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Total synthesis of lembehyne A, a neuritogenic spongean polyacetylene

Nobutoshi Murakami, Tatsuo Nakajima and Motomasa Kobayashi*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

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Abstract—The first total synthesis of lembehyne A, a neuritogenic polyacetylene from a marine sponge *Haliclona* sp., was achieved by utilizing alkyne formation with dimethyl-1-diazo-2-oxopropylphosphonate and asymmetric reduction with Alpine-borane as the key reactions.

Nerve growth factor (NGF) is a well-characterized neurotrophic factor essential for growth, differentiation, and survival of nerve cells,[1,2] and has emerged as a potential therapeutic candidate for several neurological diseases.[3,4] Since the enormous (130 kDa) and hydrophilic properties of NGF prevent it from passing through the blood–brain barrier, an alternative neurotrophic substance, having low molecular weight, is strongly needed. In the course of our research for biologically active substances from marine organisms, we recently isolated lembehyne A (**1**) from a marine sponge *Haliclona* sp. as a neuritogenic polyacetylene against PC12 cells and determined its absolute stereostructure by spectroscopic study and chemical degradation.[5] Lembehyne A (**1**) induced neuritogenesis in PC12 cells and Neuro2A cells at 2 and 0.1 μg/ml without NGF, respectively. This finding prompted us to engage in a synthetic study on lembehyne A (**1**), taking the following elucidation of the structure–activity relationship and exploration of simplified medicinal-lead compounds into account. This paper deals with the first total synthesis of **1**, which confirms our presented absolute stereostructure.

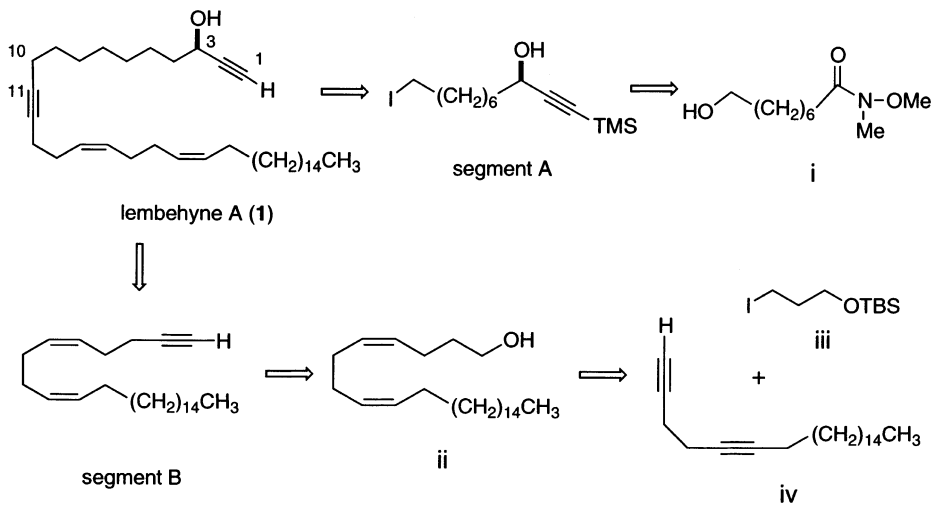

Figure 1. Retrosynthetic analysis of lembehyne A (**1**).

Keywords: lembehyne A; total synthesis; neuritogenic; marine sponge.

* Corresponding author. Fax: 81-6-6879-8219; e-mail: kobayasi@phs.osaka-u.ac.jp

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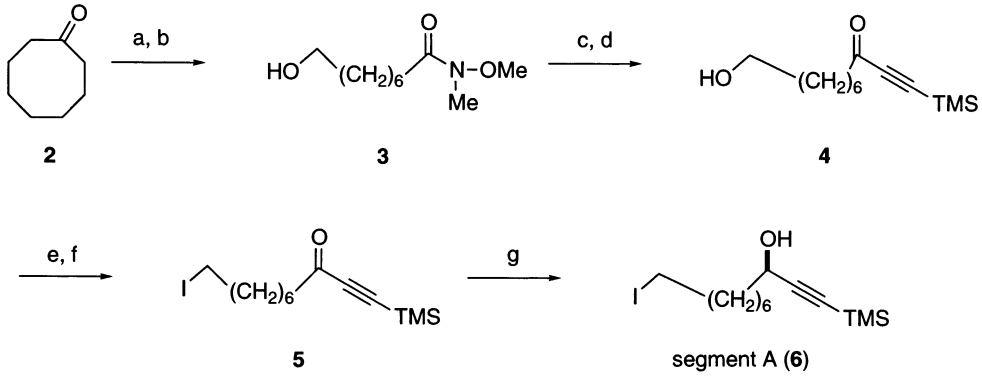


Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt; (b) MeONHMe·HCl, Me_2AlCl, CH_2Cl_2, rt, 66% two steps; (c) LiC≡CTMS, THF, −78 to 10°C; (d) TMSCl, ^{n}BuLi, THF, 83% two steps; (e) TsCl, pyridine, CH_2Cl_2, 4°C to rt; (f) NaI, acetone, 55°C, 91% two steps; (g) *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane, THF, rt, 82% (94% ee).

Our retrosynthetic analysis is illustrated in Fig. 1. Disconnection between C-10 and C-11 gives an optically active alkyl halide (segment A) with an (*R*)-3-hydroxy-1-yne moiety and a long-chain 1-alkyne (segment B) with a *Z*,*Z*-1,5-diene moiety. The 3*R*-hydroxyl function of the former segment was provided by asymmetric reduction using Alpine-borane to a propargyl ketone, which was prepared from the corresponding Weinreb amide **i**. The latter segment was facilely prepared from a diene alcohol **ii** by a one-carbon elongation using dimethyl-1-diazo-2-oxopropylphosphonate[6] via an aldehyde. The diene alcohol **ii** was formed by a coupling of a terminal alkyne **iv** and an alkyl iodide **iii**. The diyne **iv** was prepared from 4-pentyn-1-ol and 1-iodohexadecane by the same method from **ii** into segment B. This strategy was carried out as follows.

Baeyer–Villiger oxidation of cyclooctanone (**2**) using *m*-CPBA and subsequent treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of Me_2AlCl afforded a Weinreb amide **3** in 66% yield for two steps.[7] Nucleophilic substitution for **3** with lithium (trimethylsilyl)acetylide followed by TMSCl treatment to supplement the partially deprotected trimethylsilyl group provided a hydroxyalkyne **4** in 83% yield for two steps. Then, the hydroxyalkyne **4** was treated with tosyl chloride in pyridine to give the corresponding tosylate, which was subjected to nucleophilic substitution with sodium iodide to afford a keto-iodide **5** in 91% yield for two steps. Asymmetric reduction of **5** using *B* - 3 - pinanyl - 9 - borabicyclo[3,3,1]nonane (Alpine-borane),[8] which was prepared from (+)-α-pinene (97% ee) and 9-BBN, proceeded in 82% yield with high enantiomeric selectivity (94% ee) to furnish segment A (**6**) (Scheme 1).

The absolute configuration of **6** was confirmed by the modified Mosher method.[9] Namely, the distribution of $\Delta\delta$ values [$\delta(S)$-MTPA ester–$\delta(R)$-MTPA ester] shown in Fig. 2 supported the intended 3*R* configuration in **6**. The enantiomeric excess was assessed by integration of the respective signals due to the 3-proton in the ^{1}H NMR spectrum of the (*S*)-MTPA ester of **6**.

Condensation of 4-pentyn-1-ol and 1-iodohexadecane (**7**) mediated with *n*-BuLi in THF–HMPA gave a hydroxyalkyne, which was further submitted to Dess–Martin oxidation to afford an aldehyde. Construction of the terminal alkyne was carried out by a one-carbon elongation from the aldehyde using dimethyl-1-diazo-2-oxopropylphosphonate[6] to afford a diyne **8** in 57% yield for three steps. Elongation of the three-carbon unit by coupling of **8** and 3-iodopropoxy-*t*-butyldimethylsilane using *n*-BuLi, followed by hydrogenation in the presence of the Rosenmund catalyst, provided a *Z*,*Z*-diene, which was further transformed into a primary alcohol **9** by removal of the TBS group with tetrabutylammonium fluoride (TBAF). The primary alcohol **9** was converted to the desired segment B (**10**) by the same procedure for the preparation of **8** in 40% yield from **8** for five steps (Scheme 2).

Segments A (**6**) and B (**10**, 1.9 equiv. for **6**) were connected by *n*-BuLi (2.2 equiv. for **6**) treatment, and subsequent deprotection of the TBS group furnished lembehyne A (**1**) in 51% yield for two steps. The synthesized lembehyne A (**1**) was shown to be superimposable with the natural product isolated from the marine sponge by comparison of the ^{1}H–^{13}C NMR, IR, MS, and optical rotation data. Thus, the absolute stereostructure of lembehyne A (**1**) previously presented by us was confirmed. Investigation on the structure–activity relationship by use of synthetic analogs involving a search for the pharmacophore is currently in progress.

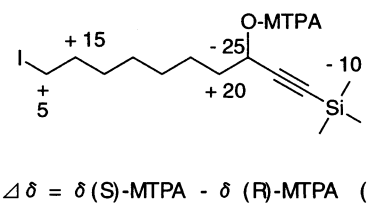
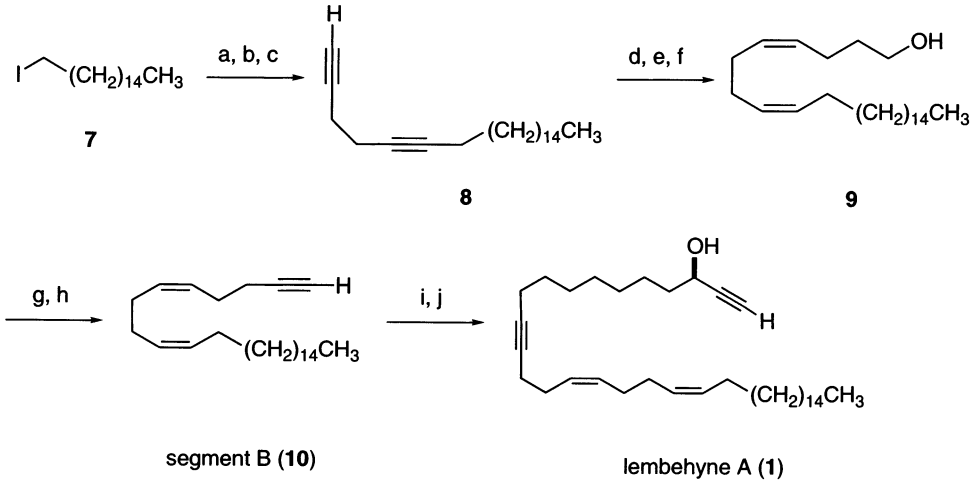


Figure 2. Confirmation of the absolute configuration at C-3 in **6**.



Scheme 2. Reagents and conditions: (a) $HC{\equiv}CCH_2CH_2CH_2OH$, ^{n}BuLi, THF, HMPA, −78 to 10°C, 80%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 85%; (c) $CH_3COCN_2PO(OMe)_2$, K_2CO_3, MeOH, rt, 84%; (d) $ICH_2CH_2CH_2OTBS$, ^{n}BuLi, THF, HMPA, −40°C to rt, 75%; (e) H_2, $Pd/BaSO_4$, quinoline, EtOH, rt; (f) TBAF, THF, rt, 89% two steps; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 84%; (h) $CH_3COCN_2PO(OMe)_2$, K_2CO_3, MeOH, rt, 72%; (i) **6**, ^{n}BuLi, THF, HMPA, −40 to 0°C, 68%; (j) TBAF, THF, rt, 75%.

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