

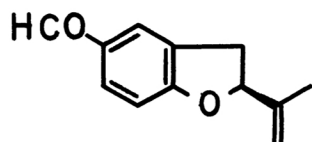
THE SYNTHESSES AND ABSOLUTE CONFIGURATIONS OF FOMANNOXIN,
 (-)-5-ACETYL-2-(1-HYDROXYMETHYLVINYL)-2,3-DIHYDROBENZOFURAN,
 AND ANODENDROIC ACID

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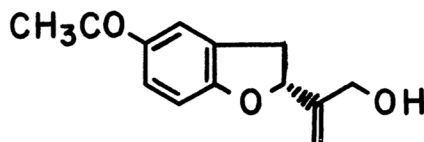
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The title compounds were synthesized from (-)-(S)- or (+)-(R)-2,3-dihydrobenzofuran-2-carboxylic acid. And their absolute configurations were determined.

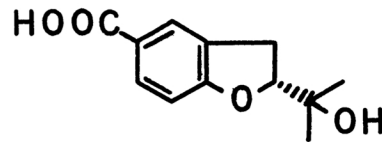
Fomannoxin¹⁾ [(+)-I], (-)-5-acetyl-2-(1-hydroxymethylvinyl)-2,3-dihydrobenzofuran²⁾ [(-)-II], and anodendroic acid³⁾ [(-)-III] have been isolated from natural sources, and the syntheses of (⁺)-II⁴⁾ and methylester of (⁺)-III³⁾ were reported. However, neither the syntheses of optically active compounds nor their absolute configurations has been studied. In this paper, we wish to report the syntheses of (+)-I, (-)-II, and (-)-III from (+)-(R)- or (-)-(S)-2,3-dihydrobenzofuran-2-carboxylic acid⁵⁾⁶⁾ (IV) and the determination of their absolute configurations of these natural products.



(+)-S-I



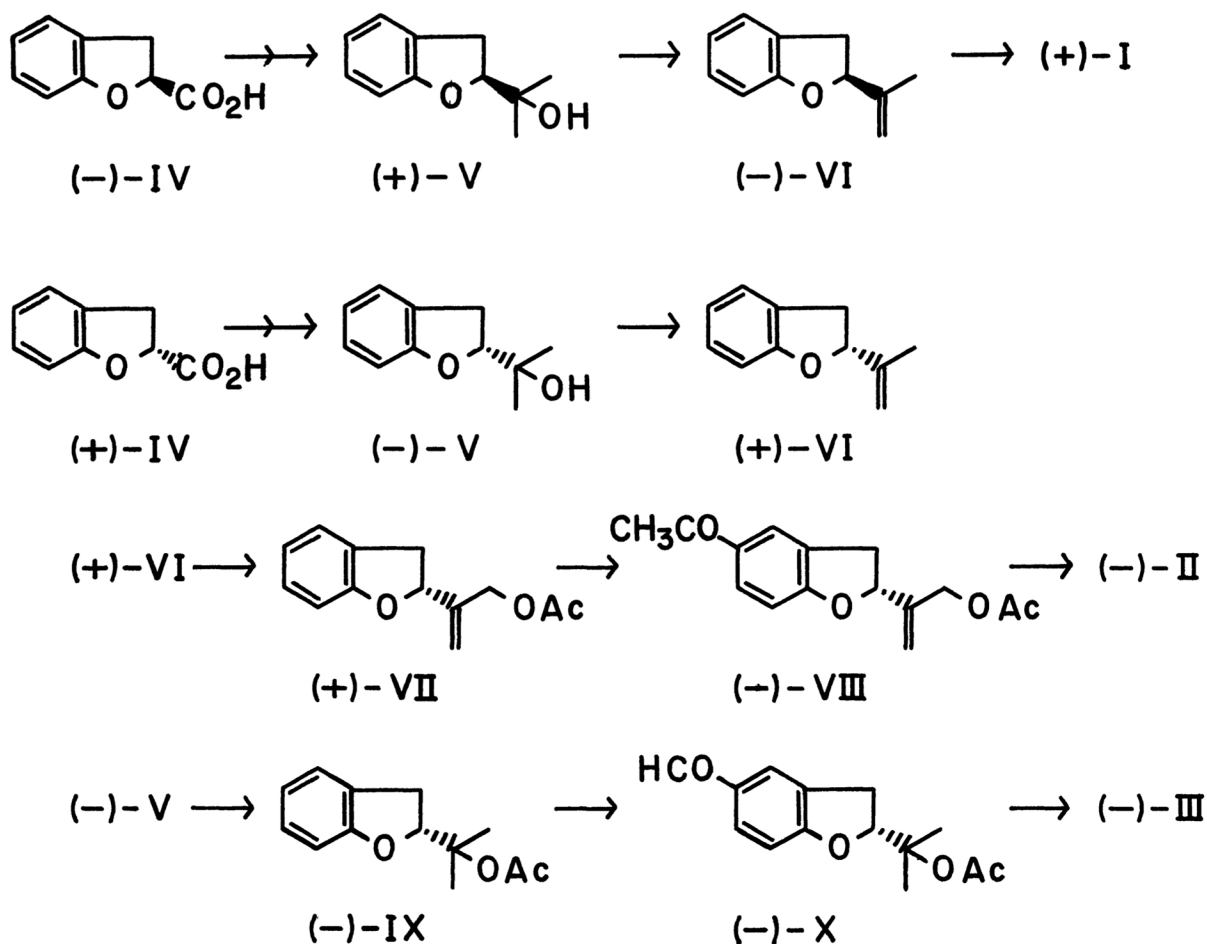
(-)-R-II



(-)-R-III

We already reported the one step synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran [(⁺)-VI] from phenol and isoprene dibromide.⁴⁾ For the syntheses of these compounds in optically active forms, effective dehydration and formylation were requested, because dehydration of (⁺)-V and formylation of the dehydration product under acidic conditions afforded 2-isopropylbenzofuran and its formylated compound, respectively.

The synthesis of optically active compound [(+)-I] was carried out from the optically active acid [(-)-(S)-IV],⁵⁾⁶⁾ $[\alpha]_D^{25} -23.6^\circ$ (c 0.564, EtOH). The alcohol [(+)-V],⁵⁾ $[\alpha]_D^{25} +37.1^\circ$ (c 0.475, EtOH), was dehydrated by heating for 16 h⁷⁾ with phenylisocyanate to (-)-VI, bp 108-110 °C/17 mmHg, $[\alpha]_D^{16} -10.4^\circ$ (c 0.540, EtOH), in 49 % yield. Then (-)-VI was formylated by heating for 1 h at 90 °C with N-methylformanilide and POCl₃, and the crude product was purified by silica gel chromatography using hexane-benzene as the solvent to give (+)-I, bp 115-130 °C/2 mmHg, $[\alpha]_D^{15} +78.2^\circ$ (c 0.284, CHCl₃), IR (neat) 1685 cm⁻¹ (C=O) [lit.¹⁾ $[\alpha]_D^{21} +88.8^\circ$ (c 0.144, CHCl₃), IR (CHCl₃) 1685 cm⁻¹], in 19 % yield. The spectral data were identical with those of natural (+)-I.¹⁾



The optically active (-)-II was synthesized from (+)-(R)-IV,⁵⁾⁶⁾ $[\alpha]_D^{20} +21.9^\circ$ (c 0.583, EtOH). After Grignard reaction followed by dehydration, (+)-VI, bp 98-107 °C (bath temp.)/17 mmHg, $[\alpha]_D^{25} +10.9^\circ$ (c 0.731, EtOH), was oxidized with selenium dioxide in acetic anhydride. The crude product was distilled and

purified by silica gel chromatography using hexane-benzene as the solvent to give (+)-VII, bp 78-130 °C (bath temp.)/ 4 mmHg, $[\alpha]_D^{27} +20.7^\circ$ (c 0.710, EtOH), in 13 % yield. The acetylation of (+)-VII with acetic acid and trifluoroacetic anhydride at room temperature gave (-)-VIII, bp 110-125 °C/5 mmHg, $[\alpha]_D^{25} -21.1^\circ$ (c 0.316, EtOH), in 74 % yield. Alkaline hydrolysis of (-)-VIII and purification by silica gel chromatography gave (-)-II, bp 145-200 °C (bath temp.)/3 mmHg, $[\alpha]_D^{25} -42.7^\circ$ (c 0.769, EtOH) [lit.²⁾ $[\alpha]_D -61.5^\circ$ (CHCl₃)]. All the spectral data were identical with those of natural (-)-II.²⁾

The optically active (-)-III was synthesized from (+)-(R)-IV,⁵⁾⁶⁾ $[\alpha]_D^{13} +21.5^\circ$ (c 0.559, EtOH). Grignard reaction and acetylation gave the acetate [(-)-IX], bp 116-116.5 °C/1 mmHg, $[\alpha]_D^{11} -45.6^\circ$ (c 0.384, EtOH), which was then formylated and purified by silica gel chromatography using benzene as the solvent to give (-)-X, bp 140-150 °C (bath temp.)/1 mmHg, $[\alpha]_D^{11} -101.8^\circ$ (c 0.452, EtOH), in 47 % yield. Oxidation of (-)-X with AgNO₃ and NaOH gave (-)-III, mp 239-241 °C, $[\alpha]_D^{15} -35.2^\circ$ (c 0.682, EtOH), IR (KBr) 1685 cm⁻¹ (C=O) [lit.³⁾ mp 212-214 °C, $[\alpha]_D^{26} -19^\circ$ (c 0.7, EtOH), IR (KBr) 1685 cm⁻¹]. All the spectral data were identical with those of natural (-)-III.³⁾

In conclusion, fomannoxin isolated from Fomes annosus has the S configuration and (-)-5-acetyl-2-(1-hydroxymethylvinyl)-2,3-dihydrobenzofuran from Helichrysum stoechas and anodendroic acid from Anodendron affine have the R configurations. It is noteworthy that the dihydrobenzofuran derivative having S configuration was isolated from the fungus, while ones having R configurations were isolated from the flowering plants.

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References and Notes

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- 7) We found that the reaction time was crucial in this dehydration. Refluxing for 20 h gave a mixture of 2-isopropenyl-2,3-dihydrobenzofuran and 2-isopropylbenzofuran, and further heating did the latter product only.

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