Note

Syntheses and Biological Activities of (2S,2'S)- and (2S,2'R)-Dimethyl 3-Phenyl-2,2'-oxydipropionate, Ether Analogues of a Plant-growth Regulator Isolated from *Botrytis squamosa*

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Ether analogues of a plant growth regulator isolated from *Botrytis squamosa*, (2S,2'S)- and (2S,3'R)-dimethyl 3-phenyl-2,2'-oxydipropionate (1), were prepared by the Williamson synthesis, and the two diastereomers were separated. The absolute configurations of both diastereomers were determined by chemical transformation. The promoting effect of both synthesize analogues on lettuce seedling growth was similar to that of the natural plant growth regulator.

(2S,2'S)-Methyl hydrogen 3-phenyl-2,2'-iminodipropionate was isolated as one of the metabolites from *Botrytis squamosa* and is known to be a toxin causing Botrytis leaf blight of onion and gray mold of scallion.15 Its promoting effects on the growth of lettuce seedlings are interesting, and we have investigated the promoting activity of its analogues having a methylene linkage instead of the imino linkage.20 In this paper, we report the synthesis of two diastereomers (1a and 1b) of the ether analogue of the plant growth regulator and the promoting effects on lettuce seedlings growth. The absolute configuration of 1a and 1b was determined by chemical synthesis, starting from (S)-alanine and (S)-phenylalanine.

Three synthetic routes to ether 1 were investigated: (route 1) the Williamson synthesis from methyl 2-bromopropionate (2) and 2-hydroxy-3-phenylpropionate (3), (route 2) the Williamson synthesis from methyl 2-bromo-3-phenylpropionate and methyl lactate, and (route 3) the oxidative ring cleavage reaction of 2-phenyl-5-methyl-2,5-dihydrofuran (route 3). Route 2 for the Williamson reaction gave many by-products, while route 3 involved difficulties in preparing the furan derivative. Route 1 gave a diastereomeric mixture of ether 1 in a quantitative yield (Scheme), the two diastereomers being easily separated by silica gel column chromatography. The reaction proceeded smoothly in THF at −10–0°C in the presence of NaH. The two diastereomers, 1a and 1b, exhibited well-separated peaks both by silica gel liquid chromatography and gas chromatography. Therefore, even if racemic methyl 2-bromopropionate was used, the two diastereomers could be easily separated at this stage.

The 1H-NMR spectra of both 1a and 1b were almost identical, except that the methine protons attached to the asymmetric carbons (H-2, H-2') exhibited small differences in chemical shift. Assignment to H-2 and H-2' was confirmed by spin-decoupling experiments. In the 1H-NMR spectrum of 1a, the peaks centered at 3.1 ppm became an AB quartet upon irradiating the peaks centered at 4.25 ppm. Therefore, the peaks at 4.25 ppm were assigned to H-2, and the peaks at 4.04 ppm to H-2'. The methine protons of 1b were similarly assigned. The chemical shifts in the 13C-NMR spectra of 1a and 1b agreed within 2 ppm. The difference in the 1H-NMR chemical shifts of the methine protons could be ascribed to the conformational difference between the two diastereomers.

The two diastereomers exhibited different optical rotation values: 1a, [α]D20 = −70.9°; and 1b, +23.8°. Since (S)-3 and racemic 2 were used in the Williamson reaction, the two diastereomers had the same configuration at C-2', and the opposite configuration at C-2'. To determine the configuration at C-2', the Williamson reaction was carried out by using (S)-3 and (S)-2. The main product in the reaction was 1a, indicating that 1a had an (R) configuration at C-2'. Therefore, (−)-1a was found to be (2S,2'R)- and (−)-1b to be (2S,2'S)-dimethyl 3-phenyl-2,2'-oxydipropionate. The circular dichroism (CD) spectra of (−)-1a and (−)-1b recorded in ethanol exhibited a positive Cotton effect at 220 nm ((−)-1a, [θ]20 = 2050; (−)-1b, [θ]20 = 1030). A positive Cotton effect was also observed for (S)-phenylalanine methyl ester at 220 nm. These results suggest that the positive Cotton effects of (−)-1a and (−)-1b reflect the configuration at C-2, the closest carbon to the phenyl chromophore.

The effects of (−)-1a and (+)-1b on the growth of lettuce seedlings are shown in Fig. The lengths of the hypocotyl and root are shown in comparison to the lengths from a control experiment. Promoting effects were observed for both (−)-1a and (−)-1b, (−)-1a exhibiting its maximum promoting effect at 100 ppm, and

![Diagram](image)

**Fig. 1.** Effects of (−)-1a, (+)-1b and BSF-A (Methyl Hydrogen 3-Phenyl-2,2'-iminodipropionate) on Lettuce Seedling Growth.

○, (−)-1a; ▲, (+)-1b; ○, BSF-A.
(+)-1b at 300 ppm. It is noteworthy that the promoting effects of both (−)-1a and (+)-1b were similar to those of the natural plant growth regulator. These observations can be summarized as follows: (1) the ether linkage of 1 and the imino linkage of the natural plant growth regulator exhibited similar promoting effects, and (2) the absolute configuration at C-2' did not affect the promoting effects to any great extent.

**Experimental**

**Materials.** (+)-Methyl 2-bromopropionate was purchased from Tokyo Kasei Ind. (S)-Methyl 3-phenyl-2-hydroxypropionate ([α]D) = −5.4 (c = 2.0, in CHCl3), lit.1) ([α]D) = −7.6 (c = 2.0 in CHCl3); (S)-Methyl 2-bromopropionate was prepared from (S)-phenylalanine by the reported method.2) (+)-(S)-Bromopropionate was prepared by methylation of (S)-2-bromopropionic acid3) with diazomethane, while (S)-2-bromopropionic acid was prepared from (S)-alanine by treating it with sodium nitrite and potassium bromide in 5% aqueous sulfuric acid.4) ([α]D) = −26.7 (neat, lit. [α]D) = −27.2 (neat); Sodium hydride (60% oil suspension) was purchased from Nacalai Tesque and used as received, and tetrahydrofuran (THF) was distilled from 5A molecular sieves.

**Measurements.** Infrared spectra were recorded by a Shimadzu IR-4200 FT infrared spectrometer, while 1H- and 13C-NMR spectra were obtained with a JEOL JNM-GX 270 FT FMR spectrometer. Optical rotation was recorded by a Horiba SEPA-200 instrument.

**Preparation of (2S,2'S)- and (2S,2'R)-dimethyl 3-phenyl-2'-oxypyridopionate (1).** Five grams of (+)-methyl 2-bromopropionate (2) and 3.6 g of (S)-methyl 2-hydroxy-3-phenylpropionate (3) were dissolved in 26 ml of THF. After the solution had been cooled to −40°C, 0.72 g of sodium hydride was added. The mixture was allowed to warm to 0°C and stirred at 0°C until gas evolution ceased (about 20 min). Stirring was continued for 2 h more at room temperature. To the reaction mixture was then added 1 ml of water, before the solution was neutralized with dilute hydrochloric acid. The solvent was removed at reduced pressure, and the residue was taken up in a water-diethyl ether mixture. The ethereal layer was separated, and the aqueous layer was extracted twice with ether. The combined ethereal layer was evaporated in vacuo to give 5.3 g of a pale yellow oil. Thin-layer chromatography (TLC) analysis on silica gel column chromatography (ethyl acetate-n-hexane = 1:2) indicated the product to consist of two fractions, (−)-1a ([R] = 0.59) and (+)-1b ([R] = 0.48). These fractions were separated by silica gel column chromatography (ethyl acetate-n-hexane = 1:2). The separated fractions were treated with decolorizing carbon to give colorless oils, the yields of (−)-1a and (+)-1b being 2.7 g and 2.0 g, respectively.

**References**


