/z*: 454 $[M]^+$; $C_{31}H_{50}O_2$; found (%): C, 81.84; H, 11.10; calc. for $C_{31}H_{50}O_2$ (%): C, 81.88; H, 11.08. *2-(((13Z,17Z)-21-phenylhenicosa-13,17-dien-1-yl)oxy)tetrahydro-2H-pyran (**5c**).* Yield, 82%; R_f = 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34-1.90 (32H, m, CH_2), 2.03-2.29 (8H, m, CH_2), 3.40-3.96 (4H, m, CH_2-O), 4.64 (1H, t, *J* = 6 Hz, CH-O), 5.42-5.68 (2H, m, CH=), 7.21-7.44 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 19.71, 25.63, 26.26, 26.90, 27.36, 27.40, 27.53, 29.41–29.86, 30.84, 33.61, 62.17, 67.65, 98.76, 125.85, 128.36, 128.39, 128.49, 128.94, 130.26, 130.60, 141.08; MS (MALDI-TOF), *m/z*: 468 $[M]^+$; $C_{32}H_{52}O_2$; found (%): C, 81.94; H, 11.11; calc. for $C_{32}H_{52}O_2$ (%): C, 81.99; H, 11.08.

*THP-deprotection of ether (**5(a–c)**) was carried out with p-TsOH in CH_2Cl_2/MeOH using known method [26]. (13Z,17Z)-19-phenylnonadeca-13,17-dien-1-ol (**6a**).* Yield, 78%; R_f = 0.42 (hexane/EtOAc—5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.69 (22H, m, CH_2), 1.94-2.28 (6H, m, CH_2), 3.66 (2H, t, *J* = 6 Hz, CH_2-O), 5.39-5.65 (4H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.78, 27.32, 27.49, 29.36-29.77, 32.80, 33.57, 63.05, 125.85, 128.37, 128.40, 128.45, 128.94, 130.30, 130.66, 141.15; MS (MALDI-TOF), *m/z*: 356 $[M]^+$; $C_{25}H_{40}O$; found (%): C, 84.13; H, 11.22; calc. for $C_{25}H_{40}O$ (%): C, 84.20; H, 11.30. *(13Z,17Z)-20-phenylicosa-13,17-dien-1-ol (**6b**).* Yield, 79%; R_f = 0.42 (hexane/EtOAc—5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.69 (24H, m, CH_2), 1.94-2.28 (6H, m, CH_2), 3.66 (2H, t, *J* = 6 Hz, CH_2-O), 5.39-5.65 (4H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.78, 27.32, 27.49, 29.36-29.77, 32.80, 33.57, 63.05, 125.85, 128.37, 128.40, 128.45, 128.94, 130.30, 130.66, 141.15; MS (MALDI-TOF), *m/z*: 370 $[M]^+$; $C_{26}H_{42}O$; found (%): C, 84.22; H, 11.44; calc. for $C_{26}H_{42}O$ (%): C, 84.26; H, 11.42. *(13Z,17Z)-20-phenylhenicosa-13,17-dien-1-ol (**6c**).* Yield, 77%; R_f = 0.42 (hexane/EtOAc—5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.69 (26H, m, CH_2), 1.94-2.28 (6H, m, CH_2), 3.66 (2H, t, *J* = 6 Hz, CH_2-O), 5.39-5.65 (4H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.78, 27.32, 27.49, 29.36-29.77, 32.80, 33.57, 63.05, 125.85, 128.37, 128.40, 128.45, 128.94, 130.30, 130.66, 141.15; MS (MALDI-TOF), *m/z*: 370 $[M]^+$; $C_{27}H_{44}O$; found (%): C, 84.33; H, 11.50; calc. for $C_{27}H_{44}O$ (%): C, 84.31; H, 11.53.

*The oxidation of the alcohol (**6(a–c)**) with Dess–Martin periodinane was carried out according known procedure [27]. (13Z,17Z)-19-phenylnonadeca-13,17-dienal (**7a**).* Yield, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88-1.69 (18H, m, CH_2), 2.00-2.28 (6H, m, CH_2), 2.43 (2H, dt, CH_2), 3.43 (2H, d, Ph-CH_2), 5.31-5.63 (4H, m, =CH), 7.19-7.33 (5H, m, CH=), 9.78 (1H, t, *J* = 6 Hz, O=CH); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 22.11, 27.31, 27.34, 27.48, 29.19–29.76, 33.57, 43.93, 125.85, 128.37, 128.40, 128.45, 128.95, 130.29, 130.62, 141.14, 202.93; MS (MALDI-TOF), *m/z*: 354 $[M]^+$; $C_{25}H_{38}O$; found (%): C, 84.53; H, 10.71; calc. for $C_{25}H_{38}O$ (%): C, 84.68; H, 10.80. *(13Z,17Z)-20-phenylicosa-13,17-dien-1-ol (**7b**).* Yield, 78%; R_f = 0.42 (hexane/EtOAc—5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.69 (24H, m, CH_2), 1.94-2.28 (6H, m, CH_2), 3.66 (2H, t, *J* = 6 Hz, CH_2-O), 5.39-5.65 (4H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.78, 27.32, 27.49, 29.36-29.77, 32.80, 33.57, 63.05, 125.85, 128.37, 128.40, 128.45, 128.94, 130.30, 130.66, 141.15; MS (MALDI-TOF), *m/z*: 370 $[M]^+$; $C_{26}H_{42}O$; found (%): C, 84.24; H, 11.44; calc. for $C_{26}H_{42}O$ (%): C, 84.26; H, 11.42. *(13Z,17Z)-21-phenylhenicosa-13,17-dien-1-ol (**7c**).* Yield, 80%; R_f = 0.41 (hexane/EtOAc—5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.69 (26H, m, CH_2), 1.94-2.28 (6H, m, CH_2), 3.66 (2H, t, *J* = 6 Hz, CH_2-O), 5.39-5.65 (4H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.78, 27.32, 27.49, 29.36-29.77, 32.80, 33.57, 63.05, 125.85, 128.37, 128.40, 128.45, 128.94, 130.30, 130.66, 141.15; MS (MALDI-TOF), *m/z*: 384 $[M]^+$; $C_{27}H_{44}O$; found (%): C, 84.32; H, 11.50; calc. for $C_{27}H_{44}O$ (%): C, 84.31; H, 11.53.

*Procedure for preparation of alkyne (**8(a–c)**) was carried out according to known procedure [11]. (15Z,19Z)-21-phenyl-1-(trimethylsilyl)henicosa-15,19-dien-1-yn-3-ol (**8a**).* Yield, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.22 (9H, s, CH_3), 1.31-1.75 (22H, m, CH_2), 1.98-2.27 (6H, m, CH_2), 3.45 (2H, d, Ph-CH_2), 4.38 (1H, t, *J* = 5.0 Гц), 5.38–5.66 (2H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: -0.06, 25.15, 27.33, 27.35, 27.49, 29.27–29.78, 33.58, 37.73, 62.90, 89.23, 107.07, 125.86, 128.38, 128.42, 128.46, 128.95, 130.30, 130.65, 141.14; MS (MALDI-TOF),

m/z: 453[M]$^+$; $C_{30}H_{48}OSi$; found (%): C, 79.46; H, 10.54; calc. for $C_{30}H_{48}OSi$ (%): C, 79.57; H, 10.68. *(15Z,19Z)-22-phenyl-1-(trimethylsilyl)docosa-15,19-dien-1-yn-3-ol (**8b**).* Yield, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.22 (9H, s, CH_3), 1.31-1.75 (24H, m, CH_2), 1.98-2.27 (6H, m, CH_2), 3.45 (2H, d, Ph-CH_2), 4.38 (1H, t, *J* = 5.0 Гц), 5.38–5.66 (2H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: -0.06, 25.15, 27.33, 27.35, 27.49, 29.27–29.78, 33.58, 37.73, 62.90, 89.23, 107.07, 125.86, 128.38, 128.42, 128.46, 128.95, 130.30, 130.65, 141.14; MS (MALDI-TOF), *m/z*: 466[M]$^+$; $C_{31}H_{50}OSi$; found (%): C, 79.77; H, 10.81; calc. for $C_{31}H_{50}OSi$ (%): C, 79.76; H, 10.80. *(15Z,19Z)-23-phenyl-1-(trimethylsilyl)tricosa-15,19-dien-1-yn-3-ol (**8c**).* Yield, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.22 (9H, s, CH_3), 1.31-1.75 (26H, m, CH_2), 1.98-2.27 (6H, m, CH_2), 3.45 (2H, d, Ph-CH_2), 4.38 (1H, t, *J* = 5.0 Гц), 5.38–5.66 (2H, m, =CH), 7.20-7.34 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: −0.06, 25.15, 27.33, 27.35, 27.49, 29.27–29.78, 33.58, 37.73, 62.90, 89.23, 107.07, 125.86, 128.38, 128.42, 128.46, 128.95, 130.30, 130.65, 141.14; MS (MALDI-TOF), *m/z*: 480 [M]$^+$; $C_{30}H_{48}OSi$; found (%): C, 79.95; H, 10.88; calc. for $C_{32}H_{52}OSi$ (%): C, 79.93; H, 10.90.

*Procedure for preparation of alkyne (**1(a**–c)) was carried out according to known procedure [11]. (15Z,19Z)-21-phenylhenicosa-15,19-dien-1-yn-3-ol (**1a**).* Yield, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.78 (22H, m, CH_2), 1.92-2.26 (8H, m, CH_2), 2.48 (1H, d, CH), 3.43 (2H, d, Ph-CH_2), 4.39 (1H, t, *J* = 5.0 Гц), 5.38–5.63 (2H, m, =CH), 7.18-7.33 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.04, 27.32, 27.34, 27.48, 29.27–29.77, 33.57, 37.68, 62.36, 72.84, 85.07, 125.85, 128.37, 128.41, 128.45, 128.95, 130.31, 130.65, 141.16; MS (MALDI-TOF), *m/z*: 380 [M]$^+$; $C_{27}H_{42}O$; found (%): C, 85.11; H, 10.63; calc. for $C_{27}H_{42}O$ (%): C, 85.20; H, 10.59. *(15Z,19Z)-22-phenyldocosa-15,19-dien-1-yn-3-ol (**1b**).* Yield, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.78 (24H, m, CH_2), 1.92-2.26 (8H, m, CH_2), 2.48 (1H, d, CH), 3.43 (2H, d, Ph-CH_2), 4.39 (1H, t, *J* = 5.0 Гц), 5.38–5.63 (2H, m, =CH), 7.18-7.33 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.04, 27.32, 27.34, 27.48, 29.27–29.77, 33.57, 37.68, 62.36, 72.84, 85.07, 125.85, 128.37, 128.41, 128.45, 128.95, 130.31, 130.65, 141.16; MS (MALDI-TOF), *m/z*: 396 [M]$^+$; $C_{28}H_{44}O$; found (%): C, 84.77; H, 11.13; calc. for $C_{28}H_{44}O$ (%): C, 84.79; H, 11.18. *(15Z,19Z)-23-phenyltricosa-15,19-dien-1-yn-3-ol (**1c**).* Yield, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30-1.78 (20H, m, CH_2), 1.92-2.26 (8H, m, CH_2), 2.48 (1H, d, CH), 3.43 (2H, d, Ph-CH_2), 4.39 (1H, t, *J* = 5.0 Гц), 5.38–5.63 (2H, m, =CH), 7.18-7.33 (5H, m, CH=); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 25.04, 27.32, 27.34, 27.48, 29.27–29.77, 33.57, 37.68, 62.36, 72.84, 85.07, 125.85, 128.37, 128.41, 128.45, 128.95, 130.31, 130.65, 141.16; MS (MALDI-TOF), *m/z*: 410 [M]$^+$; $C_{29}H_{46}O$; found (%): C, 84.78; H, 11.25; calc. for $C_{29}H_{46}O$ (%): C, 84.81; H, 11.29.

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