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The Synthesis of Racemic Fomannoxin, Anodendroic Acid, and 5-Acetyl-2-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran

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2-Isopropenyl-2,3-dihydrobenzofuran was effectively prepared by two new methods. Fomannoxin and 5-acetyl-2-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran were synthesized from 2-isopropenyl-2,3-dihydrobenzofuran, while anodendroic acid was synthesized from 2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran.

Three optically active 2,3-dihydrobenzofuran derivatives, fomannoxin (**1**),1) anodendroic acid (**2**),2) and (−)-5-acetyl-2-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran (**3**),3) have been isolated from natural sources. We have already reported the synthesis of these three compounds in two short communications.4,5) Now, we wish to report the details and some added data.

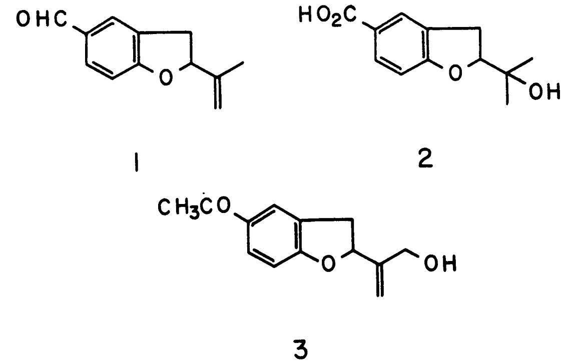

Chart 1.

For the synthesis of **1** and **3**, an effective method of preparing 2-isopropenyl-2,3-dihydrobenzofuran (**7**) is required. In 1963, DeGraw *et al.* reported the preparation of **7**.6) They prepared **7** by two methods, the Wittig reaction of 2-acetyl-2,3-dihydrobenzofuran (**4**) and the dehydration of 2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran (**5**). However, the dehydration of **5** with phosphoryl chloride–pyridine gave a mixture of **7** and 2-isopropylbenzofuran, the components of which were difficult to separate. Also, the Wittig reaction of **4** gave only a 6% yield. We studied other dehydration methods. **7** was obtained in a 49% yield by refluxing in phenyl isocyanate for 16 h. In this dehydration reaction, longer refluxing caused a isomerization to 2-isopropylbenzofuran; 2-isopropylbenzofuran was only obtained after refluxing for 60 h, while a mixture of **7** and 2-isopropylbenzofuran was obtained after 22 h. In 1958, Nickl reported that a 2-isopropenyl-2,3-dihydrobenzofuran derivative was obtained from 2,4,6-trihydroxyacetophenone and 1,4-dibromo-2-methyl-2-butene.7) Now, we have applied this reaction to phenol, thus obtaining **7** in one step in a 43% yield.

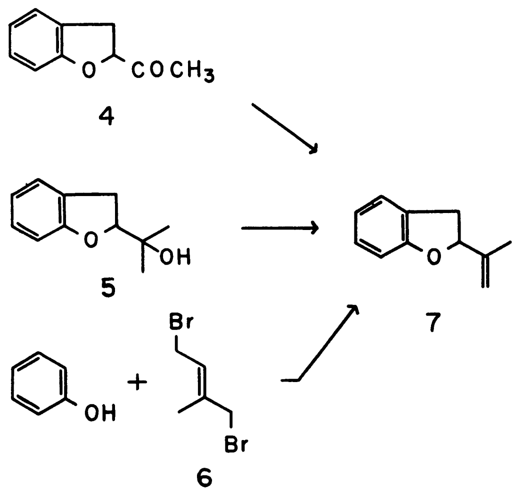

Chart 2.

Hirotani *et al.* isolated (+)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde from *Fomes annosus*; they named it fomannoxin.1) Fomannoxin had a structure very similar to that of tremetone (**16**), but it showed the opposite optical rotation and the opposite absolute configuration. This shows the existence of different biosynthetic cyclizations in different families of plants.8) First, when Nickl's method was applied to *p*-hydroxybenzaldehyde, fomannoxin was not obtained. Next, it was used in an attempt to convert 5-bromo- and 5-iodo-2-isopropenyl-2,3-dihydrobenzofuran (**8a**, **b**), obtained from *p*-bromo- and *p*-iodophenol by Nickl's method, to **1** or 2-isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid (**13**) through the corresponding Grignard reagents. However, these attempts were all unsuccessful because of the inactivity of **8a** and **8b** to magnesium metal. Then, we tried to formylate **7** to **1**; the formylation of **7** with *N*-methylformanilide–phosphoryl chloride gave the desired aldehyde (**1**) in a 41% yield. The IR and ^{1}H-NMR spectra were identical with those of natural fomannoxin.1)

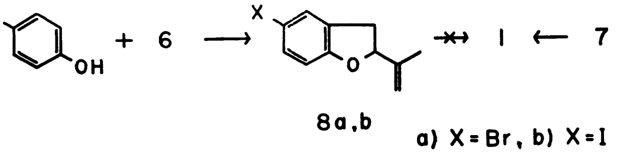

Chart 3.

Shima *et al.* isolated (−)-2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran-5-carboxylic acid (**2**) from *Anodendron affine* and named it anodendroic acid.2) The Vilsmeyer formylation of the acetate (**9**) with *N*-methylformanilide–phosphoryl chloride gave a mixture

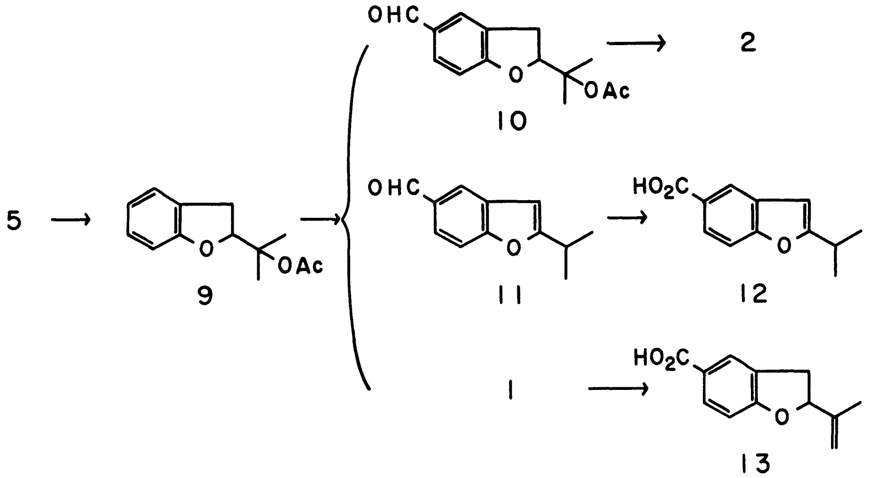

Chart 4.

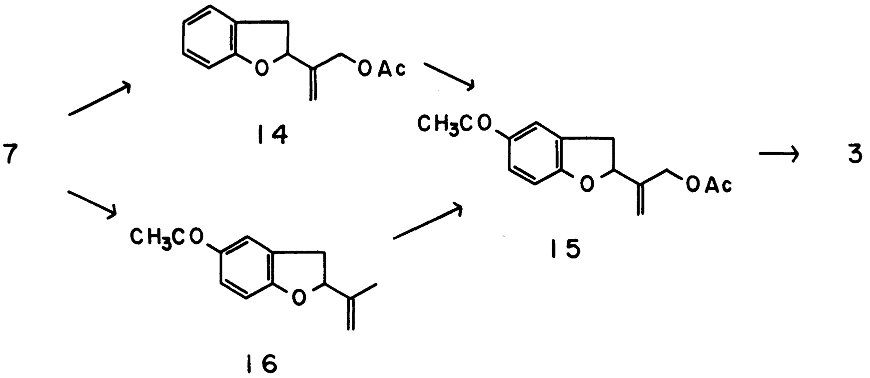

Chart 5.

of three aldehydes (**10**, **11**, and **1**; 4 : 3 : 3), which was separated to components by silica-gel chromatography. Then, these three aldehydes were oxidized to the corresponding carboxylic acids (**2**, **12**, and **13**) with silver oxide. The IR and ^{1}H-NMR spectra were identical with those of natural anodendroic acid.[2]

López and González isolated (−)-5-acetyl-2-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran (**3**).[3] The acetylation of **7** with acetic acid–trifluoroacetic anhydride at room temp gave 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran (tremetone) (**16**). The spectral data of **16** were identical with those previously reported.[6] Then, **16** was converted to **15** by treatment with selenium dioxide in acetic anhydride at 130 °C. The ^{1}H-NMR spectrum was identical with that of natural **3**.[3] The keto acetate (**15**) was also prepared in a better yield from **7** by treatment with selenium dioxide in acetic anhydride to **14**, followed by acetylation with acetic acid–trifluoroacetic anhydride. The alkaline hydrolysis of **15** gave **3**, whose spectral data were identical with those previously reported.[3]

Experimental

The boiling points and melting points were uncorrected (in boiling points: 1 mmHg=133.322 Pa); the IR spectra were measured on a Hitachi EPI-S2 spectrophotomether, and the ^{1}H-NMR spectra, on a JEOL JNM-MH-60 spectrometer.

Preparation of 7. *Method A). The Dehydration of 5*: A mixture of **5** (1.42 g, 7.98 mmol) and phenyl isocyanate (9.50 g, 79.8 mmol) was refluxed for 16 h. The subsequent fractional distillation of the reaction mixture gave **7** (0.55 g, 44%); bp 105—106 °C/18 mmHg; IR (neat): 1650 cm^{-1}; ^{1}H-NMR (neat): δ=1.7 (3H, s), 3.0 (1H, dd, J=16+10 Hz), 3.1 (1H, dd, J=16+10 Hz), 5.1 (1H, broad s), 5.2 (1H, t, J=10 Hz), 5.3 (1H, broad s), 6.9—8.1 ppm (4H, m). Found: C, 82.67; H, 7.60%. Calcd: C, 82.46; H, 7.55%.

Method B). From Phenol and 1,4-Dibromo-2-methyl-2-butene: Sodium metal (10 g) was added by small portion, into a solution of phenol (9.4 g, 0.10 mol) in dry ether (100 ml). After the addition, stirring was continued for 30 min. Then, 1,4-dibromo-2-methyl-2-butene[7] (23.4 g, 0.10 mol) was added with vigorous stirring, drop by drop, into this suspended mixture. The mixture was then refluxed for 4.5 h with stirring. After the reaction, the ether layer was decanted, and the residual sodium metal was carefully treated with ethanol. The ethanol was removed from the ethanolic solution, and the residue was acidified with 10% hydrochloric acid and then extracted with ether. The two ethereal layer obtained by the decantation and the extraction were combined and washed with a 5% aqueous sodium hydroxide solution. After drying over anhydrous sodium sulfate, the ether was removed. The resulting oil was distilled to give **7** (6.9 g, 43%) (bp 68—76 °C/2 mmHg), whose IR spectrum was identical with that of the product of the dehydration described above.

*5-Bromo-2-isopropenyl-2,3-dihydrobenzofuran (**8a**).* Upon treatment similar to that in the preparation of **7** described above, *p*-bromophenol (8.58 g, 49.6 mmol), sodium metal (5.0 g), and 1,4-dibromo-2-methyl-2-butene (11.3 g, 49.6 mmol) gave **8a** (1.9 g, 16%); bp 122—124 °C/4.5 mmHg; IR (neat): 1650 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.7 (3H, s), 2.9 (1H, dd, J=16+9 Hz), 3.1 (1H, dd, J=16+9 Hz), 4.8 (1H, broad s), 5.0 (1H, broad s), 5.0 (1H, t, J=9 Hz), 6.6 (1H, d, J=9 Hz), 6.9—7.4 ppm (2H, m). Found: C, 55.14; H, 4.90%. Calcd: C, 55.25; H, 4.64%.

*5-Iodo-2-isopropenyl-2,3-dihydrobenzofuran (**8b**).* Upon treatment similar to that in the preparation of **7** described above, *p*-iodophenol (3.0 g, 13.6 mmol), sodium metal (1.4 g), and 1,4-dibromo-2-methyl-2-butene (3.1 g, 13.6 mmol) gave **8b** (1.3 g, 33%); bp 118—119 °C/3 mmHg; IR (neat): 1655 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.8 (3H, s), (1H, dd, J=16+9 Hz), 3.3 (1H, dd, J=16+9 Hz), 5.0 (1H, broad s), 5.2 (1H, broad s), 5.2 (1H, t, J=9 Hz), 6.6 (1H, d, J=9 Hz), 7.5—7.7 ppm (2H, m). Found: C, 46.43; H, 3.60%. Calcd: C, 46.17; H, 3.88%.

*2-Isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**1**).* To a mixture of *N*-methylformanilide (4.46 g; 33.0 mmol) and phosphoryl chloride (5.05 g, 33.0 mmol), **7** (2.63 g, 16.4 mmol) was added. The mixture was then heated at 85—90 °C for 1 h with stirring. After cooling, the mixture was boiled with an aqueous sodium hydroxide solution (4 g in 20 ml) for 1 min and then extracted with ether. The ethereal layer was washed with 10% hydrochloric acid and a 5% sodium hydroxide solution, and then dried over anhydrous sodium sulfate. After the removal of the ether, the resulting oil was distilled to give **1** (1.26 g, 41%); bp 114—117 °C/2.5 mmHg; IR (neat): 1685 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.8 (3H, s), 3.2 (1H, dd, J=16+9 Hz), 3.4 (1H, dd, J=16+9 Hz), 5.1 (1H, broad s), 5.2 (1H, broad s), 5.4 (1H, t, J=9 Hz), 7.0 (1H, d, J=9 Hz), 7.7—8.0 (2H, m), 10.2 ppm (1H, s). Found: C, 76.38; H, 6.42%. Calcd: C, 76.57; H, 6.43%.

*The Formylation of **9**.* Upon treatment similar to that in the preparation of **1** described above, **9**[9] (3.26 g, 14.8 mmol), *N*-methylformanilide (5.0 g, 37.0 mmol), and phosphoryl chloride (4.5 g, 29.3 mmol) gave a mixture of three aldehydes, which were subsequently separated into components by silica-gel chromatography. The fractions eluted with benzene gave **11** (0.40 g, 14%); bp 215—225 °C/18 mmHg; IR (neat): 1690 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.4 (6H, d, J=7 Hz), 3.2 (1H, m, J=7 Hz), 6.6 (1H, s), 7.7 (1H, d, J=9 Hz), 8.0 (1H, dd, J=9+2 Hz), 8.2 (1H, d, J=2 Hz), 12.1 ppm (1H, s). Found: C, 76.29; H, 6.43% (Calcd: C, 76.57; H, 6.43%); and **1** (0.42 g, 15%). The fractions eluted by chloroform gave **10** (0.75 g, 20%); bp *ca.* 130 °C/2 mmHg (bath temperature); IR (neat): 1740, 1695 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.4 (3H, s), 1.5 (3H, s), 2.0 (3H, s), 3.3 (2H, d, J=9 Hz), 5.2 (1H, t, J=9 Hz), 7.2 (1H, d, J=9 Hz), 7.9 (1H, d, J=2 Hz), 7.9 (1H, dd, J=9+2 Hz), 10.1 ppm (1H, s). Found: C, 67.73; H, 64.41%. Calcd: C, 67.73; H, 6.50%.

*The Oxidation of **10** to **2**.* To a solution of silver nitrate (0.70 g, 41.2 mmol) in water (7 ml), sodium hydroxide (0.4 g) was added. To this silver oxide suspension, a solution of **10** (0.44 g, 17.7 mmol) in ethanol (4 ml) was added. The mixture was then refluxed for 2 h. After the reaction, the mixture was filtered, and the filtrate was washed with ether and then acidified with 10% hydrochloric acid. The crystals thus obtained were collected and recrystallized from ethanol to give **1** (0.11 g, 28%); mp 231—232 °C; IR (KBr disk): 3425, 1690 cm^{-1}; ^{1}H-NMR (in DMSO-d_6): δ=1.2 (6H, s), 3.3 (2H, d, J=9 Hz), 4.7 (1H, t, J=9 Hz), 6.9 (1H, d, J=9 Hz), 7.9 (1H, d, J=2 Hz), 7.9 ppm (1H, dd, J=9+2 Hz); ^{1}H-NMR (in pyridine-d_5): δ=1.4 (3H, s), 1.5 (3H, s), 3.3 (1H, dd, J=16+9 Hz), 3.5 (1H, dd, J=16+9 Hz), 4.9 (1H, t, J=9 Hz), 7.1 ppm (1H, d, J=9 Hz). Found: C, 70.78; H, 5.90%. Calcd: C, 70.57; H, 5.92%.

*2-Isopropylbenzofuran-5-carboxylic Acid (**12**).* Upon treatment similar to that in the oxidation of **2** described above, **11** (0.40 g, 21.3 mmol), silver nitrate (0.75 g, 44.2 mmol), and sodium hydroxide (0.4 g) gave **12** (0.14 g, 32%); mp 136.5—137.5 °C (recrystallized from ethanol–water); IR (KBr disk): 1675 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.4 (6H, d, J=7 Hz), 3.2 (1H, m, J=7 Hz), 6.6 (1H, s), 7.7 (1H, d, J=9 Hz), 8.4 (1H, dd, J=9+2 Hz), 8.6 (1H, d, J=2 Hz), 13.1 ppm (1H, s). Found: C, 70.78; H, 5.90%. Calcd: C, 70.57; H, 5.92%.

*2-Isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid (**13**).* Upon treatment similar to that in the oxidation of **2** described above, **1** (1.29 g, 6.85 mmol), silver nitrate (2.43 g, 14.3 mmol), and sodium hydroxide (1.1 g) gave **13** (0.68 g, 49%); mp 140.5—142.5 °C (recrystallized from benzene–cyclohexane); IR (KBr disk): 1675 cm^{-1}; ^{1}H-NMR (in CDCl$_3$): δ=1.8 (3H, s), 3.1 (1H, dd, J=15+9 Hz), 3.3 (1H, dd, J=15+9 Hz), 4.9 (1H, broad s), 5.1 (1H, broad s), 5.3 (1H, t, J=9 Hz), 6.8 (1H, d, J=9 Hz), 7.8 (1H, d, J=2 Hz), 8.0 (1H, dd, J=9+2 Hz), 10.6 ppm (1H, s). Found: C, 70.82; H, 5.79%. Calcd: C, 70.57; H, 5.92%.

*2-[1-(Acetoxymethyl)vinyl]-2,3-dihydrobenzofuran (**14**).* A mixture of **7** (6.7 g, 41.9 mmol), acetic anhydride (110 ml), and finely powdered selenium dioxide (4.3 g, 38.8 mmol) was refluxed for 45 min. Then, the mixture was diluted with ether and filtered. The filtrate was evaporated under reduced pressure to remove the ether and the acetic anhydride. The subsequent distillation of the residue gave **14** (1.42 g, 16%); bp 100—115 °C/4 mmHg; IR (neat): 1740 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=2.0 (3H, s), 3.1 (1H, dd, J=16+9 Hz), 3.4 (1H, dd, J=16+9 Hz), 4.7 (2H, broad s), 5.2 (1H, t, J=9 Hz), 5.2 (1H, broad s), 5.4 (1H, broad s), 6.7—7.4 ppm (4H, m). Found: C, 71.49; H, 6.53%. Calcd: C, 71.54; H, 6.47%.

*5-Acetyl-2-isopropenyl-2,3-dihydrobenzofuran (Tremetone) (**16**).* Under cooling in an ice-water bath, trifluoroacetic anhydride (7.7 g, 36.7 mmol) was added to a solution of **7** (2.9 g, 18.1 mmol) in acetic anhydride (2.2 g, 36.7 mmol). The mixture was then allowed to stand for 6 h at room temperature. After the reaction, the mixture was treated with ice water, and alkalified with a sodium hydrogencarbonate aqueous solution, and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate. After the removal of the ether, the resulting oil was distilled to give **16** (1.67 g, 46%); bp 102—105 °C/2 mmHg; IR (neat): 1670 cm^{-1}; ^{1}H-NMR (in CCl$_4$): δ=1.9 (3H, s), 2.5 (3H, s), 3.2 (1H, dd, J=16+9 Hz), 3.4 (1H, dd, J=16+9 Hz), 5.1 (1H, broad s), 5.3 (1H, broad s), 5.4 (1H, t, J=9 Hz), 7.1 (1H, d, J=9 Hz), 8.0—8.3 ppm (2H, m). Found: C, 76.96; H, 6.74%. Calcd: C, 77.20; H, 6.98%.

*2-[1-(Acetoxymethyl)vinyl]-5-acetyl-2,3-dihydrobenzofuran (**15**). Acetylation of **14**:* Upon treatment similar to that in the preparation of **16** described above, **14** (1.42 g, 6.51 mmol) was acetylated with acetic acid (0.78 g, 13.0 mmol) and trifluoroacetic anhydride (2.73 g, 13.0 mmol) to give **15** (0.79 g, 47%); bp 120—135 °C/4 mmHg; IR (neat): 1740, 1670 cm^{-1}; ^{1}H-

NMR (in CCl_4): $\delta=2.1$ (3H, s), 2.6 (3H, s), 3.4 (1H, dd, $J=15+8$ Hz), 3.6 (1H, dd, $J=15+8$ Hz), 4.9 (2H, broad s), 5.5 (1H, broad s), 5.6 (1H, t, $J=8$ Hz), 7.2 (1H, d, $J=10$ Hz), 8.1—8.4 ppm (2H, m). Found: C, 69.31; H, 6.25%. Calcd: C, 69.21; H, 6.20%.

*Selenium Dioxide Oxidation of **16***: Upon treatment similar to that in the preparation of **14** described above, **16** (1.41 g, 6.98 mmol) was oxidized with selenium dioxide (0.72 g, 6.49 mmol) in acetic anhydride (18 ml) to give **15** (0.099 g; 5.4%); bp 120—130 °C/4 mmHg; it was identical with the sample prepared from **14** in all its spectral data.

5-Acetyl-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran (3). A mixture of **15** (0.27 g, 1.04 mmol), a 10% aqueous potassium hydroxide solution (5 ml), and ethanol (10 ml) was gently refluxed for 20 min. The mixture was then diluted with ice water and extracted with ether. The removal of the ether gave an oily residue, which was subsequently purified by silica-gel chromatography to give **3** as ethanol eluents; bp 103—105 °C/3 mmHg (bath temperature); IR (neat): 3400, 1655 cm^{-1}; ^{1}H-NMR (in $CDCl_3$): $\delta=2.6$ (3H, s), 3.0 (1H, broad s), 3.3 (1H, dd, $J=19+10$ Hz), 3.5 (1H, dd, $J=19+10$ Hz), 4.3 (2H, broad s), 5.4 (2H, broad s), 5.5 (1H, t, $J=10$ Hz), 7.0 (1H, d, $J=10$ Hz), 7.9—8.2 ppm (2H, m). Found: C, 71.26; H, 6.62%. Calcd: C, 71.54; H, 6.47%.

We wish to thank Professor Hisashi Ishii (Chiba Univ.) for his valuable information about the dehydration with phenyl isocyanate. We also wish to thank Dr. Katsuhito Kondo (Tokushima University of Arts and Science) for providing a copy of the IR spectrum of natural anodendroic acid.

This paper is dedicated to Emeritus Professor Takeo Sakan on his 70th birthday.

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