Synthesis of (±)-Sordaricin

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(±)-Sordaricin, the aglycon of antifungal sordarin, was synthesized starting from bicyclo[5.3.0]decan-3-one derivative. The strained bicyclo[2.2.1]heptene framework of sordaricin was constructed by the palladium-catalyzed intramolecular Tsuji–Trost reaction.

Sordarin, isolated in 1971 as a metabolite of *Sordaria araneosa*, is a potent and selective inhibitor of fungal protein synthesis[1] (Figure 1). The diterpene aglycon of sordarin, sordaricin (**1**),[2] has a unique tetracyclic diterpene core containing *trans*-perhydroindene and bicyclo[2.2.1]heptene framework (norbornene system) with three successive quaternary centers [C(5), C(6), C(7)].[3] The complex structural feature prompted us to synthesize this compound. Commonly, norbornene systems are synthesized by the Diels–Alder reaction of cyclopentadiene derivatives and alkenes.[4] Sordaricin (**1**) has been proposed to be biosynthesized through an intramolecular [4+2]cycloaddition.[5] There have been two reports on the syntheses of sordaricin (**1**), both of which employed the postulated biogenetic intramolecular [4+2]cycloaddition as a key step.[6] Herein, we wish to report the synthesis of (±)-sordaricin (**1**), including a new synthetic strategy to construct the highly substituted norbornene system.

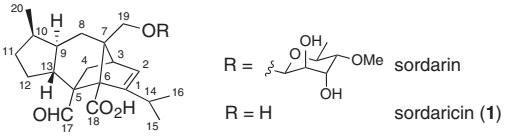
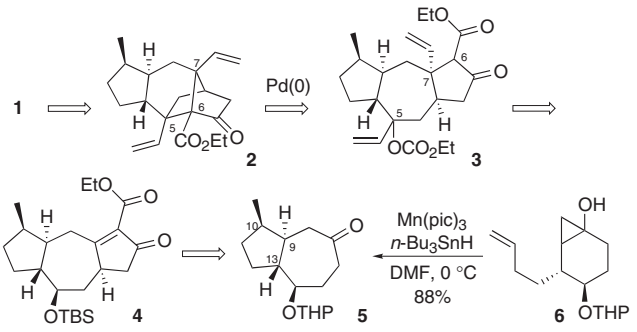


Figure 1.

The retrosynthetic analysis toward the synthesis of (±)-sordaricin (**1**) is outlined in Scheme 1. It was supposed that the sordaricin precursor **2** would be prepared from tricyclic compound **3** by palladium-catalyzed intramolecular allylation via π-allylpalladium intermediate (the Tsuji–Trost reaction).[7] The tricyclic compound **3** would be derived from bicyclic ketone **5**, which can be prepared by the oxidative radical cyclization developed in our laboratory.

The bicyclo[5.3.0]decan-3-one compound **5** including three successive chiral centers [C(10), C(9), C(13)] of the *trans*-perhydroindene part of sordaricin (**1**) could be prepared by the following procedure. Previously, we developed the β-keto radical formation by one-electron oxidation of cyclopropanols with manganese(III) tris(pyridine-2-carboxylate) [$Mn(pic)_3$].[8,9] By applying this method, cyclopropanol **6** was transformed to **5** stereoselectively by the treatment with $Mn(pic)_3$ and tributylstannane (n-Bu_3SnH) via the cyclization of β-keto radical intermediate.[9b]

The tetrahydropyranyl (THP) group of **5** was removed by acetic acid (AcOH) in THF–water, and then resulting hydroxy group was reprotected with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in DMF to afford TBS ether **7**

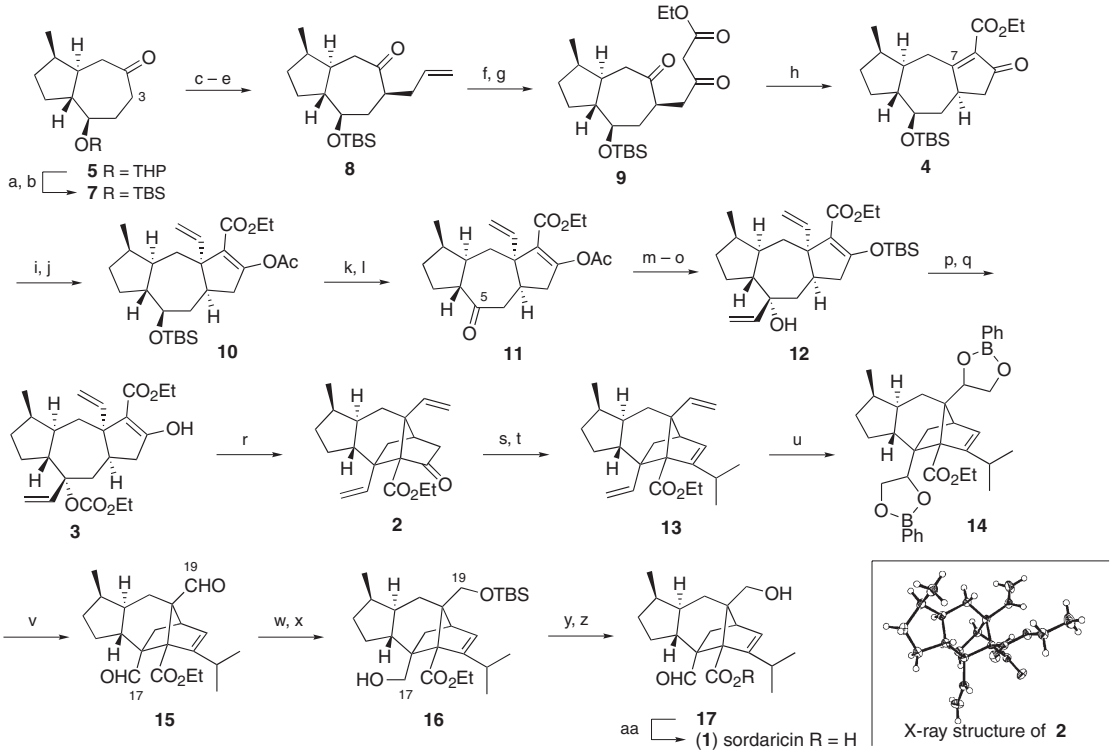


Scheme 1. Retrosynthetic analysis.

(Scheme 2). Stereoselective and regioselective allylation at C(3) of **7** was achieved via three-steps sequences:[10,11] (i) conversion to the *N*,*N*-dimethylhydrazone, (ii) allylation of the hydrazone with lithium diisopropylamide (LDA) and allyl bromide, and (iii) hydrolysis of the hydrazone to ketone **8**. Dihydroxylation of the vinyl group of **8** using osmium tetroxide, followed by $NaIO_4$-induced oxidative cleavage, provided the corresponding aldehyde, which was then converted into β-keto ester **9** by the reaction with ethyl diazoacetate in the presence of tin(II) chloride.[12] The Knoevenagel cyclization of **9** with a catalytic amount of sodium ethoxide in ethanol gave the tricyclic compound **4**. Construction of the quaternary center at C(7) was accomplished via the 1,4-addition of vinylmagnesium chloride in the presence of $CuBr \cdot SMe_2$ and trimethylsilyl chloride (TMSCl).[13] Successive acetylation of the resulting enolate afforded enol acetate **10**. Next, the TBS group of **10** was removed under the acidic conditions, and thus formed secondary alcohol was then oxidized with pyridimium chlorochromate (PCC) to ketone **11**. Chemoselective addition of vinyl Grignard reagent to the carbonyl group at C(5) of **11** proceeded smoothly at −78 °C to give the allylic alcohol, and successive replacement of acetyl group with the TBS ether provided **12**. The tertiary alcohol part of **12** was converted into ethyl carbonate, and the treatment with tetrabutylammonium fluoride (TBAF) cleaved the enol silyl ether to furnish the precursor **3** for the Pd-catalyzed intramolecular allylation.

The construction of the bicyclo[2.2.1]heptene framework of sordaricin was successfully achieved from **3**. When **3** was exposed to a catalytic amount of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] and sodium hydride, the desired intramolecular allylation proceeded to furnish the sordaricin precursor **2** in 92% yield. The structure of **2**, which contains all of the stereogenic centers of sordaricin (**1**), was secured by X-ray crystallographic analysis.[14]

The final stage of the synthesis of (±)-sordaricin is described below. The ketone **2** was converted into enol triflate, followed by the addition of the higher order cuprate[15] derived from lithium 2-thienylcyanocuprate [(2-Th)Cu(CN)Li] and isopropylmagnesium bromide in the presence of hexamethylphosphora-



Reagents and conditions: (a) AcOH, THF–H_2O, 50 °C (91%); (b) TBSCl, imidazole, DMF, rt (92%); (c) Me_2NNH_2, AcOH, EtOH, rt; (d) LDA, CH_2=$CHCH_2Br$, THF, –78 °C; (e) NaOAc, AcOH, THF–H_2O, rt (85% in 3 steps); (f) cat. OsO_4, NMO, then $NaIO_4$, THF–H_2O, rt (98%); (g) N_2CHCO_2Et, cat. $SnCl_2$, CH_2Cl_2, reflulx (quant.); (h) cat. NaOEt, EtOH, rt (70%); (i) CH_2=$CHMgCl$, cat. CuBr•SMe_2, TMSCl, HMPA, THF, –78 °C ; (j) Ac_2O, cat. DMAP, pyridine, rt (97% in 2 steps); (k) cat. TsOH•H_2O, THF–H_2O, 70 °C (95%); (l) PCC, celite, CH_2Cl_2, rt (92%); (m) CH_2=$CHMgCl$, THF, –78 °C ; (n) NaOEt, EtOH, rt; (o) TBSCl, Et_3N, cat. DMAP, CH_2Cl_2, rt (86% in 3 steps); (p) LDA, $ClCO_2Et$, THF, –78 °C → rt; (q) TBAF, THF, rt (89% in 2 steps); (r) 5 mol% $Pd(PPh_3)_4$, NaH, 1,4-dioxane, 80 °C (92%); (s) LDA, *N*-(5-chloro-2-pyridyl)triflimide, THF, –78 °C (92%); (t) *i*-PrMgBr, (2-Th)Cu(CN)Li, HMPA, THF, –78 → 0 °C (73%); (u) cat. OsO_4, NMO, $PhB(OH)_2$, CH_2Cl_2, rt; (v) $NaIO_4$, THF–H_2O, 50 °C (41% in 2 steps); (w) $NaBH_4$, EtOH, rt (90%); (x) TBSCl, imidazole, DMF, 0 °C (89%); (y) SO_3•pyridine, Et_3N, CH_2Cl_2–DMSO, rt (90%); (z) TsOH, THF–H_2O, 50 °C (quant.); (aa) *n*-PrSNa, HMPA, rt (86%).

Scheme 2.

mide (HMPA) to afford **13**. Dialdehyde **15** was derived by two-steps sequences: (i) conversion of the two vinyl groups of **13** into bisphenylboronic ester **14** by the combined use of osmium tetroxide and dihydroxyphenylborane[16] and (ii) oxidative cleavage of the phenylboronic ester with $NaIO_4$. The resulting dialdehyde of **15** was reduced to the corresponding diol by the treatment with $NaBH_4$, and selective protection of the less hindered C(19)–hydroxy group with TBS was subsequently carried out to afford **16**. Oxidation of the C(17)–hydroxy group to aldehyde, followed by desilylation with TsOH, provided sordaricin ethyl ester **17**. Finally, deethylation of ester **17** was proceeded smoothly with propanethiolate[17] to give (±)-sordaricin (**1**). The spectroscopic properties of **1** were in complete accord with the published data.[1,6a]

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