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Synthesis of (+)-Sorokinianin

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Abstract: Sorokinianin (**1**), an inhibitor of barley germination, was synthesized in optically active form employing *d*-carvone as the only chiral source. The key steps are stereoselective intra- and intermolecular aldol reactions to construct the bicyclo[3.2.1]octane system and to introduce the lactone moiety, respectively. Our synthetic **1** showed dextrorotation and the absolute configuration of natural **1** was confirmed to be 1*R*,4*R*,5*S*,6*R*,8*S*,13*S*,2'*R*. © 1997 Elsevier Science Ltd.

In 1994, Nakajima et al. isolated sorokinianin (**1**) from a culture broth of the phytopathogenic fungus, *Bipolaris sorokiniana* OB-25-1, as a novel phytotoxin which inhibits germination of barley seeds.[1] Its unique skeleton is thought to be biosynthesized from prehelminthosporol[2] and an additional C_3 unit,[3] and the absolute configuration was assumed as depicted in Fig. 1. Herein, we would like to report the synthesis of the natural enantiomer of **1**.

Our synthetic plan is shown in Fig. 1. The precursor **A** was thought to be converted into **1** by the hydroboration of the *exo*-olefin, methylenation of the ketone, and oxidative cleavage of the trisubstituted olefin followed by α-oxidation of the resulting lactone carbonyl. The side chain of **A** can be introduced

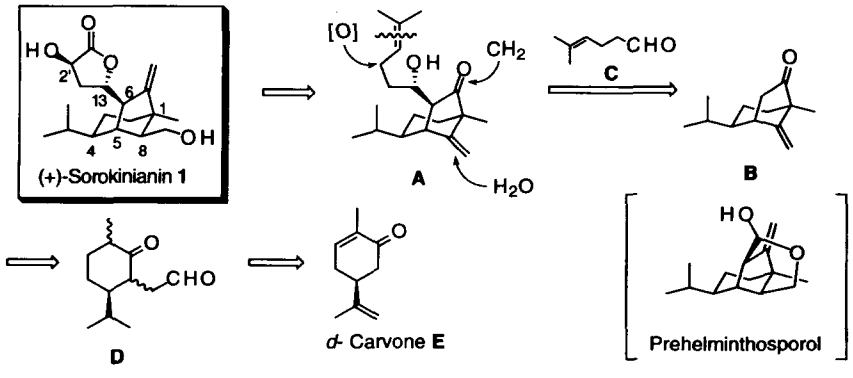
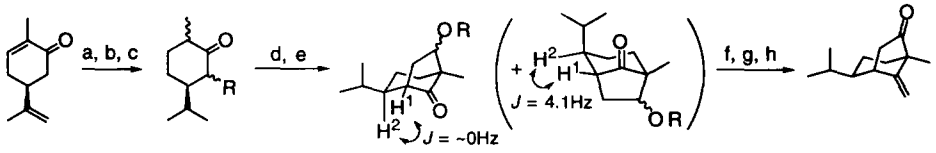


Fig. 1.

stereoselectively by an aldol reaction of **B** with **C**. The bicyclo[3.2.1]octane skeleton of **B** can be constructed by the thermodynamically controlled aldol reaction of **D**.[4] The starting material is *d*-carvone (**E**).

The first stage of our work was the construction of bicyclo[3.2.1]octane skeleton of the key intermediate **6** (=**B**) (Fig. 2). Although the preparation of *ent*-**4a** from *l*-carvone (*ent*-**2**) was reported by Yoshikoshi et al,[4] we simplified their method. After the hydrogenation of the two double bonds of **2** (98% e.e.), regioselective allylation at the less substituted α-position of the ketone (**3a**) could be accomplished by using 5.0 eq. of HMPA along with LDA in THF to give **3b** as a diastereomeric mixture in 91% yield. When a smaller amount of HMPA (1.1eq.) was used, allylation at the more substituted position took place predominantly. Ozonolysis of **3b** gave keto aldehyde (**3c**), which was then subjected to the intramolecular aldol reaction to construct the bicyclic skeleton.

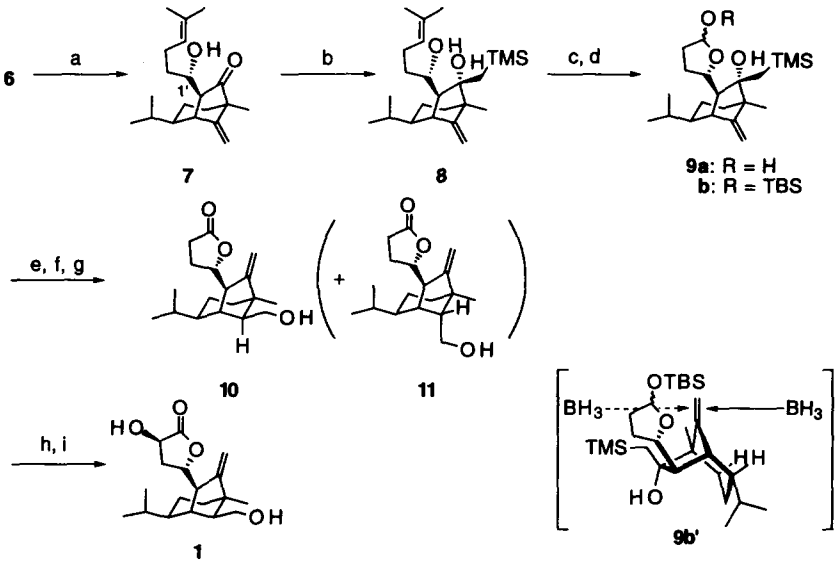
After several attempts, we found the reaction temperature dramatically changed the ratio of **4a** and **5a**. When **3c** was heated with 0.5eq. sodium methoxide in methanol under reflux for 2 h, **4a** was the major product, and **4b** and **5b** were obtained in a ratio of 2.8:1 after protection of the OH group as triethylsilyl (TES) ether followed by SiO_2 chromatographic separation. On the other hand, when the reaction was performed at room temperature for 2 h, **5a** was obtained as a sole product in 54% yield.[5] The structures of **4b** and **5b** were confirmed by the comparison of their $J_{1,2}$ values (~0 Hz for **4b** and 4.1 Hz for **5b**) in their ^{1}H-NMR spectra. The Wittig methylenation of **4b** followed by TES-deprotection and Jones' oxidation of the resulting alcohol gave the key intermediate **6** in 55% yield.



a) H_2, PtO_2, AcOEt, 94%; b) LDA, allyl bromide, THF- HMPA, 91%; c) O_3, $NaHCO_3$, MeOH; Me_2S, 95%; d) NaOMe, MeOH, Δ, 77%; e) TESCl, Imid., DMF, SiO_2 separation, 82%; f) $Ph_3P{=}CH_2$, DME, 57%; g) 2% HF, MeCN, quant.; h) Jones' reagent, Me_2CO, 97%;

Fig. 2.

The second and the final stage of our synthesis was the conversion of **6** to (+)-sorokinianin (**1**) as shown in Fig. 3. The aldol reaction of **6** with 5-methyl-4-hexenal furnished **7** and its C-1' epimer in 74% and 13% yield, respectively. In this reaction, the aldehyde attacked only on the *exo*-face of the enolate of **6** and an *erythro*-isomer was obtained predominantly.[6] Treatment of **7** with trimethylsilyl(TMS)methyllithium at -20℃ gave the diol (**8**),[7] which possesses the both precursors leading to the lactone and methylene moieties of sorokinianin (**1**). At this stage, the TMS group was retained in order to avoid the complexity of the later hydroboration in the presence of two *exo*-olefins in a molecule.



a) 5-methyl-4-hexenal, LDA, THF, 74%; b) $TMSCH_2Li$, Et_2O, 83%; c) 1 eq. O_3, $NaHCO_3$, MeOH; Me_2S, quant.; d) TBSCl, imid., DMF, quant.; e) BH_3•SMe_2, THF, 0°C; H_2O_2, 3N aq. NaOH; f) 4% HF, MeCN; g) Ag_2CO_3-Celite®, C_6H_6, 37% of **10** and 37% of **11** (3 steps); h) TESCl, imid., DMF, quant.; i) Davis' reagent, KHMDS, THF; Et_3N; 0.5N HCl, 75%

Fig. 3

Treatment of **8** with 1eq. of ozone selectively cleaved the trisubstituted double bond and a hemiacetal (**9a**) was obtained in quantitative yield. After protecting the hemiacetal OH as *t*-butyldimethylsilyl (TBS) ether, **9b** was subjected to the hydroboration reaction. Hydroboration of the *exo*-olefin of **9b** was accomplished by using borane-dimethyl sulfide complex and the subsequent oxidative work-up gave primary alcohols as a diastereomeric mixture. Without purification, the product was treated with HF in acetonitrile for the TBS deprotection and the Peterson-type elimination.[7] Subsequent Fetizon oxidation[8] gave the desired hydroxy lactone (**10**, 37% in 3 steps) and its epimer (**11**, 37% in 3 steps) after separation by Lobar® column chromatography. Although we expected that the borane would attack **9b'** from the right side rather than the left side due to the steric effect of two large substituents ($TMSCH_2$ and tetrahydrofuranyl groups), no stereoselectivity was observed in the hydroboration. The use of other reagents (thexylborane or 9-BBN) did not improve the stereoselectivity but lowered the yield. After protecting the OH group of **10** as a TES ether, the α-position of the lactone carbonyl was oxidized by treatment with KHMDS and Davis' reagent (2-benzenesulfonyl-3-phenyloxaziridine).[9,10] Subsequent acidic work-up to remove TES group afforded the target compound, sorokinianin (**1**), in 75% yield; $[\alpha]_D^{19}$ +44°(*c* 1.2, MeOH) [lit.[1]: $[\alpha]_D^{20}$ +46°(*c* 1.0, MeOH)].

The ^{1}H-NMR and IR spectra of the synthetic **1** were identical with those of the natural sorokinianin.[1,11] In addition to that, as the sign of the specific rotation of our synthetic **1** was the same as that of the natural **1**, the absolute configuration of the natural **1** was confirmed to be 1*R*,4*R*,5*S*,6*R*,8*S*,13*S*,2'*R*.

In conclusion, the first total synthesis of (+)-sorokinianin was accomplished starting from *d*-carvone as a single chiral source, and the absolute configuration of the natural **1** was unambiguously determined. The overall yield was 4% in 17 steps.

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10. Interestingly, the Davis oxidation of a dianion prepared from **10** and 2 eq. of KHMDS gave only 2'-*epi*-**1**. The protection of the primary alcohol was therefore essential for the desired stereoselectivity.
11. The solvent for ^{1}H- and ^{13}C-NMR which was omitted in ref. 1 was acetone-d_6: Nakajima, H. personal communication to H. W.

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