

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

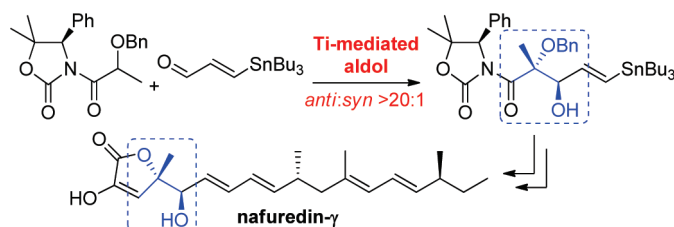
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ABSTRACT



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.

Omura 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 (K₂CO₃, 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

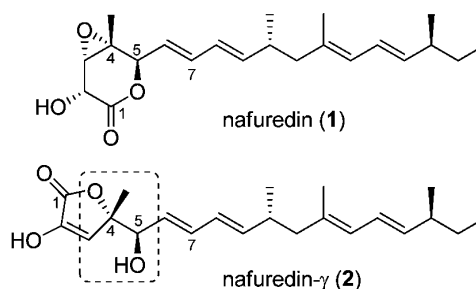


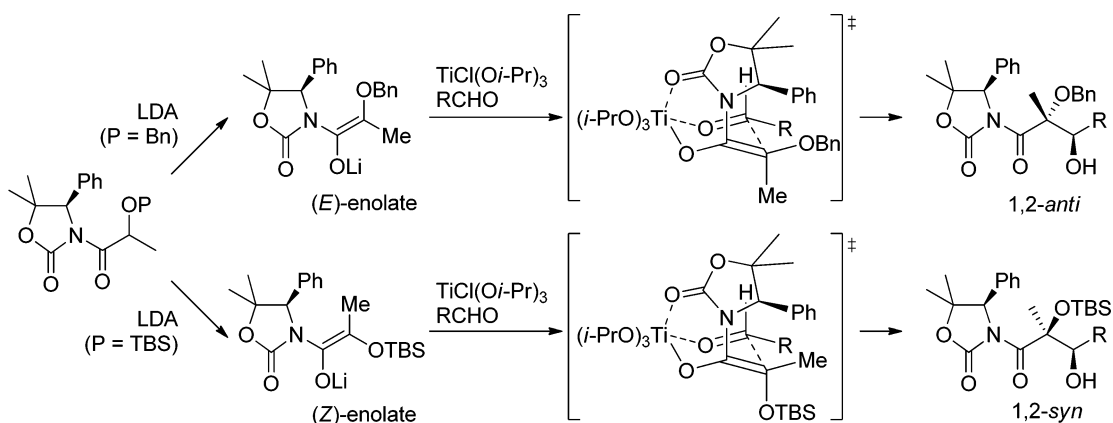
Figure 1. Nafuredin (**1**) and nafuredin- γ (**2**).

compounds constitute promising antiparasitic agents, their total syntheses have only been achieved by the group of Kuwajima and Omura.^{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

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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-one⁵ (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

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 (*2E,4E*)-hexa-2,4-dienal⁷ 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)propynal⁸ (entry 2) and (*E*)-3-iodopropenal⁹ (entry 3) were not good substrates, aldol reaction of (*E*)-3-(tributylstannyl)propenal¹⁰ (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

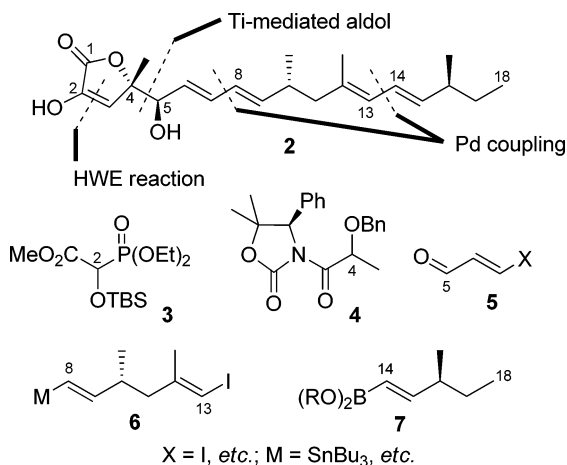


Figure 2. Synthetic strategy toward (+)-nafuredin- γ .

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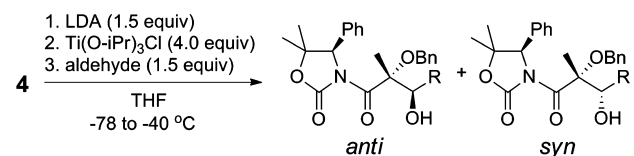
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(7) (*2E,4E*)-Hexa-2,4-dienal was prepared from ethyl sorbate through DIBAL reduction followed by MnO₂ oxidation.

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Table 1. Ti-Mediated Aldol Reaction with Unsaturated Aldehydes



entry	aldehyde	yield (%)	<i>anti:syn</i> ^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.

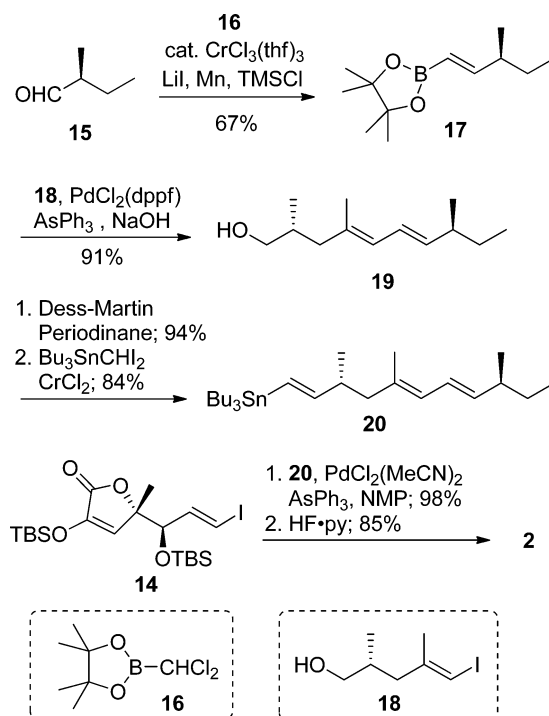
tributylstannyl group improved the stereoselectivity of the reaction. Specifically, we reasoned that electron donation from the tributylstannyl group facilitates coordination with the Ti–O bond, and the bulkiness of the tributylstannyl group stabilizes the desired transition state.

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 vinyl iodide **10**, which is compatible with the oxidative conditions used in the subsequent step. Indeed, oxidative deprotection of **10** with DDQ¹² 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-H₂SO₄, respectively. The two-step deprotection sequence from **10** to **13** was achieved with an overall yield of 84%. Subsequent oxidation of **13** with SO₃·py followed by HWE reaction with **3** based on the protocol of Kuwajima and Ōmura furnished γ -lactone **14** in 70% yield.

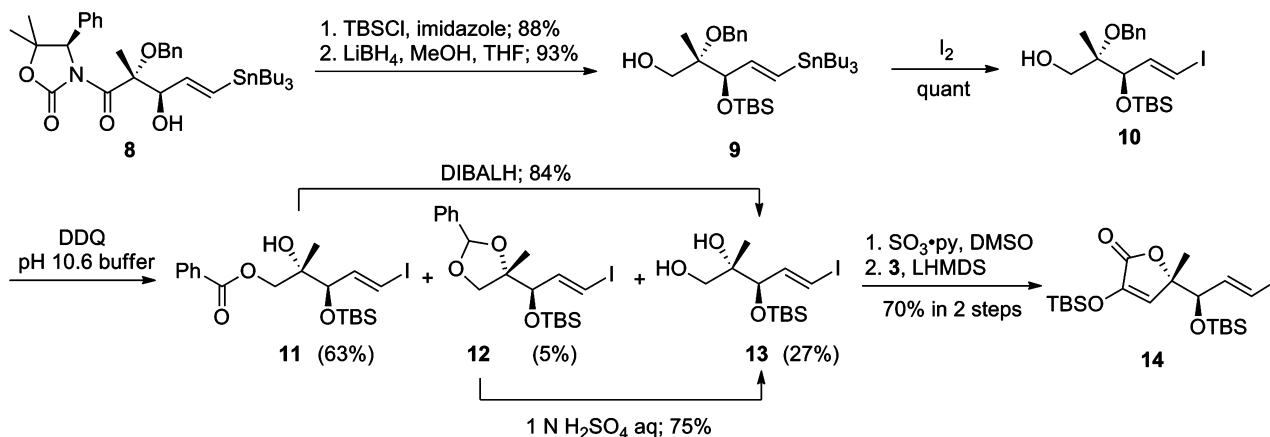
Finally, we focused on the fragment assembly to complete the total synthesis of nafuredin- γ (Scheme 3). Catalytic

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



Takai–Utimoto olefination¹³ of the known chiral aldehyde **15**¹⁴ with boronate **16** afforded vinylboronate **17**, which was subjected to Suzuki–Miyaura coupling with the known vinyl iodide **18**¹⁵ to give diene **19**. Oxidation of **19** with

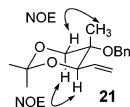
Scheme 2. Preparation of C1–C7 Fragment



Dess–Martin periodinane followed by Takai–Utimoto olefination¹⁶ 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

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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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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>.

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