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Total Synthesis of Neuritogenic Alkynes: Lembehyne B and Key Intermediate of Lembehyne A

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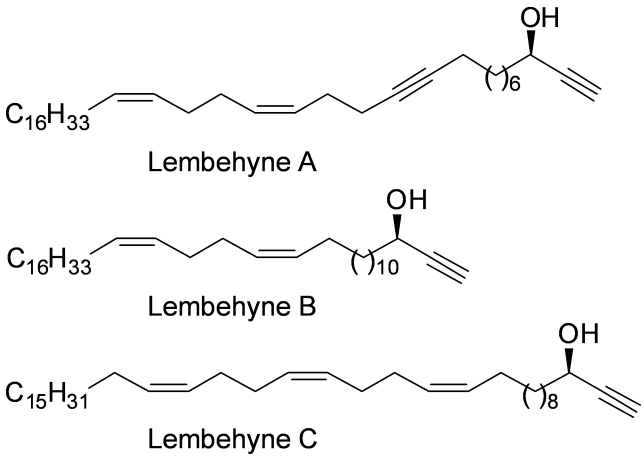
A new Ti-catalyzed cross-cyclomagnesiation of aliphatic and oxygenated 1,2-dienes with EtMgBr in the presence of Cp_2TiCl_2 was used in the key stage for the development for the first time original methods for the preparation of racemic and natural neuritogenic alkynes lembehyne B and stereoselective syntheses of (4*Z*,8*Z*)-pentacosa-4,8-dien-1-ol - the key intermediate in the total synthesis of lembehyne A.

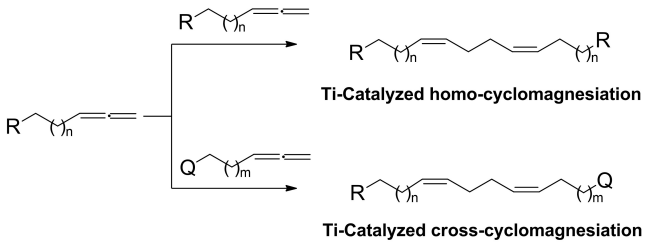
The Global Ocean biomass is a virtually inexhaustible source of organic compounds exhibiting a wide range of biological activities.[1] One of the most abundant classes of these compounds comprises natural alkynes isolated from various types of algae or freshwater and marine cyanobacteria, possessing antitumor, antimicrobial, antibacterial, antifungal, and many other types of pharmacological activity.[2] Recently it was found that the unsaturated natural acetylenic alcohols, lembehynes A–C, which are present in trace amounts in the Indonesian sea sponges *Haliclona sp.*, exhibit a considerable neuritogenic activity towards the pheochromocytoma PC12 cells and neuroblastoma Neuro2 A cells;[3] hence, these compounds can be considered as a base for development of modern drugs for treating neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's chorea, and so on).

Meanwhile, the poor accessibility and the lack of efficient methods for the synthesis of natural lembehynes considerably holds up detailed investigation of their properties and extensive utilization of their biomedical potential.

Analysis of the lembehyne structure and known approaches to total synthesis demonstrated that stereoselective formation of the 1*Z*,5*Z*-diene moiety of lembehyne is the most complicated and labor-consuming phase of the process.[4] Considering the published data, the most popular approaches to the formation of the 1*Z*,5*Z*-diene moiety are based on the Wittig reaction, alkene metathesis, alkylation of alkynes, and stereoselective reduction of 1,5-diynes.[5]



Previously, we developed Ti-catalyzed homo- and cross-cyclomagnesiation of 1,2-dienes with Grignard reagents (Scheme 1) and successfully used it in the strictly stereoselective synthesis of 1*Z*,5*Z*-dienes of a specified structure, giant macrocarbocycles, and natural 5*Z*,9*Z*-dienoic acids exhibiting antitumor activities.[6] (Scheme 1).



R = alkyl, aryl, cyclo, hetero;
Q = SiR_3, NR_2, OTHP, OEE, OBn.

Scheme 1. Ti-Catalyzed homo- and cross-cyclomagnesiation.

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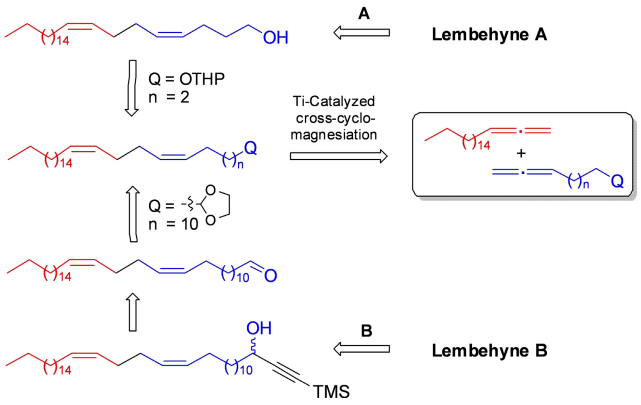
Relying on our previous results, we put forward the idea of applicability of the developed cross-cyclomagnesiation reaction of oxygenated and aliphatic allenes for the synthesis of neuritogenic acetylenic alcohols — lembehynes A and B.[3,4]

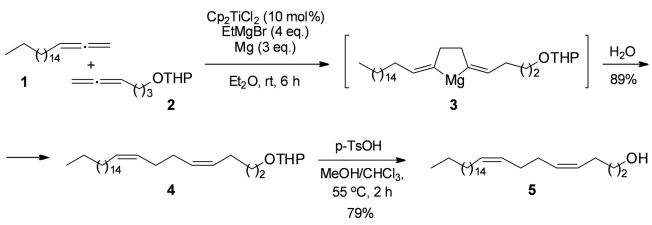
In order to choose the optimal synthetic pathway, we initially performed the retrosynthetic analysis of lembehynes A and B. The synthesis of the (4*Z*,8*Z*)-pentacosa-4,8-dien-1-ol, the key monomer in the lembehyne A synthesis, is based on cross-cyclomagnesiation of 1,2-nonadecadiene and 4,5-hexadienol tetrahydropyran ether (Scheme 2, A). The total synthesis of



Scheme 2. Retrosynthetic analysis of lembehyne A and B.

lembehyne B includes cross-cyclomagnesiation of 1,2-nonadecadiene and 2-tetradeca-12,13-dien-1-yl-1,3-dioxolane to give (13*Z*,17*Z*)- tetraconta-13,17-dienal as the first step and the stereoselective formation of the terminal propargyl moiety at the subsequent synthetic stages (Scheme 2, B).

As the first stage of implementation of the developed synthetic pathway (pathway A), we carried out cross-cyclomagnesiation of available 1,2-nonadecadiene (**1**)[7] and 4,5-hexadienol tetrahydropyran ether (**2**)[6g] with EtMgBr in the presence of Mg metal (halide ion acceptor) and the Cp_2TiCl_2 catalyst (10 mol. %). The reaction proceeded via the formation of magnesacyclopentane **3**, which was hydrolyzed to give (4*Z*,8*Z*)-pentacosa-4,8-dien-1-ol tetrahydropyran ether **5** in 89% yield (Scheme 3). Refluxing tetrahydropyran ether **4** in a MeOH-



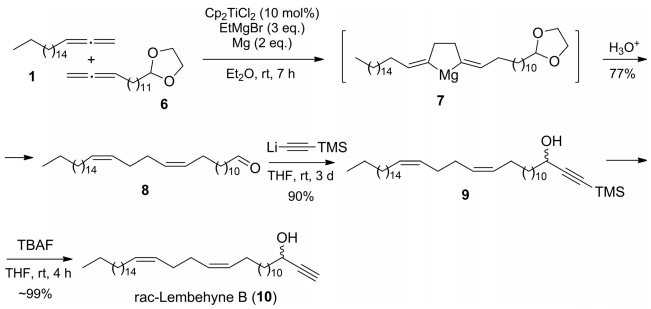
Scheme 3. Short synthesis of (4*Z*,8*Z*)-pentacosa-4,8-dien-1-ol (**5**).

$CHCl_3$ (1:1) mixture in the presence of p-TsOH afforded the target (4*Z*,8*Z*)-pentacosa-4,8-dien-1-ol (**5**) in a ~70% total yield.

Unsaturated alcohol **5** can be used in the total synthesis of lembehyne A in subsequent transformations according to previously published scheme.[4]

The high chemoselectivity towards the unsymmetrical magnesacyclopentane **3** is apparently associated with the diethyl ether as the solvent, in which the intermolecular catalytic cyclomagnesiation of aliphatic terminal allenes was not observed.[6b] When introducing a slight excess of aliphatic 1,2-diene **1** under the reaction conditions selected for the cross-cyclomagnesiation between functionally substituted 1,2-dienes and aliphatic 1,2-dienes, the yield of symmetrical magnesacyclopentanes was only 2%, suggesting that the catalytic homo-cyclomagnesiation reaction of 1,2-dienes is suppressed.

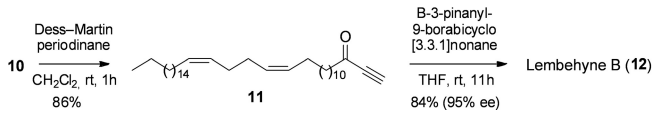
In continuation of these studies with the aim to synthesize lembehyne B we carried out cross-cyclomagnesiation of 1,2-nonadecadien (**1**) and 2-tetradeca-12,13-dien-1-yl-1,3-dioxolane (**6**) with EtMgBr in the presence of Mg metal (halide ion acceptor) and a catalytic amount of Cp_2TiCl_2 (10 mol.%) (**1:6:**EtMgBr:Mg:[Ti] = 12:10:30:20:0.1, Et_2O, 20–22°C, 7 h). The reaction proceeding via the formation of magnesacyclopentane **7** furnished, after acid hydrolysis of the reaction mixture, the key synthon, namely, (13*Z*,17*Z*)-tetraconta-13,17-dienal (**8**), in one preparative step in ~77% yield (Scheme 4). The last-



Scheme 4. Total synthesis of rac-lembehyne B.

mentioned product reacts with lithium trimethylsilylacetylenide,[7] prepared in advance by the reaction of equimolar amounts of trimethylsilylacetylene and n-BuLi in THF, to give silane **9** in 90% yield over a period of 3 days at room temperature. The removal of the trimethylsilyl protection on treatment with trimethylbutylammonium fluoride (TBAF) in THF gives within 4 h racemic lembehyne B (**10**) in a nearly quantitative yield (Scheme 4).

In the next stage, racemic lembehyne B was converted to its natural stereoisomer with the 3*R*-configuration of the hydroxyl group at C-3. The Dess-Martin periodinane oxidation of alkynol **10** in CH_2Cl_2 at room temperature for 1 h gave (15*Z*,19*Z*)-hexaconta-15,19-dien-1-yl-3-one (**11**) in 86% yield (Scheme 5). The stereoselective reduction of ketone **11** was performed with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-borane reagent),[8] prepared in advance from (+)-α-pinene



Scheme 5. Stereoselective formation of the 3*R*-hydroxyl function on terminal stage of the total synthesis of natural lembehyne B.

(98% ee) and 9-borabicyclo[3.3.1]nonane. The reduction gave lembehyne B in 84% yield and with 95% ee.

The absolute configuration of the 3*R*-hydroxyl group of lembehyne B (**12**) was confirmed using the Mosher analysis.[9] All analytical parameters for compound **12** were in full accordance with previously published data.[3c]

In summary, we developed a short route for the synthesis of (4*Z*,8*Z*)-pentacosa-4,8-dien-1-ol, the key monomer in the total synthesis of lembehyne A, and developed for the first time original methods for the preparation of racemic and natural lembehyne B in which the new high-yield cross-cyclomagnesiation reaction of oxygenated and aliphatic 1,2-dienes with Grignard reagents and catalytic amounts of Cp_2TiCl_2 is used in the key stage of the process. In our opinion, the developed reactions bear huge synthetic potential for the preparation of stereochemically pure natural biologically active compounds. 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 determining the biological activity and elucidating the structure-activity relationships.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Catalytic cross-cyclomagnesiation · Homogeneous catalysis · Lembehynes · Neuritogenic alkynes · 1,2-dienes

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