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Total Synthesis of Nafuredin, a Selective NADH-fumarate Reductase Inhibitor

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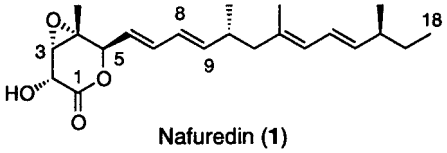
ABSTRACT



Nafuredin (**1**)

Total synthesis of nafuredin, a selective NADH-fumarate reductase inhibitor, has been accomplished by a convergent approach. The C1–C8 and C9–C18 segments were derived efficiently from D-glucose and (*S*)-(−)-2-methyl-1-butanol, respectively, coupled by stereoselective Julia olefination, and converted to nafuredin.

In the course of our screening for NADH-fumarate reductase (NFRD) inhibitors, nafuredin (**1**), which is potentially a selective antiparasitic agent,[1,2] was isolated from the fermentation broth of a fungal strain, *Aspergillus niger* FT-0554. Nafuredin (**1**) inhibited NFRD of *Ascaris suum* with an IC_{50} value of 12 nM. The target of **1** was revealed as complex I, and **1** showed selective inhibition of 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 prompted us to undertake the total synthetic study. We previously reported the elucidation of the absolute configuration of **1** by degradation and synthetic studies.[3] In this Letter, we wish to report the first total synthesis of nafuredin (**1**).

We envisioned a convergent approach toward nafuredin (**1**) via a stereoselective one-pot Julia olefination[4] between sulfone **3** and aldehyde **4** followed by appropriate functional group elaboration of the resulting **2** (Scheme 1). Requisite stereocontrol on the lactol moiety of **3** could be performed by using D-glucose derivative **7** previously prepared in our laboratory,[3] and use of commercially available (*S*)-(−)-2-methyl-1-butanol **6** would allow enantioselective construction of the side chain segment **4** via Wittig olefination and Evans alkylation.

On the basis of the synthetic plan, we initially prepared aldehyde **4** as follows (Scheme 2). The starting material **6** was converted to the known (14*E*)-alcohol **8** in 50% overall yield by a slight modification of Kitahara's procedure,[5] e.g., oxidation with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO),[6] Wittig olefination, and DIBAL reduction. Allylic oxidation of **8** with MnO_2 followed by Wittig olefination with (1-carboethoxyethylidene)triphenylphosphorane afforded the desired (12*E*,14*E*)-dienyl ester **9** in 62% yield (two steps).

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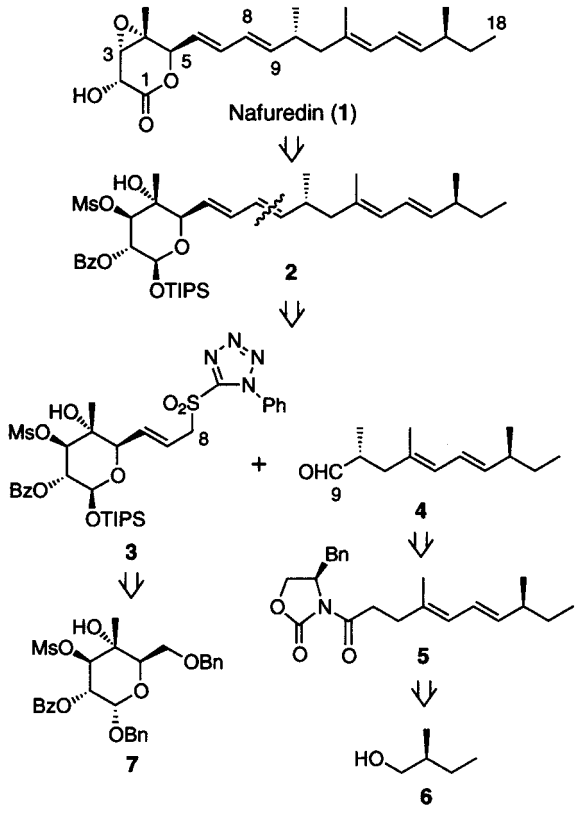
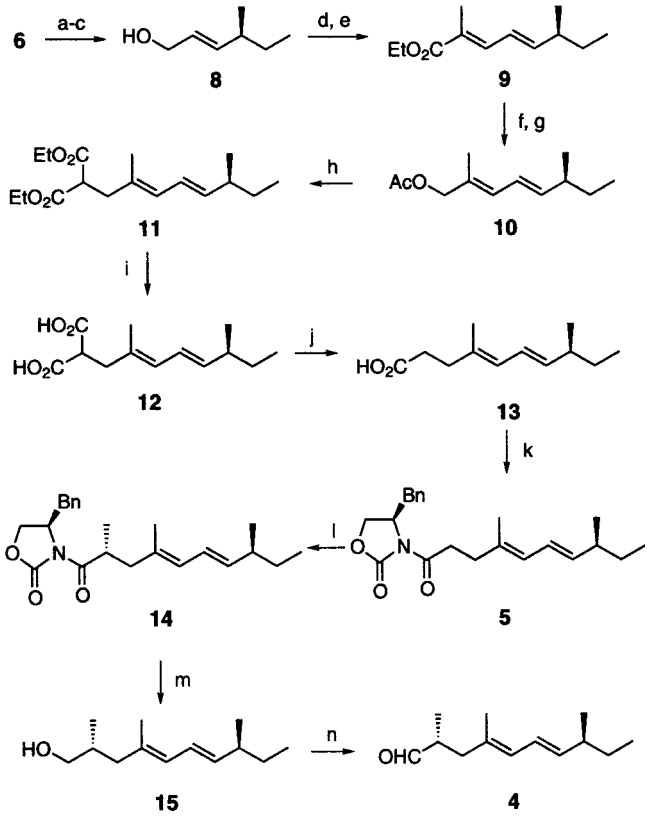
Scheme 1



Scheme 2[a]



[a] (a) TEMPO, NaClO, KBr, CH_2Cl_2; (b) $Ph_3P{=}CHCO_2Me$, benzene, 50 °C; (c) DIBAL, CH_2Cl_2, −78 °C; (d) MnO_2, CH_2Cl_2; (e) $Ph_3P{=}CMeCO_2Et$, benzene, 50 °C; (f) DIBAL, CH_2Cl_2, −78 °C; (g) Ac_2O, Et_3N, catalytic DMAP, CH_2Cl_2; (h) diethyl malonate, NaH, catalytic $Pd(PPh_3)_4$, THF, 50 °C; (i) KOH, MeOH−H_2O; (j) Cu_2O, CH_3CN, reflux; (k) PivCl, Et_3N, THF, 0 °C, then (*R*)-4-benzyl-2-oxazolidinone, *n*-BuLi, THF, −78 to 0 °C; (l) NaHMDS, MeI, THF, −78 °C; (m) $LiBH_4$, EtOH (1.1 equiv), Et_2O, 0 °C; (n) Dess−Martin periodinane, CH_2Cl_2.

DIBAL reduction of the ester **9** and acetylation of the resulting allyl alcohol furnished acetate **10**, quantitatively. Treatment of **10** with diethyl malonate and sodium hydride in the presence of a catalytic amount of $Pd(PPh_3)_4$ led to diester **11** quantitatively, which was subjected to alkali hydrolysis to afford dicarboxylic acid **12**. Decarboxylation of **12** with copper(I) oxide[7] gave monocarboxylic acid **13** in 71% overall yield from **11**. Acid **13** was converted to a mixed anhydride by treatment with pivaloyl chrolide and then acylated with (*R*)-4-benzyl-2-oxazolidinone[8] to produce **5**, quantitatively. Methylation of **5** with sodium hexamethyldisilazide (NaHMDS) and methyl iodide gave **14** in 85% yield with its epimer (5% yield). The absolute configuration of the newly introduced C10 methyl group was tentatively assigned as the desired *R* according to the empirical rule generally accepted[9] and could be confirmed by completion of the total synthesis. Reductive removal[10] of the chiral auxiliary with $LiBH_4$ and oxidation of the resulting alcohol **15** with Dess−Martin periodinane[11] afforded the desired aldehyde **4** in 85% overall yield.

The sulfone **3** corresponding to the C1−C8 segment was prepared as illustrated in Scheme 3. Debenzylation of D-glucose derivative **7** by hydrogenolysis with palladium hydroxide led to triol **16** quantitatively. Protection of the primary alcohol as the TBS ether followed by treatment with TIPSOTf furnished β-TIPS glycoside **17** in 74% yield (two steps). Selective deprotection of the TBS ether was performed by treatment with the TBAF−$BF_3{\cdot}Et_2O$ complex,[12] giving diol **18** in 95% yield.[13] Oxidation of **18** with Dess−Martin periodinane followed by Horner−Wadsworth−Emmons reaction of the corresponding aldehyde with allyl diethylphosphonoacetate, LiCl, and diisopropylethylamine[14] afforded (6*E*)-α,β-unsaturated allyl ester **19** in 75% yield (two

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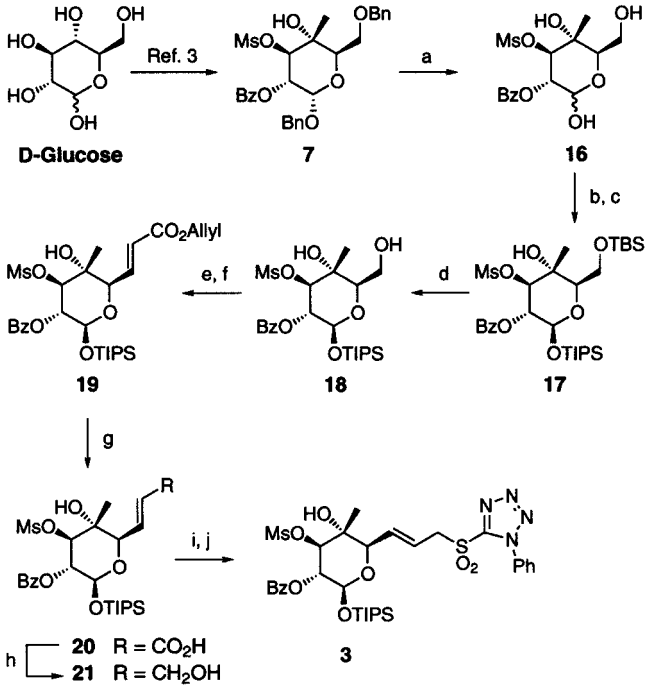
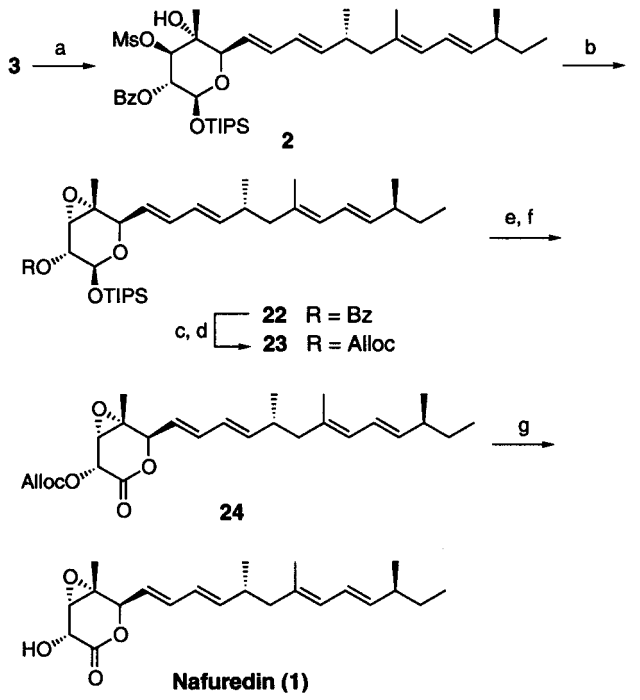
Scheme 3[a]



[a] (a) H_2, $Pd(OH)_2$, EtOH; (b) TBSCl, *i*-Pr_2NEt, DMF; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (d) TBAF, $BF_3{\cdot}Et_2O$, CH_3CN; (e) Dess−Martin periodinane, CH_2Cl_2; (f) $(EtO)_2P(O)CH_2CO_2$allyl, *i*-Pr_2NEt, LiCl, CH_3CN; (g) catalytic $Pd(PPh_3)_4$, $NaBH_4$, EtOH; (h) MeO_2CCl, Et_3N, THF, then $LiAlH(t\text{-}BuO)_3$; (i) DEAD, PBu_3, 1-phenyl-1*H*-tetrazole-5-thiol, THF; (j) H_2O_2, catalytic $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, EtOH.

Scheme 4[a]



[a] (a) KHMDS (2 equiv), THF, then **4**; (b) NaH, THF; (c) DIBAL, CH_2Cl_2; (d) AllocCl, DMAP, pyridine; (e) HF·pyridine, THF; (f) Dess−Martin periodinane, CH_2Cl_2; (g) HCO_2H, Et_3N, catalytic $Pd(PPh_3)_4$, THF.

steps). Deprotection of the allyl ester by treatment with a catalytic amount of $Pd(PPh_3)_4$ and sodium borohydride afforded carboxylic acid **20** quantitatively. Acid **20** was subjected to reduction with lithium tri-*tert*-butoxyaluminohydride through the formation of a mixed anhydride with methyl chloroformate to produce allyl alcohol **21** in 71% yield. Mitsunobu reaction[15] of **21** with 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation with H_2O_2 in the presence of a molybdenum(VI) catalyst[16] furnished the desired sulfone **3** in 96% yield (two steps).

Under the influence of potassium hexamethyldisilazide (KHMDS, 2 equiv in this case),[4b] the one-pot Julia olefination between **3** and **4** could be effected to provide the desired (6*E*,8*E*,12*E*,14*E*)-alcohol **2** in 79% yield as a single isomer[17] (Scheme 4). Treatment of **2** with sodium hydride gave epoxide **22** in 99% yield. Epoxide **22** was subjected to DIBAL reduction in order to remove the benzoyl group,[18] and subsequent protection with allyl chloroformate furnished **23** in 88% yield (two steps). The TIPS protecting group in **23** was then removed by exposure to HF·pyridine, and the resulting lactol was oxidized with Dess−Martin periodinane to afford lactone **24** in 77% yield (two steps). Finally, removal of the allyloxycarbonyl group by treatment with HCO_2H and Et_3N in the presence of a catalytic amount of $Pd(PPh_3)_4$ gave nafuredin (**1**) in 92% yield. Synthetic nafuredin (**1**) was identical with natural (**1**) in all respects ($[\alpha]_D$, ^1H and ^{13}C NMR, IR, FAB-MS, and inhibitory activity against NFRD).

In conclusion, we have achieved the first total synthesis of nafuredin. Investigations of the structure−activity relationship and biological studies of **1** are currently in progress.

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

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(17) On warming up at this stage, epoxide formation could not be effected.

(18) Attempts to remove the benzoyl group under various basic conditions at the final step in the total synthesis did not afford nafuredin (**1**) without decomposition.