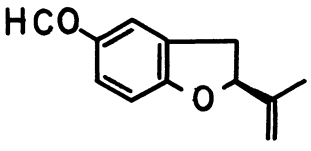
CHEMISTRY LETTERS, pp. 1581-1984, 1980.

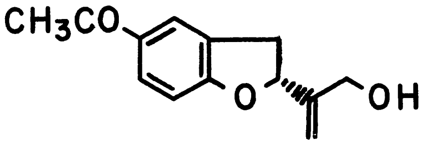
THE SYNTHESES AND ABSOLUTE CONFIGURATIONS OF FOMANNOXIN, (-)-5-ACETYL-2-(1-HYDROXYMETHYLVINYL)-2,3-DIHYDROBENZOFURAN, AND ANODENDROIC ACID

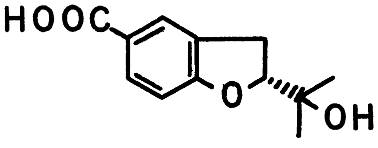
Yoshiyuki KAWASE, Seiji YAMAGUCHI, Osamu INOUE, Michiko SANNOMIYA,
and Kazuko KAWABE
Department of Chemistry, Faculty of Science, Toyama University,
Gofuku, Toyama 930

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

Fomannoxin[1] [(+)-I], (-)-5-acetyl-2-(1-hydroxymethylvinyl)-2,3-dihydrobenzofuran[2] [(-)-II], and anodendroic acid[3] [(-)-III] have been isolated from natural sources, and the syntheses of (±)-II[4] and methylester of (±)-III[3] 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 acid[5][6] (IV) and the determination of their absolute configurations of these natural products.

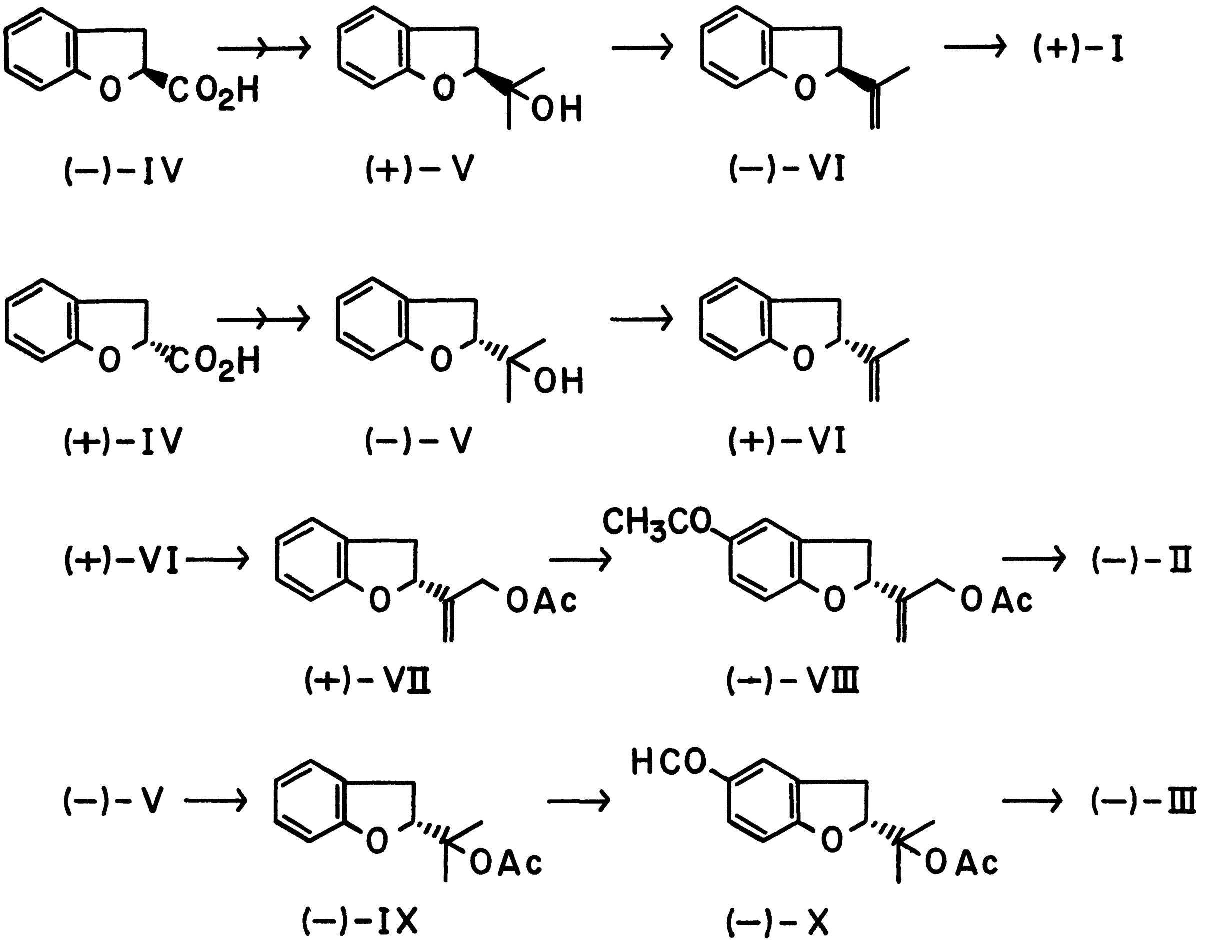

(+)-S- I


(-)-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],$^{5)6)}$ $[\alpha]_D^{9}$ −23.6° (c 0.564, EtOH). The alcohol [(+)-V],$^{5)}$ $[\alpha]_D^{25}$ +37.1° (c 0.475, EtOH), was dehydrated by heating for 16 h$^{7)}$ with phenylisocyanate to (−)-VI, bp 108-110 °C/17 mmHg, $[\alpha]_D^{16}$ −10.4° (c 0.540, EtOH), in 49 % yield. Then (−)-VI was formylated by heating for 1 h at 90 °C with N-methylformanilide and $POCl_3$, 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° (c 0.284, $CHCl_3$), IR (neat) 1685 cm^{-1} (C=O) [lit.$^{1)}$ $[\alpha]_D^{21}$ +88.8° (c 0.144, $CHCl_3$), IR ($CHCl_3$) 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° (c 0.583, EtOH). After Grignard reaction followed by dehydration, (+)-VI, bp 98-107 °C (bath temp.)/17 mmHg, $[\alpha]_D^{25}$ +10.9° (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° (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° (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° (c 0.769, EtOH) [lit.[2] $[\alpha]_D$ -61.5° ($CHCl_3$)]. 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° (c 0.559, EtOH). Grignard reaction and acetylation gave the acetate [(-)-IX], bp 116-116.5 °C/1 mmHg, $[\alpha]_D^{11}$ -45.6° (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° (c 0.452, EtOH), in 47 % yield. Oxidation of (-)-X with $AgNO_3$ and NaOH gave (-)-III, mp 239-241 °C, $[\alpha]_D^{15}$ -35.2° (c 0.682, EtOH), IR (KBr) 1685 cm^{-1} (C=O) [lit.[3] mp 212-214 °C, $[\alpha]_D^{26}$ -19° (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.

We thank Prof. Ishii (Chiba Univ.) for his valuable information of the dehydration with phenylisocyanate.

References and Notes

1) M.Hirotani, J. O'Reilly, D.M.X. Donnelly, and J. Polonsky, Tetrahedron Lett., 1977, 651.

2) S.V. López and B.R. González, Anal. Quimica., 67, 879 (1971).

3) K. Shima, S. Hisada, and I. Inagaki, Yakugaku Zasshi, 92, 1410 (1972). We thank Dr. K. Shima (Tokushima Bunri Univ.) for providing a copy of the spectrum of anodendroic acid.

4) Y. Kawase, S. Yamaguchi, S. Kondo, K. Shimokawa, Chem. Lett., 1978, 253.

5) D.M. Bowen, J.I. DeGraw,Jr, V.S. Shah, and W.A. Bonner, J. Med. Chem.,6, 315 (1963).

6) W.A. Bonner, N.I. Burke, W.E. Fleck, R.K. Hill, J.A. Joul, B. Sjoberg, and J.H. Zalkow, Tetrahedron, 20, 1419 (1964).

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.

(Received September 18, 1980)