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The first total synthesis of lembehyne B

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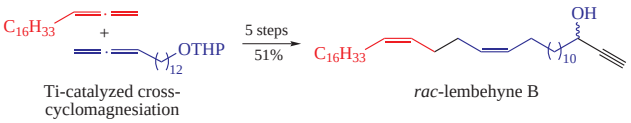
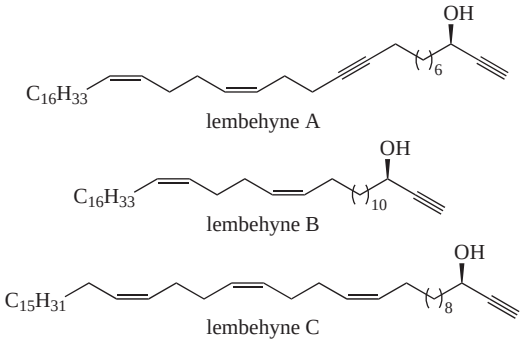
The total synthesis of lembehyne B was accomplished in five steps in 51% total yield. The cross-cyclomagnesiation of two allenic components, nonadeca-1,2-diene and pentadeca-13,14-dien-1-ol tetrahydropyranyl ether, with EtMgBr in the presence of Mg and Cp_2TiCl_2 catalyst (10 mol%) was used in the key step of the synthesis.



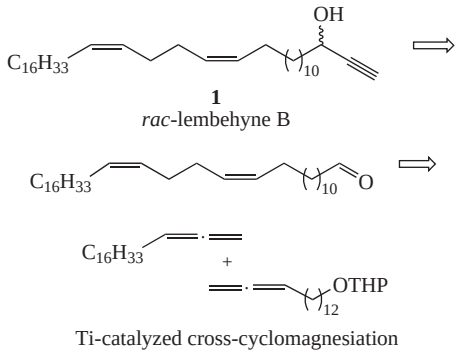
Lembehynes, which are isolated in trace amounts from the Indonesian marine sponge of *Haliclona sp.*,[1,2] are representatives of a large group of acetylenic alcohols of marine origin exhibiting a broad spectrum of biological activities, in particular, antitumor, neuritogenic, and antibacterial ones.[3–7] Lembehynes A, B, and C presenting in very low concentrations are capable to induce neuronal differentiation of the pheochromocytoma PC12 and neuroblastoma Neuro2A cells.[1,2]



Out of the above-listed neuritogenic alkynes, the total syntheses have been reported only for lembehyne A[2] and some its saturated analogues,[8] which were used for experimental investigation of the relationship between the structures and biological activities of these compounds. Biological activity of synthetic analogues of lembehynes was found to depend appreciably on the hydrocarbon chain length and on the stereoconfiguration of the hydroxyl group at C(3). Both 3*S*- and 3*R*-isomers show neuritogenic activity, the activity being higher for the latter isomer.[8,9] Hence, lembehynes are of considerable scientific and commercial interest for the design of new drugs for treating human neurodegenerative diseases.

Analysis of the lembehyne A–C structures and the proposed route for the total synthesis of lembehyne A shows that formation of the (*Z*,*Z*)-1,5-diene moiety is the most labor-consuming step.[2] In our opinion, this circumstance is a key factor hampering full scale testing of lembehynes for various types of biological activity. Previously, we developed Ti-catalyzed cross-cyclomagnesiation of functional aliphatic 1,2-dienes using Grignard reagents,[10–13] leading, in one preparative step, to stereoselective formation of O-, N-, and Si-containing long-chain compounds with a (*Z*,*Z*)-1,5-diene moiety in a specified position.[14–21] Herein, we suggested that the use of this reaction in the key step of lembehyne synthesis would markedly simplify the synthesis and, hence, would make this class of compounds available for research and drug design purposes. In this communication, we present the application of catalytic cross-cyclomagnesiation of 1,2-dienes in the total synthesis of *rac*-lembehyne B **1**.

To select the optimal synthetic route, we first performed the retrosynthetic analysis of lembehyne B, including the sequence of cross-cyclomagnesiation of two allenic components, obtaining (13*Z*,17*Z*)-tetraconta-13,17-dienal, and formation of the terminal propargyl moiety at the final step (Scheme 1).



Scheme 1

The first step of the synthesis comprised cross-cyclomagnesiation of nonadeca-1,2-diene **2** and pentadeca-13,14-dien-1-ol tetrahydropyranyl ether **3** with EtMgBr in the presence of Mg metal and the Cp_2TiCl_2 catalyst (10 mol%) *via* the formation of magnesacyclopentane **4**, which was hydrolyzed to give (13*Z*,17*Z*)-tetraconta-13,17-dienol tetrahydropyranyl ether **5** in 88% yield (Scheme 2). The next removal of the tetrahydropyranyl protection[22] and oxidation of unsaturated alcohol **6** with the Dess–Martin periodinane[23] afforded (13*Z*,17*Z*)-tetraconta-13,17-dienal **7** in ~64% yield over the two steps. The reaction of pre-synthesized lithium trimethylsilylacetylenide with aldehyde **7**

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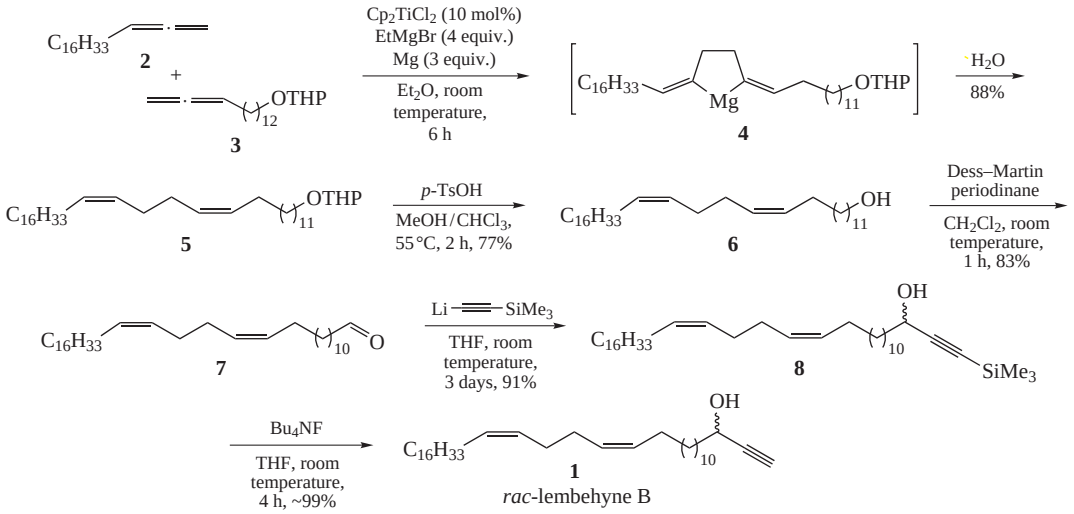

Scheme 2

and removal of the trimethylsilyl protection with Bu_4NF furnished the target lembehyne B in an overall yield of ~51%.†

The structures of synthesized compounds **1**–**7** were established by mass spectrometry, ^1H and ^{13}C NMR spectroscopy and 2D heteronuclear correlation experiments (HSQC, HMBC).

† All reactions were carried out under inert atmosphere. Dichloromethane was distilled from P_2O_5 prior to use. The ether solvents were dried over Na. Commercial Dess–Martin periodinane and Cp_2TiCl_2 (Aldrich) were used as received. One- (^1H, ^{13}C) and two-dimensional heteronuclear (HSQC, HMBC) NMR spectra were recorded on a Bruker Avance-400 instrument.

*2-(Pentadeca-13,14-dien-1-yloxy)tetrahydro-2*H*-pyran* **3**. Paraformaldehyde (2.6 g), copper iodide (3.4 g, 17.8 mmol), and dicyclohexylamine (14.0 ml, 70.4 mmol) were sequentially added to a solution of 2-(tetradec-13-yn-1-yloxy)tetrahydro-2*H*-pyran (10.0 g, 34.0 mmol) in anhydrous dioxane (120 ml). The resulting mixture was heated under reflux for 24 h. The addition of 2 M HCl (50 ml) and extraction with diethyl ether were followed by treatment of the organic layer with $NaHCO_3$, water, and brine and drying with anhydrous $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane–ethyl acetate, 30 : 1) to afford product **3** (8.1 g, 78%) as colourless liquid. IR (film, ν/cm^{-1}): 2928, 2851, 1463, 1379, 1354, 1301, 1248, 1108, 1068, 815, 722. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24–1.42 (m, 18 H), 1.49–1.62 (m, 6 H), 1.71 (m, 1H), 1.83 (m, 1H), 1.99 (m, 2 H), 3.38 (m, 1H), 3.49 (m, 1H), 3.73 (m, 1H), 3.87 (m, 1H), 4.58 (m, 1H), 4.64 (m, 2 H), 5.08 (m, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 208.5 (C), 98.8 (CH), 90.0 (CH), 74.4 (CH_2), 67.6 (CH_2), 62.2 (CH_2), 30.8 (CH_2), 29.8 (CH_2), 29.6 (4 C, CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 25.5 (CH_2), 19.7 (CH_2). Found (%): C, 77.69; H, 11.73. Calc. for $C_{20}H_{36}O_2$ (%): C, 77.87; H, 11.76.

*2-[(13*Z*,17*Z*)-Tetraconta-13,17-dien-1-yloxy]tetrahydro-2*H*-pyran* **5**. Diethyl ether (30 ml), nonadeca-1,2-diene **2** (1.27 g, 4.8 mmol), 2-(pentadeca-13,14-dien-1-yloxy)tetrahydro-2*H*-pyran **3** (1.23 g, 4.0 mmol), EtMgBr (16.0 mmol) (as 1.5 M solution in Et_2O), Mg powder (0.29 g, 12.0 mmol) and Cp_2TiCl_2 (0.1 g, 0.4 mmol) were placed in a glass reactor with stirring under argon (~0 °C). The reaction mixture was warmed-up to room temperature (20–22 °C) and stirred for 6 h, then treated with a 5% solution of NH_4Cl in H_2O (20 ml) and extracted with diethyl ether (2×100 ml). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Silica gel column chromatography (hexane–EtOAc, 35:1) of the residue gave compound **5** (1.98 g, 88%) as a pale yellow oily liquid. IR (film, ν/cm^{-1}): 2929, 2853, 1465, 1384, 1360, 1303, 1256, 1110, 1075, 815, 722. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3 H, *J* 6 Hz), 1.25–1.41 (m, 46 H), 1.52–1.63 (m, 6 H), 1.72–1.73 (m, 1H), 1.84–1.86 (m, 1H), 2.03–2.09 (m, 8 H), 3.36–3.42 (m, 1H), 3.48–3.54 (m, 1H), 3.72–3.77 (m, 1H), 3.86–3.91 (m, 1H), 4.58–4.61 (m, 1H), 5.34–5.43 (m. 4 H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 130.3 (2 C, CH), 129.1 (2 C, CH), 98.8 (CH), 67.7 (CH_2), 62.2 (CH_2), 31.9 (CH_2), 30.8 (CH_2), 29.8–29.3 (21 C, CH_2), 27.4 (2 C, CH_2), 27.3 (2 C, CH_2), 26.3 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 19.7 (CH_2), 14.1 (Me). MS (MALDI-TOF), *m*/*z*: 574 $[M]^+$. Found (%): C, 81.29; H, 12.94. Calc. for $C_{39}H_{74}O_2$ (%): C, 81.46; H, 12.97.

*(13*Z*,17*Z*)-Tetraconta-13,17-dien-1-ol* **6** was obtained using the deprotection procedure.[22] Yield 77%. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3 H, *J* 6 Hz), 1.25–1.42 (m, 46 H), 1.52–1.63 (m, 3 H), 2.03–2.09 (m, 8 H), 3.64–3.67 (m, 2 H), 5.35–5.45 (m, 4 H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 130.4 (2 C, CH), 129.2 (2 C, CH), 63.1 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 29.8–29.3 (19 C, CH_2), 27.4 (2 C, CH_2), 27.2 (2 C, CH_2), 25.7 (CH_2), 22.7 (CH_2), 19.7 (CH_2), 14.1 (Me). MS (MALDI-TOF), *m*/*z*: 490 $[M]^+$. Found (%): C, 83.02; H, 13.57. Calc. for $C_{34}H_{66}O$ (%): C, 83.19; H, 13.55.

*(13*Z*,17*Z*)-Tetraconta-13,17-dien-1-al* **7** was obtained by the Dess–Martin oxidation method.[22] Yield 83%. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3 H, Me, *J* 6 Hz), 1.23–1.48 (m, 46 H, CH_2), 2.04–2.10 (m, 8 H, =CH–C*H*$_2$), 2.42–2.45 (m, 2 H, O=CH–C*H*$_2$), 5.39–5.40 (m, 4 H, =CH), 9.78–9.79 (m, 1H, O=CH). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 202.9 (CH), 130.4 (CH), 129.1 (CH), 43.9 (CH_2), 31.9 (CH_2), 29.2–29.7 (22 C, CH_2), 27.4 (2 C, CH_2), 27.3 (2 C, CH_2), 22.7 (CH_2), 22.1 (CH_2), 14.1 (Me). MS (MALDI-TOF), *m*/*z*: 488 $[M]^+$. Found (%): C, 83.39; H, 13.16. Calc. for $C_{34}H_{64}O$ (%): C, 83.53; H, 13.20.

*(15*Z*,19*Z*)-1-(Trimethylsilyl)hexatriaconta-15,19-dien-1-yn-3-ol* **8**. A solution of BuLi (1.5 M in hexane, 4 ml) was added dropwise to a solution of trimethylsilylacetylene (0.58 g, 6 mmol) in THF (10 ml) at –40 °C. The solution was stirred at –40 to 0 °C for 1 h. Then this solution was added dropwise to THF solution of dienal **7** (1.5 g, 3.08 mmol) at –10 °C. The reaction mixture was warmed-up to room temperature (20–22 °C) and stirred for 3 days, then treated with a 5% solution of NH_4Cl in H_2O (20 ml) and extracted with diethyl ether (2×100 ml). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Silica gel column chromatography of the residue gave compound **8** (1.64 g, 91%) as a pale yellow oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.19 (s, 9 H, Me), 0.90 (t, 3 H, Me, *J* 6 Hz), 1.25–1.72 (m, 49 H, CH_2), 2.04–2.11 (m, 8 H, =CH–C*H*$_2$), 4.37 (t, 1H, HO–C*H*, *J* 5 Hz), 5.38–5.41 (m, 4 H, =CH). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 130.4 (CH), 129.2 (CH), 106.9 (C), 89.3 (CH), 62.9 (CH), 37.7 (CH_2), 31.9 (CH_2), 29.2–29.8 (22 C, CH_2), 27.4 (2 C, CH_2), 27.3 (2 C, CH_2), 25.1 (CH_2), 22.7 (CH_2), 14.1 (Me), –0.11 (3 C, Me). MS (MALDI-TOF), *m*/*z*: 587 $[M]^+$. Found (%): C, 79.62; H, 12.66. Calc. for $C_{39}H_{74}OSi$ (%): C, 79.79; H, 12.70.

rac-*Lembehyne B* **1**. Bu_4NF (1 M in THF, 1.2 equiv.) was added to a solution of compound **8** (1.17 g, 2 mmol) in THF (10 ml) at 0 °C, and the mixture was stirred at room temperature for 6 h. The reaction mixture was treated with saturated aqueous NaCl and extracted with diethyl ether (2×50 ml). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Silica gel column chromatography of the residue gave compound **1** (1.07 g, 99%) as a colourless powder. The spectral data of compound **1** were identical to previously published for lembehyne B.[8]

In conclusion, we developed the first original five-step synthesis of racemic lembehyne B using the new Ti-catalyzed cross-cyclomagnesiation of two aliphatic 1,2-dienes with Grignard reagents in the key step. In our opinion, this approach bears great synthetic potential for the preparation of stereopure natural biologically active compounds, and currently we are engaged in active research along this line aimed at implementation of stereoselective methods for the synthesis of the whole range of natural lembehynes and their analogues, in particular, to perform full-scale pharmacological investigations for elucidating the biological activity and structure–activity relationships.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.03.004.

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