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Integral Stereocontrolled Synthesis of a Spiro-norlignan, Sequosempervirin A: Revision of Absolute Configuration

Yuji Ito, Kazunori Takahashi, Hiromasa Nagase, and Toshio Honda*

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

honda@hoshi.ac.jp

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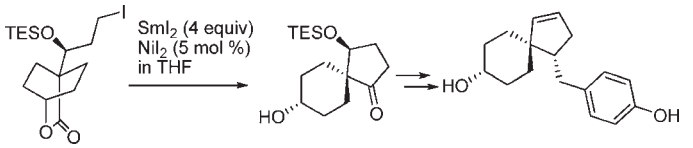
ABSTRACT



A novel synthetic path to sequosempervirin A was established by employing a samarium diiodide promoted intramolecular Barbier-type reaction of the lactonic iodide, in which the key structural feature, a spiro[4.5]decane ring system, could be constructed by controlling the stereochemistry of the hydroxyl group at the 8-position. The absolute configuration of natural sequosempervirin A was revised to be 4*S* based on this synthesis.

Sequosempervirin A **1** was isolated from dried and powdered branches and leaves of *Sequoia sempervirens* (Taxodiaceae) as the first naturally occurring norlignan compound.

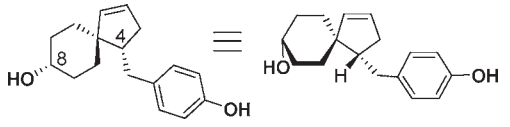


Figure 1. Originally proposed structure for the natual sequosempervirin A **1**.

The structure of sequosemperivirin A, including its absolute configuration, was determined to be (4*R*)-4-(4-hydroxybenzyl)spiro[4.5]dec-1-en-8-ol on the basis of results obtained by using spectroscopic methods and results of its X-ray crystallographic analysis (Figure 1).[1] Acetone extracts of *S. sempervirens* exhibited antifungal activities toward *Candida glabrata* (IC_{50} = 15.98 μg/mL), and both the acetone and MeOH extracts were found to inhibit the proteolytic activity of cathepsin B (IC_{50} = 4.58 and 5.49 μg/mL, respectively).[2]

Synthesis of sequosempervirin A has been reported by Maity and Ghosh in 2007,[3] in which an orthoester Claisen rearrangement and a ring-closing metathesis were exploited as the key reactions to construct the basic carbon framework. In their synthesis, however, deoxygenation at the 3-position (sequosempervirin A numbering) and also reduction of the ketone at the 8-position resulted in the mixture of regio- and stereoisomeric compounds, respectively, providing the target compound in 2% overall yield in 13 steps.

The crucial step for synthesis of sequosempervirin A obviously lies in the facile construction of a spiro[4.5]dec-1-ene system by controlling the stereochemistry of the hydroxyl group at the 8-position, since this stereogenic center was located far from any functional groups in the target compound.

Our own interest in construction of this unique structural feature grew out of a desire to develop an entirely new route for the total synthesis of sequosempervirin A with integrated stereocontrol of all of the stereogenic centers.

The retrosynthetic route to sequosempervirin A is illustrated in Scheme 1.

Approaching the synthesis from a retrosynthetic perspective, we envisioned the following scheme: the target

(1) Zhang, Y.-M.; Tan, N.-H.; He, M.; Lu, Y.; Shang, S.-Q.; Zheng, Q.-T. *Tetrahedron Lett.* **2004**, *45*, 4319–4321.

(2) Zhang, Y.-M.; Tan, N.-H.; Yang, Y.-B.; Lu, Y.; Cao, P.; Wu, Y.-S. *Chem. Biodivers.* **2005**, *2*, 497–505.

(3) Maity, S.; Ghosh, S. *Tetrahedron Lett.* **2007**, *48*, 3355–3358.

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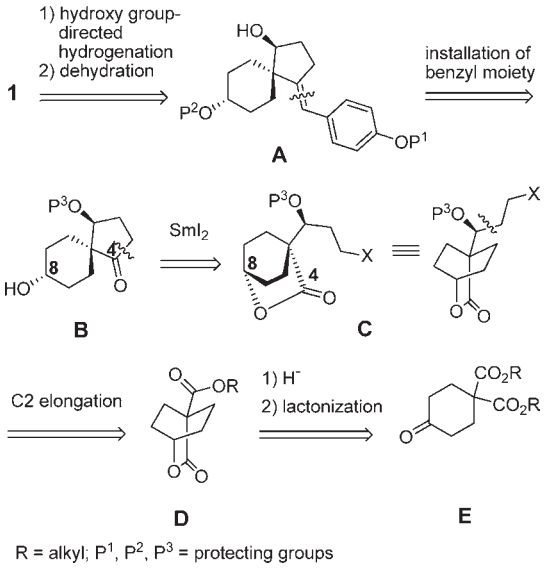
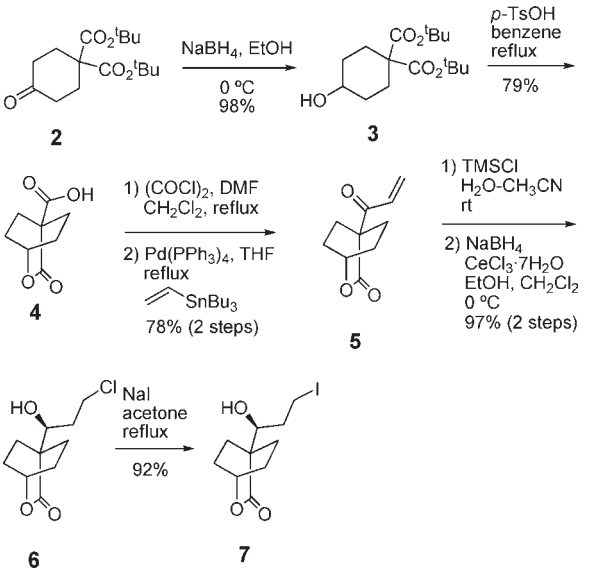
Scheme 1. Retrosynthetic Route to Sequosempervilin A



Scheme 2. Preparation of Bicyclic Iodo-lactone **7**



compound **1** would be derived from an alcohol **A** by employing a hydroxyl group-directed hydrogenation to control the stereochemistry at the 4-position, followed by dehydration. A benzylidene derivative **A** would be obtained from a cyclopentanone derivative **B** by installation of a benzyl moiety. Compound **B** would be accessible from a bicyclo-compound **C** via a samarium diiodide promoted Barbier-type reaction. A bicyclic halide **C** would be prepared from a 4-oxocyclohexane-1,1-dicarboxylate **E**, via a bicylic lactone **D**, by several steps involving reduction of a ketone, lactonization, two-carbon elongation, and so on.

A principal advantage offered by Scheme 1 is the ready construction of the key spiro[4.5]decane ring system by controlling the stereochemistry of the hydroxyl group at the 8-position via a samarium diiodide promoted Barbier-type reaction of a bicyclic compound **C** in one step.

Our synthesis commenced with the synthesis of a bicyclic lactone, which was easily accessible from 4-oxocyclohexanone-1,1-dicarboxylate, as follows (Scheme 2).

Reduction of **2**[4] with $NaBH_4$, followed by lactonization of the resulting alcohol **3** with *p*-TsOH in refluxing benzene, afforded the bicyclic acid **4**. Treatment of **4** with oxalyl chloride gave the acid chloride, which was then coupled with (tributylvinyl)stannane in the presence of tetrakis(triphenylphosphine)palladium in THF[5] to provide acrylate derivative **5**. After addition of hydrogen chloride to **5**, the resulting keto-chloride was reduced with $NaBH_4$ to give secondary alcohol **6** in 97% yield from **5**. Chloride **6** was further converted to the corresponding iodide **7** with NaI in acetone.

First, we attempted a samarium diiodide promoted Barbier-type reaction[6,7] of **7** in THF in the presence or absence of an additive under various reaction conditions; however, formation of a reductive dehalogenation compound was observed as the major isolable product in these reaction conditions, probably due to the presence of the

(4) Thalji, R. K.; McLaughlin, M. L.; Watkins, S. F.; Fronczek, F. R. *Acta Crystallogr., Ser. E* **2006**, *E62*, o2584–o2585.

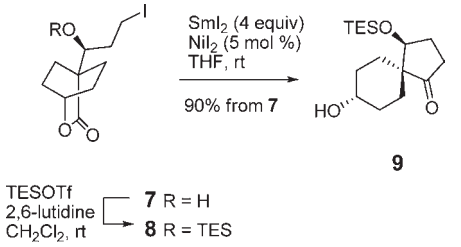
(5) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301–302. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.

(6) For recent reviews of SmI_2-mediated reaction, see: (a) Inanaga, J. *J. Org. Synth. Chem.* **1989**, *47*, 200–211. (b) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15–23. (c) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943–961. (d) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. (f) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345–347. (g) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354. (h) Nomura, R.; Endo, T. *Chem.—Eur. J.* **1998**, *4*, 1605–1610. (i) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–778. (j) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751. (k) Agarwal, S.; Greiner, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2033–2042. (l) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (m) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422–438. (n) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3404. (o) Jung, D. Y.; Kim, Y. H. *Synlett* **2005**, 3019–3032. (p) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637. (q) Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19–45. (r) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (s) Honda, T. *Heterocycles* **2010**, *81*, 2719–2747. (t) Honda, T. *Heterocycles* **2011**, *83*, 1–46.

(7) For selected examples, see: (a) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, *17*, 901–912. (b) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487–1490. (c) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773–774. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112–4120. (e) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216–7227. (f) Kunishima, M.; Hioki, K.; Kono, K.; Sakuma, T.; Tani, S. *Chem. Pharm. Bull.* **1994**, *42*, 2190–2192. (g) Helion, F.; Namy, J. L. *J. Org. Chem.* **1999**, *64*, 2944–2946. (h) Kunishima, M.; Yoshimura, K.; Nakata, D.; Hioki, K.; Tani, S. *Chem. Pharm. Bull.* **1999**, *47*, 1196–1197. (i) Carroll, G. A.; Little, R. D. *Org. Lett.* **2000**, *2*, 2873–2876. (j) Di Scala, A.; Garbacia, S.; Helion, F.; Lannou, M. I.; Namy, J. L. *Eur. J. Org. Chem.* **2002**, 2989–2995. (k) Lannou, M. I.; Helion, F.; Namy, J. L. *Tetrahedron Lett.* **2002**, *43*, 8007–8010. (l) Xu, X.; Zhang, Y. *Synth. Commun.* **2003**, *33*, 3551–3559. (m) Tamiya, H.; Goto, K.; Matsuda, F. *Org. Lett.* **2004**, *6*, 545–547. (n) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2005**, *7*, 553–556. (n) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813–3816. (o) Nishikawa, K.; Nakahara, H.; Shirokura, Y.; Nogata, Y.; Yoshimura, E.; Umezawa, T.; Okino, T.; Matsuda, F. *Org. Lett.* **2010**, *12*, 904–907.

secondary hydroxyl group which might act as a proton donor. Therefore, triethylsilyl derivative **8** was employed to find the best conditions for a samarium diiodide promoted Barbier-type reaction, and we found that nickel(II) iodide was the best additive[8] for this conversion to furnish the desired product **9** in high yield (Scheme 3).

Scheme 3. SmI_2-Promoted Barbier-Type Reaction of **8**



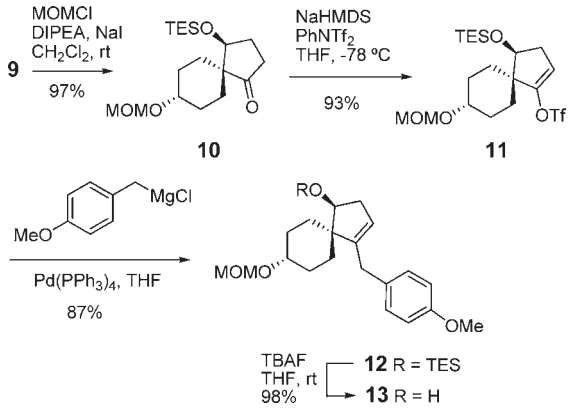
It is noteworthy that the samarium diiodide promoted Barbier-type reaction of **8** led to the construction of a spiro-[4.5]decane ring system, in which the hydroxyl group at the 8-position was fixed as only one diastereoisomeric form.

To synthesize the target compound, a stereoselective installation of a benzyl moiety at the carbonyl carbon of **10**, derived from **9** by methoxymethylation, would be required.

The attempted preparation of a benzylidene-type derivative (**A** in Scheme 1) by Wittig reaction of **10** with *p*-methoxybenzyltriphenylphosphonium bromide in the presence of a base gave none of the desired product, unfortunately. Treatment of **10** with *p*-methoxybenzylmagnesium bromide provided a small amount of an addition product. A samarium diiodide promoted Barbier-type reaction of **10** with *p*-methoxybenzyl bromide also unfortunately gave the addition product in low yield.

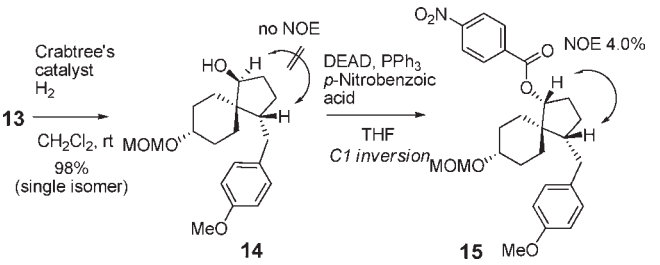
To our delight, a coupling reaction of triflate **11** derived from **10** with *p*-methoxybenzylmagnesium chloride in the presence of a palladium catalyst[9] afforded cyclopentene derivative **12**, in good yield, which was further transformed to alcohol **13** upon treatment with TBAF (Scheme 4).

Scheme 4. Preparation of Homoallyl Alcohol **13**



The stereochemistry at the 4-position was successfully controlled by a hydroxyl group directed hydrogenation with Crabtree's catalyst[10] to give **14** as a single stereoisomer.

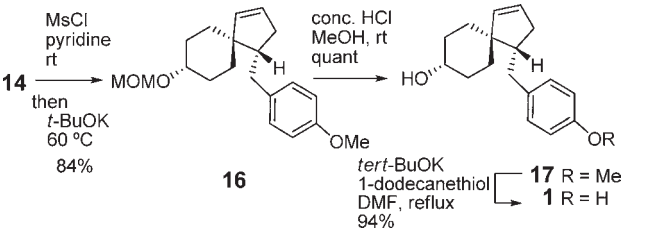
Scheme 5. Stereochemical Determination of **14**



The stereochemistry of **14** was determined by NOE experiments by comparison with its diastereoisomeric derivative **15** obtained from **14** and 4-nitrobenzoic acid by a Mitsunobu reaction,[11] as depicted in Scheme 5.

By establishing a synthetic route to the basic skeleton of the natural product with the desired stereochemistries, we completed the synthesis of racemic sequosempervirin A as follows.

Scheme 6. Synthesis of Sequosempervirin A **1**



Dehydration of the secondary hydroxyl group was achieved in two steps involving mesylation of **14**, followed by elimination of the mesylate to provide cyclopentene derivative **16** in 84% yield from **14** (Scheme 6). Finally, sequential removal of the protecting groups of **16** upon treatment with conc. hydrochloric acid and potassium 1-dodecanethiolate[12] with the resulting alcohol **17** afforded racemic sequosempervirin A, mp 141–144 °C [lit.,[1] 172–174 °C (optically active); lit.,[3] 169–170 °C (racemic)] in 18 steps in 28.9% overall yield. The spectroscopic data of the

(8) Machrouhi, F.; Hamann, B.; Namy, J. L.; Kagan, H. B. *Synlett* **1996**, 633–634.

(9) (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144a–144a.

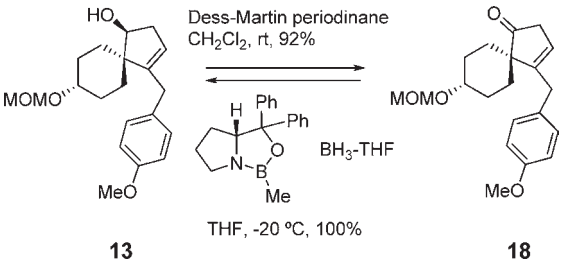
(10) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.

(11) (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Dodge, J. A.; Nissen, J. S.; Presnell, M. *Org. Synth.* **1996**, *73*, 110–115.

(12) Yamamoto, N.; Fujii, H.; Imaide, S.; Hirayama, S.; Nemoto, T.; Inokoshi, J.; Tomoda, H.; Nagase, H. *J. Org. Chem.* **2011**, *76*, 2257–2260.

synthesized compound were comparable with those reported in the literatures.[1,2]

Scheme 7. Preparation and Asymmetric Reduction of Homoallyl Alcohol **18**



To accomplish the total synthesis of natural sequosempervirin A, the requisite chirality was constructed by an asymmetric reduction of the prochiral ketone **18**, derived from alcohol **13** by Dess–Martin periodinane oxidation. Treatment of **18** with (*R*)-Me-CBS and a BH_3–THF complex[13] in THF at −20 °C afforded chiral **13** with 91% ee[14] (Scheme 7).

Although the absolute configuration of the newly generated chiral center could not be determined, it was assumed to be (*R*) on the basis of the previous systematic work.[13] Conversion of chiral **13** to the natural **1** was achieved by adopting the same procedures as those described for the synthesis of racemic **1**. The spectroscopic data of the chiral compound **1**, mp 180–181 °C [lit.,[1] 172–174 °C], were similar to those of the natural **1**; however, the sign of the optical rotation, $[\alpha]_D$ −39.4 (*c* 0.6, MeOH), was opposite to the reported value for the natural product {lit.,[1] $[\alpha]_D$ +24.7 (*c* 0.6, MeOH)}.

To solve this confusion stemming from the different optical rotation values, we decided to determine the absolute configuration of our synthesized compound by X-ray crystallographic analysis, and the results of X-ray analysis clearly showed that the synthesized compound has an (*R*)-configuration at the 4-position.[15] The ORTEP drawing of the synthesized compound was depicted in Figure 2. These results clearly indicated that the original assignment[1] for the absolute configuration of the natural product was not correct, and it should be revised to (4*S*)-4-(4-hydroxybenzyl)spiro[4.5]dec-1-en-8-ol, an enantiomer of **1**.[16]

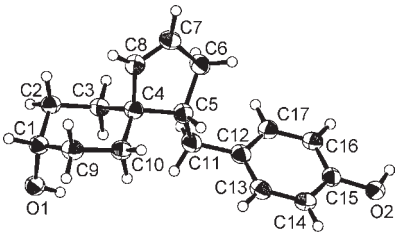


Figure 2. ORTEP drawing of (−)-**1**.

In summary, we were able to establish an entirely new and stereocontrolled route for construction of a spiro[4.5]decane ring skeleton with a reasonably high yield, in which a samarium diiodide promoted intramolecular Barbier-type reaction was involved as the key step. By exploiting this strategy, we succeeded in a concise stereocontrolled synthesis of a norlignan, (−)-sequosempervirin A, starting from the known cyclohexanone derivative **2** in 20 steps in 26.6% overall yield. This synthesis also proved that the natural compound is an enantiomer of the originally proposed structure **1** and should be revised to (4*S*)-4-(4-hydroxybenzyl)spiro[4.5]-dec-1-en-8-ol.

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Supporting Information Available. Experimental details, compound characterization, and cif file for compound (−)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org

(13) For recent reviews of CBS reduction, see: (a) Corey, E. J.; Heral, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (b) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784.

(14) The enantiomeric excess was determined to be 91% by HPLC analysis with the chiral column CHIRALPAK OD-3 (Daicel Chemical Industries, Ltd.).

(15) The absolute structure was deduced based on the Flack parameter, −0.2(3), using 1102 Friedel pairs. X-ray crystallographic data for compound **1** have been deposited to the Cambridge Crystallographic Data Centre and assigned the deposition number CCDC 831216 for **1**.

(16) Careful reading of the original reference led to the conclusion that the absolute configuration of the natural product has not been determined by its X-ray analysis, unfortunately.