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Tetrahedron Letters 44 (2003) 6441–6444

TETRAHEDRON LETTERS

Total synthesis of nafuredin-γ, a γ-lactone related to nafuredin with selective inhibitory activity against NADH-fumarate reductase

Tohru Nagamitsu,[a] Daisuke Takano,[a] Kazuro Shiomi,[a] Hideaki Ui,[a] Yuichi Yamaguchi,[b] Rokuro Masuma,[b] Yoshihiro Harigaya,[a] Isao Kuwajima[b,c] and Satoshi Ōmura[b,*]

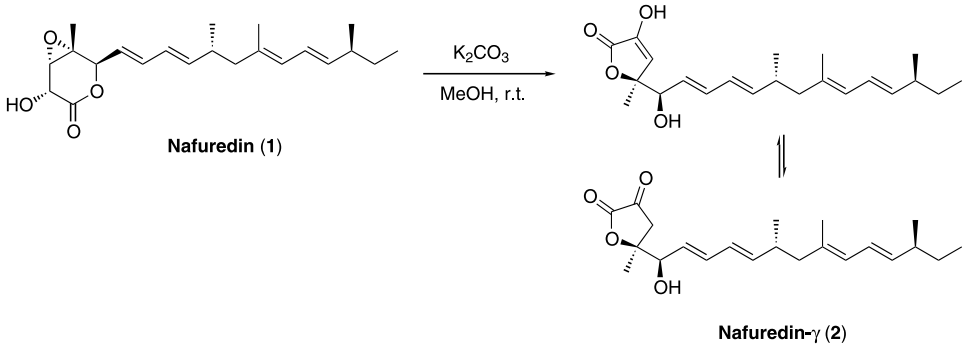
[a]*School of Pharmaceutical Science, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[b]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[c]*CREST, The Japan Science and Technology Corporation (JST), 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*

Received 7 June 2003; revised 20 June 2003; accepted 25 June 2003

Abstract—Nafuredin-γ (**2**) converted from nafuredin (**1**) under mild basic conditions showed the same inhibitory activity and selectivity against NADH-fumarate reductase as **1**. Total synthesis of **2**, a proposed active form of **1**, has been accomplished by a convergent approach using Stille coupling.

Nafuredin (**1**)[1,2] was isolated from the fermentation broth of a fungal strain, *Aspergillus niger* FT-0554, in the course of our screening for NADH-fumarate reductase (NFRD) inhibitors. **1** inhibited NFRD of *Ascaris suum* with an IC_{50} value of 12 nM and showed selective inhibition of its target enzyme complex I in helminth mitochondria. In addition, **1** exerted anthelmintic activity against *Haemonchus contortus* in in vivo trials with sheep.[1] These useful biological activities of **1** attracted our attention, and we previously reported the elucidation of the absolute configuration[3] and the total synthesis[4] of **1**.

During the course of the total synthetic studies of **1**, we discovered that **1** was converted to a novel γ-lactone derivative (**2**) under mild basic conditions (K_2CO_3 in MeOH) as shown in Scheme 1, which existed as a mixture of keto-enol tautomers.[5] We named the γ-lactone derivative (**2**) nafuredin-γ. Since nafuredin-γ (**2**) is not detected in the above fermentation broth[6] at all, **2** is not produced directly by the above strain and is formed only from **1** under the basic conditions via enolization, opening of the epoxide, and formation of the γ-lactone. We expected **2** to have inhibitory activity against NFRD as well as **1** because the conversion of **1**,



Scheme 1.

* Corresponding author. Tel.: +81-3-5791-6101; fax: +81-3-3444-8360; e-mail: omura-s@kitasato.or.jp

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doi:10.1016/S0040-4039(03)01583-1

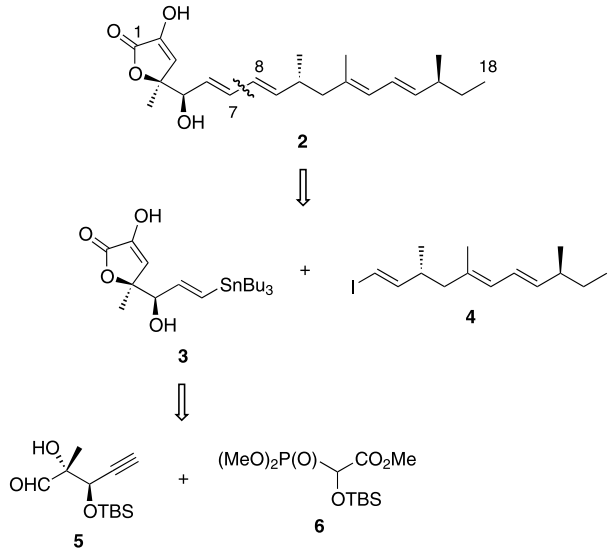
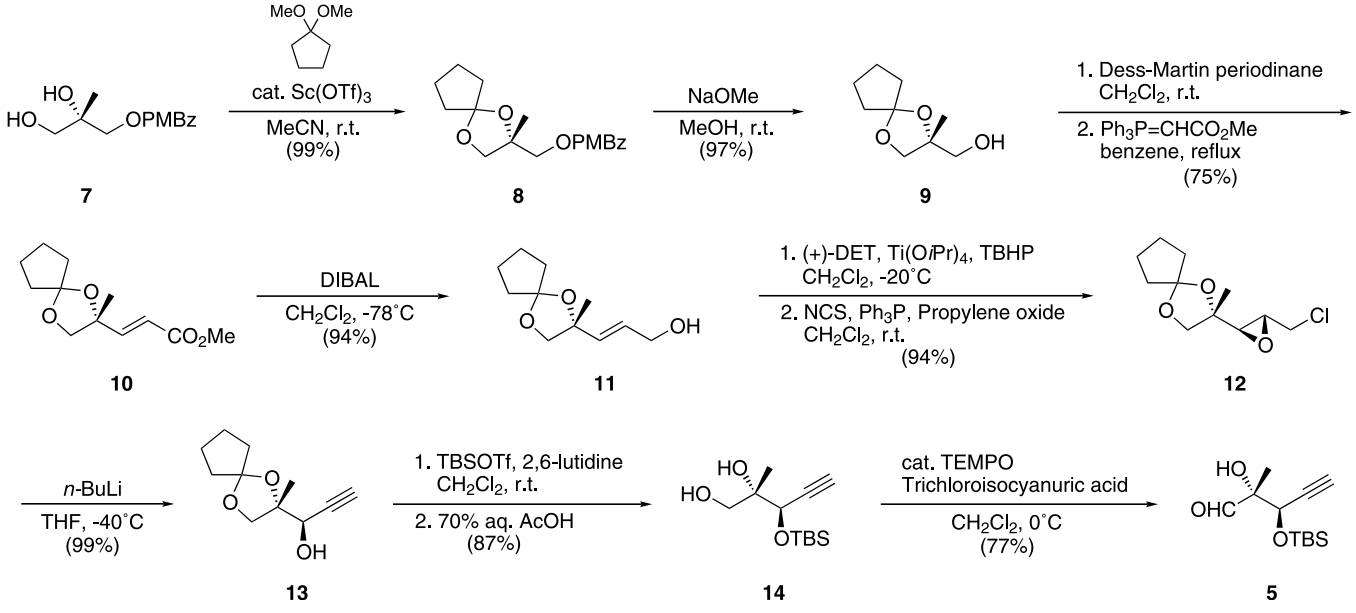


Figure 1.

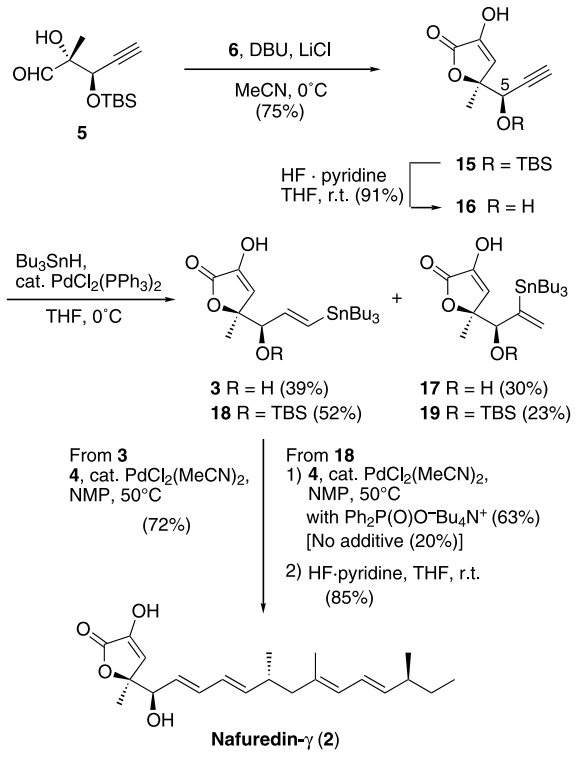
possessing the labile β,γ-epoxycarbonyl unit, to **2** is likely to occur under the assay conditions for NFRD. We tested the inhibitory activity against NFRD of **2**. Our test of the inhibitory activity against NFRD proved **2** shows the same inhibitory activity and selectivity as **1**, which suggests the possibility that **2** may be an active form of **1** and may permit a structural simplification of the lactone moiety in the structure–activity relationship studies of **1**. We report herein the total synthesis of nafuredin-γ (**2**).

As outlined in Figure 1, our synthetic strategy of nafuredin-γ (**2**) is convergent and involves the assembly of C1–C7 segment **3** and C8–C18 segment **4**[7] by Stille coupling at the final step, which will give us a simple and efficient way to synthesize various nafuredin-γ derivatives with modification at the side chain moiety. The enol lactone **3** could be constructed by Hornor–Emmons reaction of aldehyde **5** with a known phosphonate **6** followed by hydrostannylation.

We started from the known diol **7** (97% e.e.)[8] to lead to the aldehyde **5** as shown in Scheme 2. Although acetalization of **7** under usual conditions (cyclopentanone and a catalytic amount of TsOH in benzene) caused serious racemization,[9] treatment with cyclopentanone dimethylacetal in the presence of $Sc(OTf)_3$ catalyst[10] gave **8** almost quantitatively. Cleavage of the *p*-methoxybenzoyl ester with sodium methoxide in methanol produced **9** in 97% yield. Oxidation of **9** with Dess–Martin periodinane[11] followed by Wittig reaction with methyl (triphenylphosphoranylidene)acetate furnished **10** in 75% yield in two steps. The resulting ester was reduced with DIBAL to give allyl alcohol **11** in 94% yield. Sharpless asymmetric epoxidation[12] of **11** using (+)-diethyl tartrate provided the corresponding epoxide (94% d.e.), which was further converted to chloride **12** by treatment with NCS and Ph_3P in the presence of propylene oxide as a chloride ion scavenger[13] in 94% yield in two steps. Base-induced elimination[14] of **12** with *n*-BuLi furnished **13** in 99% yield. Silyl ether protection of **13** with TBSOTf and 2,6-lutidine followed by hydrolysis of cyclopentylidene acetal with 70% aq. AcOH led to diol **14** in 87% yield in two steps. Subsequent oxidation of the primary alcohol in **14** with 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and trichloroisocyanuric acid[15] gave the desired aldehyde **5** in 77% yield, while DMSO oxidation (Swern conditions and Parikh–Doering conditions), Dess–Martin oxidation and TEMPO–NaClO–KBr oxidation lowered the product yield accompanied with decomposition of the product. The use of trichloroisocyanuric acid as co-oxidant in TEMPO oxidation of **14** was crucial for high yield and reproducibility.



Scheme 2.



Scheme 3.

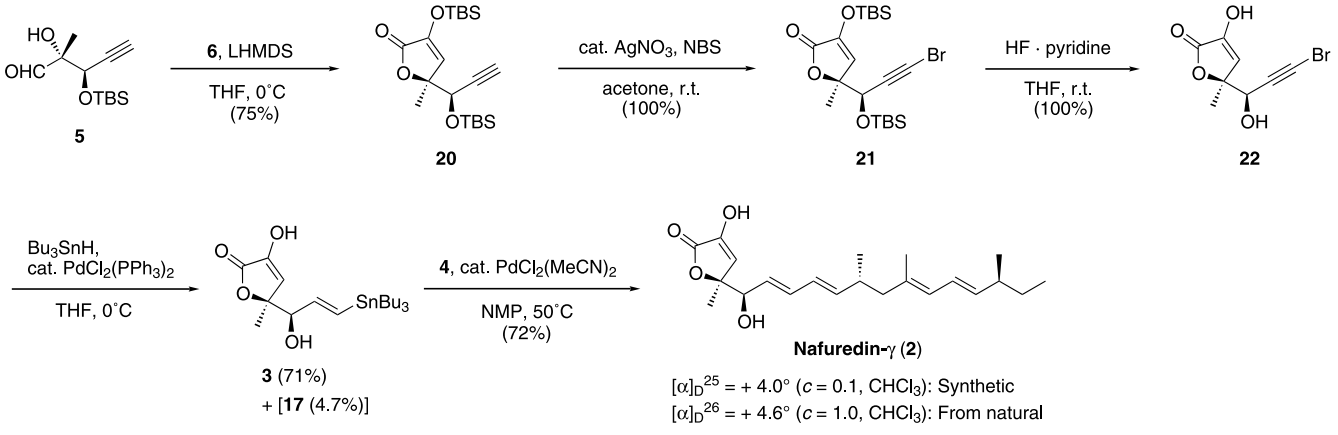
Hornor–Emmons reaction of **5** with the known phosphonate **6**[16] in the presence of DBU and LiCl[17] afforded γ-lactone **15** in 75% yield, which was treated with HF·pyridine to give **16** in 91% yield (Scheme 3). Subsequent palladium-catalyzed hydrostannylation[18] of **16** with Bu_3SnH and $PdCl_2(PPh_3)_2$ proceeded with non-regioselectivity, yielding the desired *E*-alkenylstannane **3** (39%) and its regioisomer **17** (30%). After separation by silica gel chromatography, Stille coupling[19] between **3** and vinyl iodide **4** in the presence of $PdCl_2(MeCN)_2$ gave nafuredin-γ (**2**) in 72% yield. Although the total synthesis of **2** was achieved, we needed a more effective hydrostannylation procedure with higher regioselectivity for large-scale and analog synthesis of **2**. We also examined hydrostannylation of the TBS ether **15**, and **18** was obtained in 52% yield along with its regioisomer **19** (23%). Subsequent Stille coupling of **18** with **4** could not be effected so well under the same conditions, but addition of $Ph_2P(O)O^-Bu_4N^{+}$[20] improved the yield of the coupling product, which afforded nafuredin-γ (**2**) in 85% yield by removal of the TBS ether group with HF·pyridine. But these moderate yields in hydrostannylation and Stille coupling were still far from satisfactory.

Next, we focused on the high regioselectivity of a palladium-catalyzed hydrostannylation of alkynyl bromides reported by Guibé et al.[21] Although bromination of the terminal alkynes **15** and **16** led to decomposition of substrates, TBS protected enol ether **20**, which was constructed by Hornor–Emmons reaction of **5** with **6** and LHMDS in 75% yield, afforded alkynyl bromide **21** quantitatively by treatment with NBS and $AgNO_3$[22] (Scheme 4). Removal of the TBS ether group with HF·pyridine gave enol **22** quantitatively. Subsequent palladium-catalyzed hydrostannylation of **22** provided the desired *E*-alkenylstannane **3** in 71% yield with high regioselectivity (**3**:**17** = 15:1), which was finally converted to nafuredin-γ (**2**) in good yield as mentioned above. Synthetic nafuredin-γ (**2**) was identical with that derived from natural nafuredin (**1**) in all respects[23] ($[\alpha]_D$, ^1H and ^{13}C NMR, IR, FAB-MS and inhibitory activity against NFRD).

In conclusion, we have discovered nafuredin-γ (**2**), a proposed active form of nafuredin (**1**), and achieved its first total synthesis. Further investigation of the structure-activity relationship and biological studies of **1** and **2** are currently in progress.

Acknowledgements

This study was supported in part by the Grand of 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology, Japan. T. N. acknowledges a Kitasato University research grant for young researchers.



Scheme 4.

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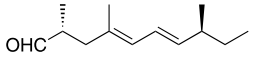
6. *Aspergillus niger* FT-0554 was cultured at 27°C for 6 days to produce **1**, whose fermentation broth showed pH 2 in 1 day and further kept it for 5 days.
7. Compound **4** was derived from aldehyde **I** ($CrCl_2$, CHI_3, THF–dioxane, rt, 81%), which was previously prepared by our laboratory for the total synthesis of **1**.



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23. Physical and spectroscopic data. For nafuredin-γ (**2**): $[\alpha]_D^{25}=+4.0$ (*c* 0.1, $CHCl_3$): IR (KBr) 3374, 2960, 2925, 2858, 1754, 1737, 1660, 1261, 1101 cm^{-1}: HRMS [FAB, *m*-NBA] *m*/*z* $(M+H)^+$ 361.2372; calcd for $C_{22}H_{33}O_4$: M+H 361.2379: ^1H NMR (270 MHz, $CDCl_3$) enol δ 0.86 (t, 3H, $J=7.6$ Hz, H-18), 0.97 (d, 3H, $J=6.7$ Hz, 10-Me), 0.99 (d, 3H, $J=6.6$ Hz, 16-Me), 1.32 (m, 2H, H-17), 1.46 (s, 3H, 4-Me), 1.70 (s, 3H, 12-Me), 1.91–2.12 (m, 3H, H-11 and H-16), 2.36–2.43 (m, 1H, H-10), 4.25 (d, 1H, $J=7.3$ Hz, H-5), 5.46 (dd, 1H, $J=14.8$, 7.6 Hz, H-15), 5.50 (dd, 1H, $J=15.5$, 7.3 Hz, H-6), 5.70 (dd, 1H, $J=15.5$, 7.3 Hz, H-9), 5.76 (d, 1H, $J=10.9$ Hz, H-13), 6.00 (dd, 1H, $J=15.5$, 10.2 Hz, H-8), 6.15 (s, 1H, H-3), 6.18 (dd, 1H, $J=14.8$, 10.9 Hz, H-14), 6.30 (dd, 1H, $J=15.5$, 10.2 Hz, H-7), ketone δ 0.86 (t, 3H, $J=7.6$ Hz, H-18), 0.97 (d, 3H, $J=6.7$ Hz, 10-Me), 0.99 (d, 3H, $J=6.6$ Hz, 16-Me), 1.32 (m, 2H, H-17), 1.54 (s, 3H, 4-Me), 1.70 (s, 3H, 12-Me), 1.91–2.12 (m, 3H, H-11 and H-16), 2.32 (d, 1H, $J=18.8$ Hz, 1/2 H-3), 2.36–2.43 (m, 1H, H-10), 3.03 (d, 1H, $J=18.8$ Hz, 1/2 H-3), 4.21 (m, 1H, H-5), 5.46 (dd, 1H, $J=14.8$, 7.6 Hz, H-15), 5.50 (dd, 1H, $J=15.5$, 7.3 Hz, H-6), 5.70 (dd, 1H, $J=15.5$, 7.3 Hz, H-9), 5.76 (d, 1H, $J=10.9$ Hz, H-13), 6.00 (dd, 1H, $J=15.5$, 10.2 Hz, H-8), 6.18 (dd, 1H, $J=14.8$, 10.9 Hz, H-14), 6.30 (dd, 1H, $J=15.5$, 10.2 Hz, H-7).