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Total Synthesis of (+)-Nafuredin-γ Using a Highly Stereoselective Ti-Mediated Aldol Reaction

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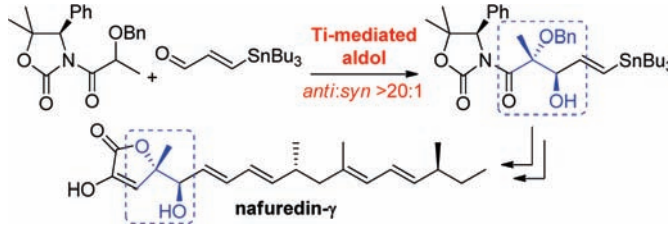
ABSTRACT



An efficient total synthesis of (+)-nafuredin-γ has been achieved in 10 steps from (*E*)-3-(tributylstannyl)propenal. The synthesis features direct construction of an *anti*-1,2-diol moiety via a Ti-mediated aldol reaction of lactyl derivative and rapid fragment assembly, which relied on well-established Pd chemistry.

Ōmura et al. reported the isolation of nafuredin (**1**) from the fungus *Aspergillus niger* FT-0554 as a novel and selective NADH-fumarate reductase complex I inhibitor (Figure 1).[1] They also reported that treatment of **1** with a weak base (K_2CO_3, MeOH) gave the γ-lactone derivative, named nafuredin-γ (**2**).[2] Given that **2** displays the same inhibitory activity and selectivity as **1**, it is likely that the lactone is the biologically active form.[2b] However, although these compounds constitute promising antiparasitic agents, their total syntheses have only been achieved by the group of Kuwajima and Ōmura.[1d,2a,c] Structurally, **1** and **2** have highly oxygenated core skeletons bearing a hydrophobic tetraene side chain. The left-half moiety (C1−C7) of **1** possesses four contiguous stereogenic centers, and that of **2** is simplified to *anti*-1,2-diol (C4−C5) consisting of secondary and tertiary alcohol groups. We therefore set nafuredin-γ (**2**) as a target

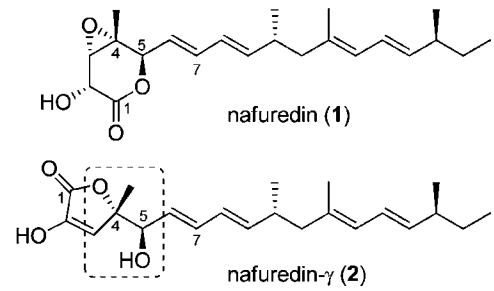


Figure 1. Nafuredin (**1**) and nafuredin-γ (**2**).

(1) (a) Ōmura, S.; Miyadera, H.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Nagamitsu, T.; Takano, D.; Sunazuka, T.; Harder, A.; Kölbl, H.; Namikoshi, M.; Miyoshi, H.; Sakamoto, K.; Kita, K. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 60–62. (b) Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Nagamitsu, T.; Takano, D.; Sunazuka, T.; Namikoshi, M.; Ōmura, S. *J. Antibiot.* **2001**, *54*, 234–238. (c) Takano, D.; Nagamitsu, T.; Ui, H.; Yamaguchi, Y.; Shiomi, K.; Masuma, R.; Kuwajima, I.; Ōmura, S. *Tetrahedron Lett.* **2001**, *42*, 3017–3020. (d) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2001**, *3*, 2289–2291.

(2) (a) Nagamitsu, T.; Takano, D.; Shiomi, K.; Ui, H.; Yamaguchi, Y.; Masuma, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Tetrahedron Lett.* **2003**, *44*, 6441–6444. (b) Shiomi, K.; Ui, H.; Suzuki, H.; Hatano, H.; Nagamitsu, T.; Takano, D.; Miyadera, H.; Yamashita, T.; Kita, K.; Miyoshi, H.; Harder, A.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2005**, *58*, 50–55. (c) Nagamitsu, T.; Takano, D.; Seki, M.; Arima, S.; Ohtawa, M.; Shiomi, K.; Harigaya, Y.; Ōmura, S. *Tetrahedron* **2008**, *64*, 8117–8127.

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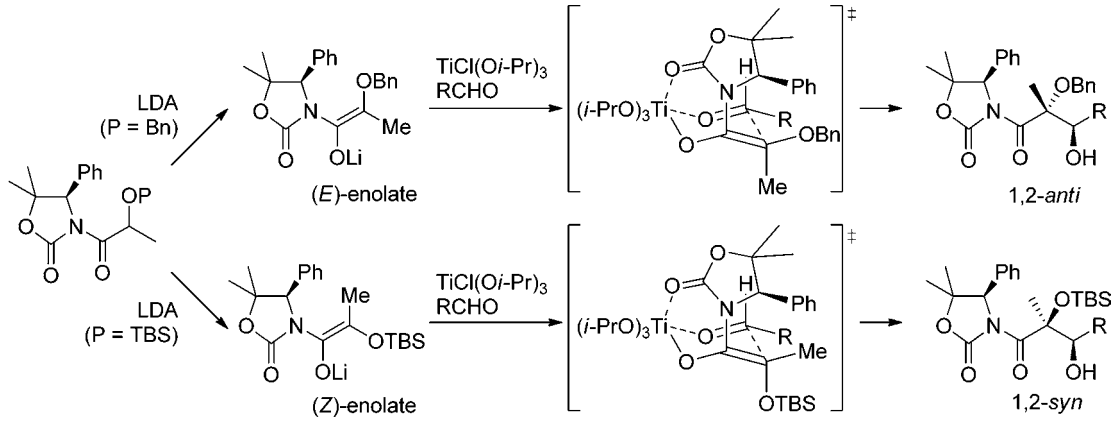
Scheme 1. Ti-Mediated Aldol Reaction of Lactyl-Bearing Chiral Oxazolidin-2-one



molecule. Generally, Sharpless asymmetric dihydroxylation of (*Z*)-trisubstituted alkenes gives *anti*-1,2-diols in low enantioselectivity. In fact, Kuwajima and Ōmura adopted a stepwise approach to construct the *anti* relationship of the C4−C5 asymmetric centers of **2** instead of asymmetric dihydroxylation.

We previously reported a novel methodology for the stereoselective construction of 1,2-diols,[3,4] including secondary and tertiary alcohols, by a Ti-mediated aldol reaction of lactyl-bearing chiral oxazolidin-2-one[5] (Scheme 1). Thus, the protecting group of the alcohol in the lactyl moiety (Bn or TBS) controls the stereochemistry of lithium enolate, resulting in the stereoselective formation of an *anti*- or *syn*-diol derivative through chelation-controlled Zimmerman−Traxler-type transition states. We reasoned that the *anti*-1,2-diol unit of **2** could be effectively constructed by using our methodology. Herein, we describe a highly convergent and efficient total synthesis of (+)-**2** which illustrates the capability of our novel synthetic approach.

Our synthetic strategy is depicted in Figure 2. Inspection of the nafuredin-γ molecule suggests it can be synthesized

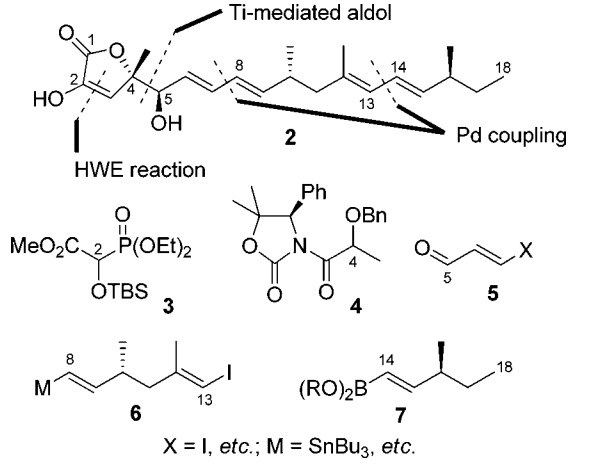


Figure 2. Synthetic strategy toward (+)-nafuredin-γ.

from five component parts: phosphonate **3**,[6] lactyl derivative **4**, aldehyde **5**, iodide **6**, and boronate **7**. We planned that each of these five fragments would be assembled as follows: C2−C3 by Horner−Wadsworth−Emmons (HWE) reaction (as reported by Kuwajima and Ōmura),[2a,c] C4−C5 by Ti-mediated aldol reaction, and C7−C8 and C13−C14 by Pd-catalyzed coupling reactions. In this modular approach, the order of fragment assembly is crucial, especially for the C4−C5 bond formation. The reactivity and stereoselectivity of the aldol reaction forming the C4−C5 bond is likely to be highly dependent on the substituent X of **5** at C7. We initially investigated the Ti-mediated aldol reaction of lactyl derivative **4** with various unsaturated aldehydes.

The results of the Ti-mediated aldol reaction are summarized in Table 1. We planned the aldol reaction to be conducted at a late stage after Pd-catalyzed C−C bond formation at C7−C8. Thus, we first attempted the aldol reaction with (2*E*,4*E*)-hexa-2,4-dienal[7] as a model compound (entry 1). Unfortunately, the reaction with dienal gave aldol product in only moderate yield with unsatisfactory selectivity. Next, we surveyed aldehydes that gave aldol products suitable for Pd-catalyzed coupling reactions. Although 3-(trimethylsilyl)-propynal[8] (entry 2) and (*E*)-3-iodopropenal[9] (entry 3) were not good substrates, aldol reaction of (*E*)-3-(tributylstannyl)propenal[10] (entry 4) predominantly gave the desired *anti*-aldol product (>20:1)[11] in high yield. We postulated that the electronic and steric effect of the

(3) (a) Kamino, K.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 5249–5252. (b) Murata, Y.; Kamino, K.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2002**, *43*, 8121–8123.

(4) For recent examples, see: (a) Crimmins, M. T.; Shamszad, M.; Mattson, A. E. *Org. Lett.* **2010**, *12*, 2614–2617. (b) Ohtani, T.; Tsukamoto, S.; Kanda, H.; Misawa, K.; Urakawa, Y.; Fujimaki, T.; Imoto, M.; Takahashi, Y.; Takahashi, D.; Toshima, K. *Org. Lett.* **2010**, *12*, 5068–5071.

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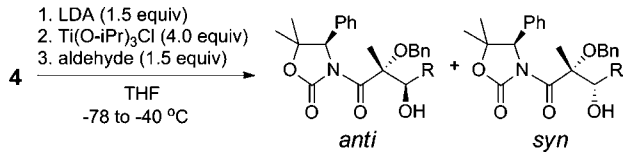
(6) Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663–666.

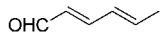
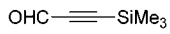
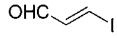
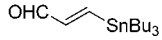
(7) (2*E*,4*E*)-Hexa-2,4-dienal was prepared from ethyl sorbate through DIBAL reduction followed by MnO_2 oxidation.

(8) Velcicky, J.; Lanver, A.; Lex, J.; Prokop, A.; Wieder, T.; Schmalz, H. G. *Chem.—Eur. J.* **2004**, *10*, 5087–5110.

(9) (a) Marek, I.; Meyer, C.; Normant, J. F. *Org. Synth., Coll.* **1998**, *9*, 510–515. (b) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666–3667.

Table 1. Ti-Mediated Aldol Reaction with Unsaturated Aldehydes



entry	aldehyde	yield (%)	*anti*:*syn*[a]
1		66	2:3
2		60	6:1
3		44	10:1
4		80	>20:1

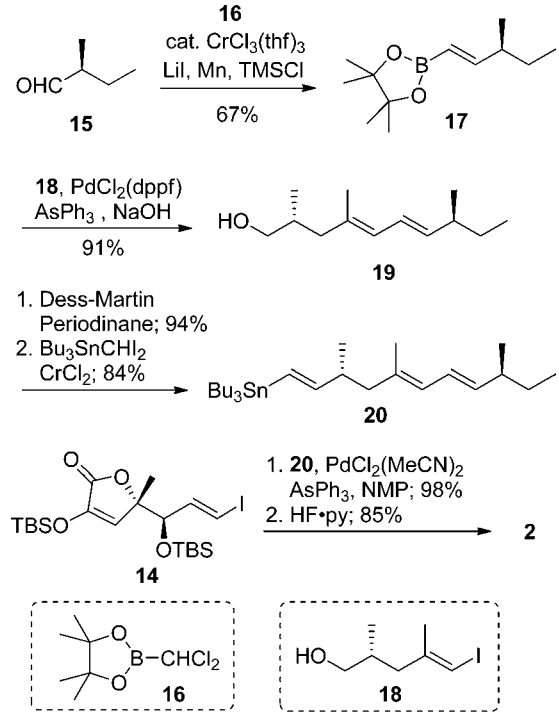
[a] Diastereomeric ratio was determined by H NMR.

tributylstannyl group improved the stereoselectivity of the reaction. Specifically, we reasoned that electron donation from the tributylstannyl group facilitates coordination with the Ti−O bond, and the bulkiness of the tributylstannyl group stabilizes the desired transition state.

With the *anti*-1,2-diol **8** in hand, we commenced the synthesis of nafuredin-γ (Scheme 2). Protection of the secondary alcohol **8** followed by reductive cleavage of the chiral auxiliary group gave alcohol **9**. Extensive attempts (hydrogenolysis, Lewis acidic conditions, oxidative and reductive conditions) to remove the benzyl group of **9** were unsuccessful, resulting in decomposition of the vinylstannyl moiety. Stannane **9** was then converted to vinyliodide **10**, which is compatible with the oxidative conditions used in the subsequent step. Indeed, oxidative deprotection of **10** with DDQ[12] gave diol **13**, along with benzoate ester **11** and benzylidene acetal **12**. Both side products **11** and **12** were transformed to diol **13** by treatment with DIBALH and 1N−H_2SO_4, respectively. The two-step deprotection sequence from **10** to **13** was achieved with an overall yield of 84%. Subsequent oxidation of **13** with SO_3•py followed by HWE reaction with **3** based on the protocol of Kuwajima and Ōmura furnished γ-lactone **14** in 70% yield.

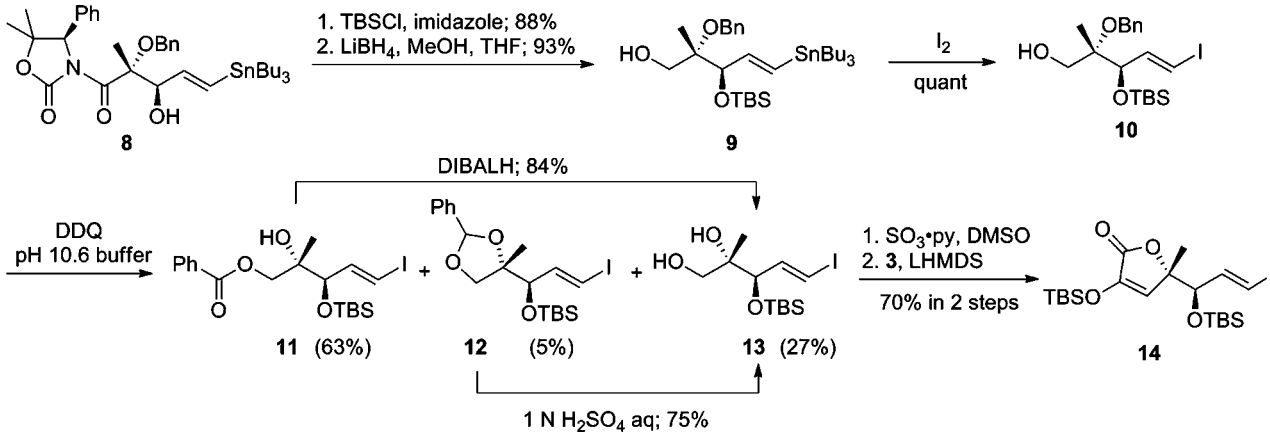
Finally, we focused on the fragment assembly to complete the total synthesis of nafuredin-γ (Scheme 3). Catalytic

Scheme 3. Completion of the Total Synthesis of (+)-Nafuredin-γ



Takai−Utimoto olefination[13] of the known chiral aldehyde **15**[14] with boronate **16** afforded vinylboronate **17**, which was subjected to Suzuki−Miyaura coupling with the known vinyliodide **18**[15] to give diene **19**. Oxidation of **19** with

Scheme 2. Preparation of C1−C7 Fragment



Dess−Martin periodinane followed by Takai−Utimoto olefination[16] furnished vinylstannane **20**. By modifying the conditions by Kuwajima and Ōmura,[2a,c] Stille coupling with γ-lactone **14** and vinylstannane **20** was achieved in excellent yield. Deprotection of the resulting compound afforded (+)-nafuredin-γ in 32% overall yield from lactyl derivative **4** (10 steps). All of the spectral data obtained from our synthetic (+)-nafuredin-γ were in accordance with those reported by Ōmura et al.[2]

In conclusion, the efficient total synthesis of (+)-nafuredin-γ has been achieved. The characteristic features of our synthetic route were: (1) direct construction of an *anti*-1,2-diol moiety via a Ti-mediated aldol reaction of lactyl derivative developed by our group and (2) rapid fragment assembly, which relied on well-established Pd chemistry.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102501K

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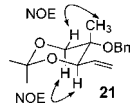
(11) The relative stereochemistry was determined by NMR studies of acetonide derivative **21**.



The absolute stereochemistry was estimated to be shown according to our previous examples. Finally, the stereochemistry was confirmed by the transformation to nafuredin-γ. See Supporting Information.

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(13) Takai, K.; Kunisada, Y.; Tachibana, Y.; Yamaji, N.; Nakatani, E. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1581–1586.

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(15) Zhu, G.; Negishi, E. *Chem.—Eur. J.* **2008**, *14*, 311–318.

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