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ASYMMETRIC SYNTHESIS OF (-)-VERRUCOSAPYRONE A BY BIOCATALYST AND DETERMINATION OF ITS ABSOLUTE CONFIGURATION

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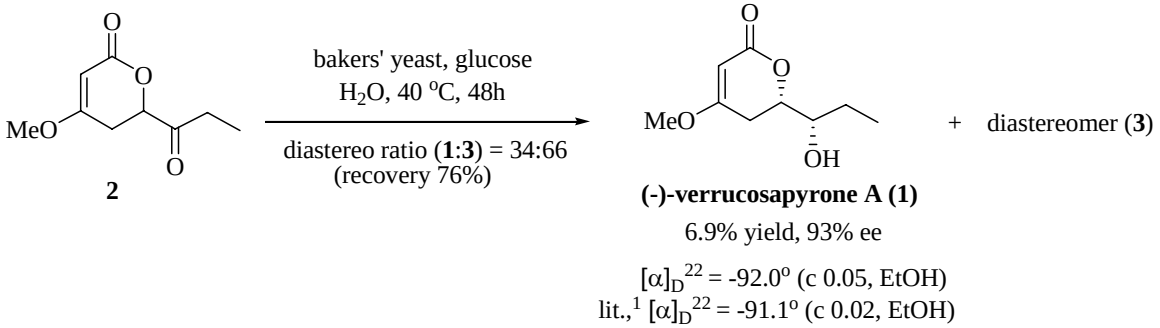
Abstract – An asymmetric synthesis of (-)-verrucosapyrone A was achieved by the use of biocatalyst. Absolute configuration of verrucosapyrone A was also investigated.

(-)-Verrucosapyrone A (**1**) was a new δ-lactone compound, which was isolated from *Penicillium nordicum* by Rahbeak and coworkers in 2003.[1] Its absolute configuration is not clarified yet because only a trace amount of compound is available from natural source. Although a related δ-lactone compound, pestalotin,[2] is well known as a plant growth promoter,[2a] a biological activity of verrucosapyrone A (**1**) has not been studied so far. We recently reported the efficient first total synthesis of (±)-verrucosapyrone A.[3] Herein we report the asymmetric synthesis of (-)-verrucosapyrone A (**1**) and investigation of its absolute configuration.

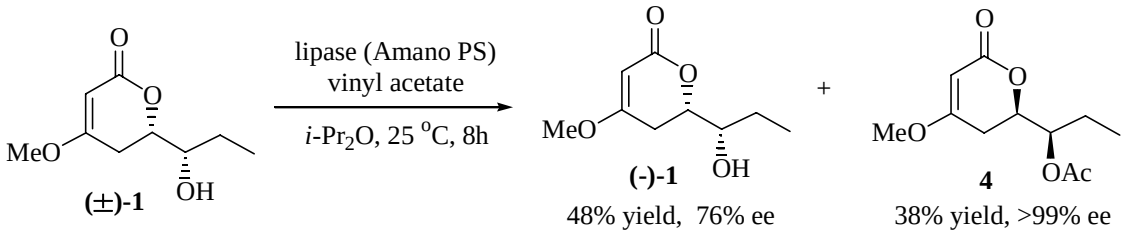
First, we investigated the bakers' yeast reduction of δ-lactone (**2**)[3] for the asymmetric synthesis of verrucosapyrone A (**1**) (Scheme 1). When **2** was treated with bakers' yeast, the reaction proceeded for first 24h. But after another 24h, the reaction was stagnant and the starting material was recovered in 76% yield. The reduced product was obtained as a 34:66 diastereo mixture of (-)-verrucosapyrone A (**1**) and its



Scheme 1

diastereomer (**3**) in 20% yield. These diastereo isomers were separated by silica gel flash chromatography and pure (-)-verrucosapyrone A (**1**) was obtained, which has the same sign of rotation to the authentic natural product. After conversion to MTPA ester, its ee was determined as 93% by the ^{1}H NMR analysis.

Next, we investigated the optical resolution of racemic δ-lactone (±)-(**1**) by lipase for the asymmetric synthesis of (-)-verrucosapyrone A (**1**) (Scheme 2). This (±)-**1** was prepared by the reduction of δ-lactone (**2**) with $NaBH_4$.[3] By the optical resolution of lipase (Amano PS), (+)-**1** was acetylated faster than (-)-**1**. After separation of the crude product by silica gel flash chromatography, (-)-verrucosapyrone A (**1**) was obtained in 48% yield with 76% ee, which was determined by 300MHz NMR analysis of the derived MTPA ester.



Scheme 2

Then we investigated the absolute configuration of (-)-verrucosapyrone A (**1**). For the investigation of the absolute configuration at C-1', we used Mosher's method[4] after conversion of (-)-**1** to the corresponding (*S*)-MTPA and (*R*)-MTPA esters. The values of Δδ (δ_S-δ_R) are shown in Figure 1.

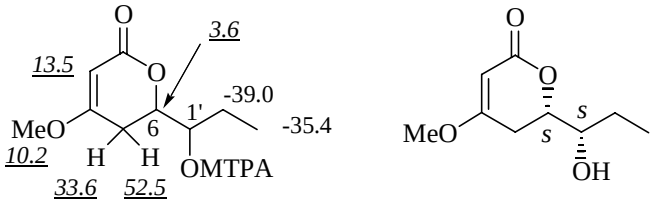


Figure 1. The values of Δδ and supposed absolute configuration of (-)-verrucosapyrone A

As shown in Figure 1, the values of Δδ at the left side of MTPA ester are positive. On the other hand, the values of Δδ at the right side of MTPA ester are negative. These results showed the absolute configuration of C-1' is *S*.[4] Concerning the absolute configuration of C-6, there is a CD spectral data of the authentic natural product.[1] From the comparison with that of the related compound,[2b] we guess the absolute configuration of C-6 is *S*. Based on these results, we concluded that the absolute configuration of

(-)-verrucosapyrone A (**1**) is (C-6: *S*; C-1': *S*) as shown in Figure 1.

In conclusion, we have developed the asymmetric synthesis of (-)-verrucosapyrone A by the use of bakers' yeast or lipase. Furthermore absolute configuration of verrucosapyrone A was determined by Mosher's method as (C-6: *S*; C-1': *S*).

EXPERIMENTAL

NMR spectra were recorded on a JEOL JNM-AL300 instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Thermo Nicolet Avatar 360T2 infrared spectrophotometer. Elemental analyses were performed on a Perkin-Elmer 2400 series Ⅱ CHNS/O analyzer. For thin-layer chromatography aluminum sheets Merck silica gel coated 60 F254 plates were used and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Merck silica gel 60 N (spherical, neutral) (40-50 μm) was used for the flash chromatography. Melting points were obtained in open capillary tubes on a Mel-Temp-II hot stage microscope.

Bakers' yeast reduction of 2 for (-)-verrucosapyrone A (1): To a stirring solution of glucose (175 mg) and bakers' yeast (105 mg) in water (5 mL) was added δ-lactone (**2**) (20 mg, 0.11 mmol) at 40 ^{o}C. And bakers' yeast (105 mg) and glucose (175 mg) were added every 12h. After 48h of stirring, the reaction mixture was filtered through Celite. The filtrate was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residual crude products were purified by column-chromatography (hexane:EtOAc= 2:1 to 1:2) to give (-)-**1** (1.4 mg, 6.9%).

Optical resolution of (±)-1 for (-)-verrucosapyrone A (1): To a stirring solution of δ-lactone (±)-(**1**) (50 mg, 0.27 mmol) and vinyl acetate (80 mg, 0.80 mmol) in *i*-Pr_2O (5 mL) was added Lipase (Amano PS, 30 mg) at 25 ^{o}C. After stirring for 8h, the reaction mixture was filtrated through Celite. Then the solvent was evaporated and residual crude products were purified by column-chromatography (hexane:EtOAc= 2:1 to 1:1) to give (-)-**1** (24 mg, 48%).

(-)-Verrucosapyrone A (1).[1] White solid; mp = 90-93 ^{o}C (lit.,[1] mp = 93-95 ^{o}C); $[\alpha]^{22}_{D}$ -92.0^{o} (c 0.05, EtOH) {lit.,[1] $[\alpha]^{22}_{D}$ -91.1^{o} (c 0.02, EtOH)}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.05 (t, *J*=7.5 Hz, 3H), 1.63-1.73 (m, 2H), 2.35 (dd, *J*=3.9, 17.1 Hz, 1H), 2.88 (ddd, *J*=1.8, 12.9, 17.1 Hz, 1H), 3.53-3.60 (m, 1H), 3.84 (s, 3H), 4.42 (dt, *J*=3.9, 12.9 Hz, 1H), 5.22 (d, *J*=1.8 Hz,1H); ^{13}C NMR (75 MHz, CD_3OD) δ 10.6, 26.5, 30.2, 57.0, 74.1, 79.9, 90.1, 170.3, 176.4; IR (neat): 3442, 2966, 1694, 1621, 1225. Spectral data were identical with those of the authentic sample.[1]

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