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## CONCISE SUBSTRATE-CONTROLLED ASYMMETRIC TOTAL SYNTHESIS OF (+)-3-(Z)-DIHYDRORHODOPHYTIN

Byungsook Kim,<sup>a</sup> Te-ik Sohn,<sup>a</sup> Sanghee Kim,<sup>a</sup> Deukjoon Kim,<sup>\*a</sup> and Jongkook Lee<sup>b</sup>

<sup>a</sup>The Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151-742, Korea

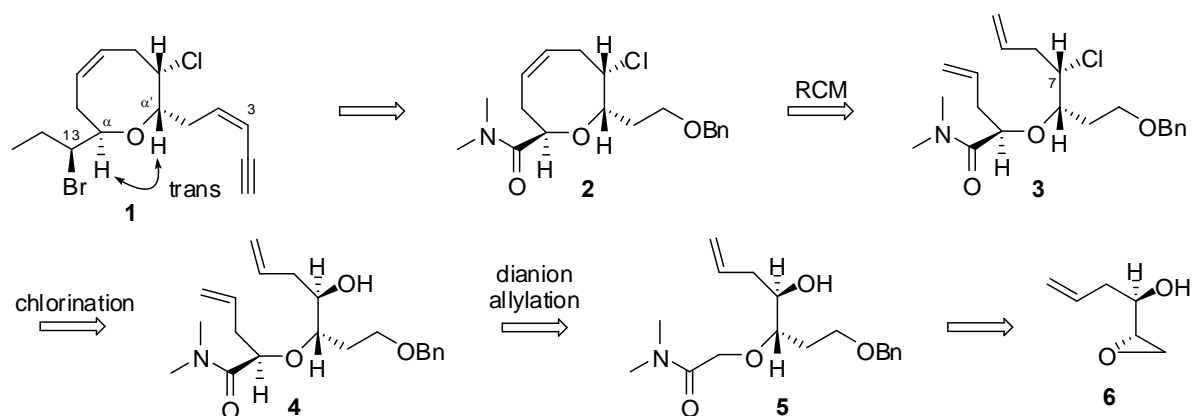
<sup>b</sup>Bio-organic Science Division, Korea Research Institute of Chemical Technology, PO Box 107, Yuseong, Daejeon 305-600, Korea

e-mail: deukjoon@snu.ac.kr

**Abstract** – The first asymmetric total synthesis of (+)-3-(Z)-dihydrorhodophytin (**1**) has been accomplished in 15 steps in 17% overall yield from readily available starting material **6** in a substrate-controlled manner. Key steps in our synthesis are a highly stereoselective dianion alkylation for the synthesis of the  $\alpha,\alpha'$ -*anti*-RCM substrate and a strategy for the introduction of the chlorine function.

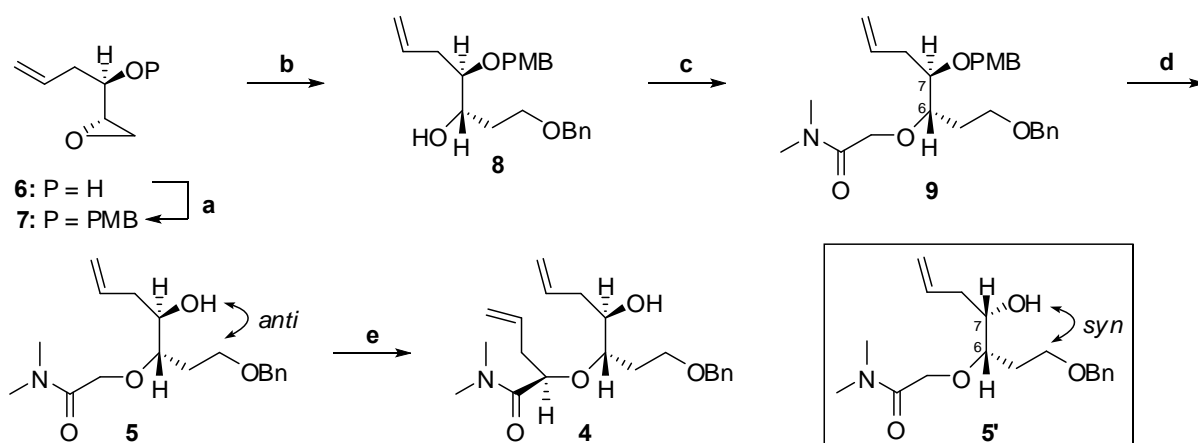
(+)-3-(Z)-Dihydrorhodophytin (**1**) was isolated from the sea hare *Aplysia braziliana* in 1979 and was shown to possess fish antifeedant activity.<sup>1</sup> The structure and absolute stereochemistry of this C15 nonisoprenoid metabolite were elucidated by a combination of spectroscopic analysis and X-ray crystallography.<sup>1</sup> Reported herein is a completely substrate-controlled asymmetric synthesis of this interesting  $\alpha,\alpha'$ -*trans*-oxocene marine natural product based upon a highly stereoselective dianion alkylation for the synthesis of an  $\alpha,\alpha'$ -*anti*-RCM substrate.

As shown in Scheme 1, we envisaged that (+)-3-(Z)-dihydrorhodophytin (**1**) could be elaborated from key  $\alpha,\alpha'$ -*trans*-disubstituted chloro oxocene **2**, which in turn could be prepared from chloro diene **3** by a ring-closing metathesis. It should be emphasized that it is critical to introduce the chlorine atom at C(7) of diene alcohol **4** prior to the RCM step (vide infra). We further envisioned that key  $\alpha,\alpha'$ -*anti*-diene alcohol **4** could be stereoselectively secured by our dianion alkylation methodology<sup>2</sup> using hydroxy amide **5**. Further analysis indicated that hydroxy amide **5** should be readily available from known epoxy alcohol **6**.



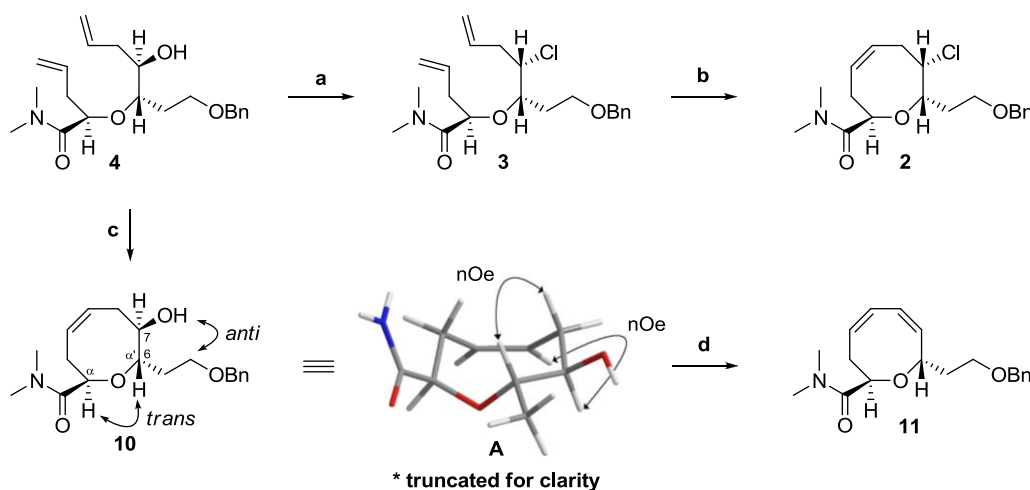
Scheme 1. Retrosynthetic Plan

The synthesis commenced by preparing key alkylation substrate **5** from known alcohol **6**<sup>3</sup> in four steps as shown in Scheme 2. Thus, protection of alcohol **6** with a PMB group, followed by opening of the resultant epoxide **7** with (benzyloxy)methyl lithium,<sup>4</sup> afforded the one-carbon homologated alcohol **8** in 70% yield for the two steps. Williamson etherification of alcohol **8** with *N,N*-dimethyl  $\alpha$ -chloroacetamide and oxidative removal of the PMB group from the resulting  $\alpha$ -alkoxy amide **9** with wet DDQ<sup>5</sup> then provided the required alkylation precursor **5** in a highly efficient manner (94%, two steps). To our satisfaction, the crucial dianion alkylation of hydroxy amide **5** by successive treatment with LiHMDS and then allyl iodide produced the desired  $\alpha,\alpha'$ -*anti*-diene **4** as virtually a single stereoisomer in 85% yield. It is interesting to note that the observed diastereoselectivity in the dianion alkylation of C(6)/C(7)-*anti*-isomer **5** is far superior to that of the previously reported *syn*-isomer **5'** (>50:1 vs. 6:1).<sup>2a</sup>



**Scheme 2.** Dianion Alkylation. *Reagent and Conditions:* a) NaH, PMBCl, TBAI, DMF, 0 °C to rt, 4.5 h, 86%; b) LiCH<sub>2</sub>OBn, BF<sub>3</sub>·Et<sub>2</sub>O, Et<sub>2</sub>O, -78 °C, 30 min, 81%; c) NaH, ClCH<sub>2</sub>CONMe<sub>2</sub>, THF/DMF (3:1), 0 °C to rt, 15 h, 96%; d) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 8.0 buffer (9:1), 0 °C, 3 h, 98%; e) LiHMDS, allyl iodide, THF, -78 to 0 °C, 2 h, 85%.

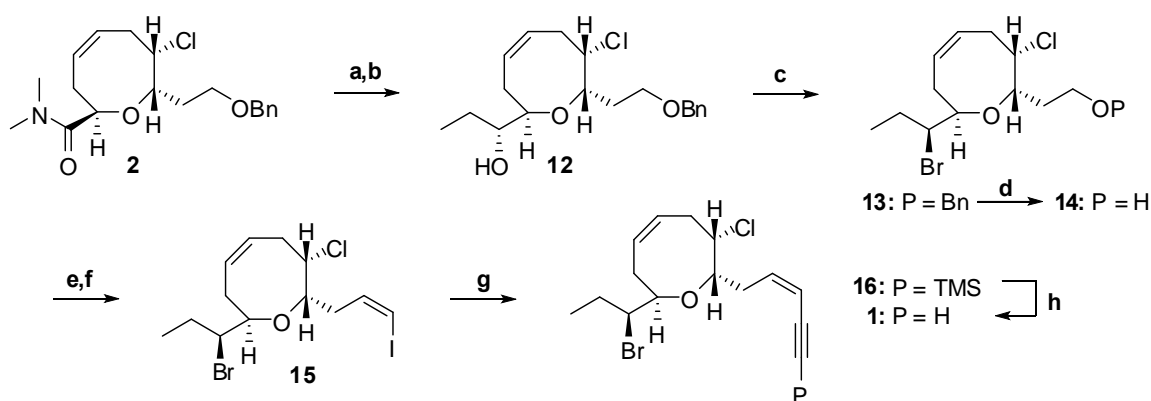
With  $\alpha,\alpha'$ -*anti*-diene alcohol **4** available in multigram quantities, we directed our attention to synthesis of key chloro oxocene **2**. Chlorination of the acyclic secondary homoallylic alcohol **4** with inversion of configuration by the Hooz protocol,<sup>6</sup> followed by RCM<sup>7</sup> of the resultant chloro diene **3** with the first-generation Grubbs' Ru catalyst, afforded key oxocene **2** in 79% overall yield for the two steps (Scheme 3). Our extensive experience in this field suggested that  $\alpha,\alpha'$ -*trans*, C(6)/C(7)-*anti* system such as **10** represents the worst substrate for halogenation with inversion of configuration among the four possible diastereomeric oxocene alcohols. This result is probably due to steric hindrance to backside approach of the incoming chloride in the preferred *syn*-conformation **A** of **10**.<sup>8-10</sup> In fact, chlorination of  $\alpha,\alpha'$ -*trans*-alcohol **10**, prepared by RCM of diene alcohol **4**, led to complete elimination, even under the improved chlorination conditions of Boeckman,<sup>9a</sup> to give diene **11** as the sole product (83%).



**Scheme 3.** Chlorination and Ring-Closing Metathesis. <sup>a</sup>Reagent and Conditions: a)  $\text{CCl}_4$ ,  $\text{Oct}_3\text{P}$ , 1-methylcyclohexene, toluene, 0 °C to 70 °C, 3 h, 81%; b)  $\text{Cl}_2(\text{Cy}_3\text{P})_2\text{Ru}=\text{CHPh}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 2 h, then DMSO, rt, 12 h, 97%; c)  $(\text{H}_2\text{IMes})(\text{Cy}_3\text{P})\text{Cl}_2\text{Ru}=\text{CHPh}$ ,  $\text{Ti}(\text{OiPr})_4$ ,  $\text{CH}_2\text{Cl}_2$ , 40 °C, 3.5 h, then DMSO, rt, 12 h, 67%; d)  $\text{CCl}_4$ ,  $\text{Oct}_3\text{P}$ , 1-methylcyclohexene, toluene, rt to 70 °C, 2 h, 83%.

Conversion of key chloro oxocene intermediate **2** to (+)-3-(*Z*)-dihydrorhodophytin (**1**) was accomplished in an uneventful sequence similar to that employed for our synthesis of (+)-3-(*Z*)-pinnatifidenyne,<sup>9b</sup> as summarized in Scheme 4. Our direct ketone synthesis protocol<sup>9b</sup> on  $\alpha$ -alkyloxy amide **2** with ethylmagnesium bromide, followed by L-Selectride reduction<sup>6b,11</sup> of the resulting ethyl ketone in a Felkin-Ahn sense, provided secondary alcohol **12** as a single isomer in 88% yield for the two steps. Introduction of the bromine functionality at C(13) with inversion of configuration in the presence of the chlorine atom under the Hooz conditions completed elaboration of the C(12) side chain to give bromide **13** in 93% yield.

Next, we turned our attention to incorporation of the (*Z*)-enyne side chain to complete the synthesis. For this purpose, removal of the benzyl group in bromide **13** by exposure to wet DDQ afforded alcohol **14** in 67% yield. Dess-Martin periodinane oxidation<sup>12</sup> of primary alcohol **14** and subsequent Stork-Zhao olefination<sup>13</sup> of the resulting aldehyde produced (*Z*)-vinyl iodide **15** as a single isomer in 84% yield from alcohol **14**. Sonogashira coupling reaction<sup>14</sup> of (*Z*)-vinyl iodide **15** with (trimethylsilyl)acetylene in the presence of (Ph<sub>3</sub>P)<sub>4</sub>Pd/CuI provided the desired (*Z*)-enyne **16** (98%). Finally, removal of the trimethylsilyl protecting group with TBAF delivered (+)-3-(*Z*)-dihydrorhodophytin (**1**) in 84% yield. Spectral data and specific rotation of the synthetic material were in good agreement with those of the natural product.<sup>15</sup>



**Scheme 4.** Completion of the Synthesis. *Reagent and Conditions:* a) EtMgBr, THF, 0 °C to rt, 30 min, 89%; b) L-Selectride, THF, -78 °C, 1 h, 99%; c) CBr<sub>4</sub>, Oct<sub>3</sub>P, pyridine, toluene, 0 °C to 70 °C, 1 h, 93%; d) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 8.0 buffer (9/1), 0 °C, 5 h, 67%; e) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 4 h, 93%; f) [Ph<sub>3</sub>PCH<sub>2</sub>I]I, NaHMDS, THF, -78 °C to rt, 30 min, 90%; g) TMS-acetylene, (Ph<sub>3</sub>P)<sub>4</sub>Pd, CuI, Et<sub>2</sub>NH, rt, 1 h, 98%; h) TBAF, THF, -40 °C, 30 min, 84%.

In summary, a concise and highly stereoselective asymmetric total synthesis of (+)-3-(*Z*)-dihydrorhodophytin (**1**) has been accomplished in 15 steps in 17% overall yield from readily available starting material **6** in a completely substrate-controlled manner. Our synthesis features a highly stereoselective dianion alkylation, a strategy for the demanding introduction of the chlorine function into the oxocene skeleton, and an RCM as key steps.

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15.  $R_f$  0.38 (*n*-hexane/ethyl acetate, 20/1);  $[\alpha]_D^{25} +61.7$  ( $c$  0.1,  $\text{CHCl}_3$ ; lit.,<sup>1</sup>  $[\alpha]_D^{25} +74.8$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.03 (ddd,  $J = 8.0, 8.0, 11.0$  Hz, 1 H), 5.79-5.90 (m, 2 H), 5.58 (ddd,  $J = 1.0, 1.0, 11.0$  Hz, 1 H), 4.21 (dd,  $J = 6.5, 8.0$  Hz, 1 H), 4.06-4.10 (m, 2 H), 3.90 (ddd,  $J = 2.5, 7.5, 11.0$  Hz, 1 H), 3.16 (d,  $J = 2.0$  Hz, 1 H), 2.55-2.70 (m, 5 H), 2.46 (ddd,  $J = 7.5, 11.0, 14.5$  Hz, 1 H), 2.19 (dddd,  $J = 3.0, 7.0, 7.0, 7.0, 14.5$  Hz, 1 H), 1.74-1.83 (m, 1 H), 1.08 (t,  $J = 7.0$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  140.3, 130.2, 127.6, 111.5, 82.8, 80.1, 79.6, 73.4, 64.2, 60.3, 35.3, 33.5, 30.13, 30.14, 12.2; HRMS (CI) found 331.0460 [calcd for  $\text{C}_{15}\text{H}_{21}\text{OBrCl}(\text{M}+\text{H})^+$  331.0464].