[Chem. Pharm. Bull. 28(10)3007—3012(1980)]

Biogenetic-type Synthesis of 3,4-Dihydro-8-hydroxy-3-phenylisocoumarin (Studies on the β-Carbonyl Compounds connected with the β-Polyketides. V)[1]

Naoki Takeuchi and Seisho Tobinaga

Showa College of Pharmaceutical Sciences[2]

(Received May 8, 1980)

A biogenetic-type synthesis of a dihydroisocoumarin, 3,4-dihydro-8-hydroxy-3-phenylisocoumarin (**1**), from *trans*-cinnamaldehyde (**13**) modelled on the polyketide mode of biosynthesis is described.

Keywords——β-polyketides; biogenetic-type synthesis; condensation reaction; pyrones; dihydroisocoumarins; base catalyzed cyclization

In the preceding paper, we reported that the triketone **3**, 8-phenyl-7-octene-2,4,6-trione, which was derived from benzylidene dehydroacetic acid (**2**), afforded the acidic compound **4** *via* an intramolecular Michael-type condensation reaction, and that the condensation product **4** could be transformed into phenols.[1] These results prompted us to attempt biogenetic-type syntheses of polyketide-derived natural products. This paper deals with the biogenetic-type synthesis of dihydroisocoumarin **1**, selected as a test case.

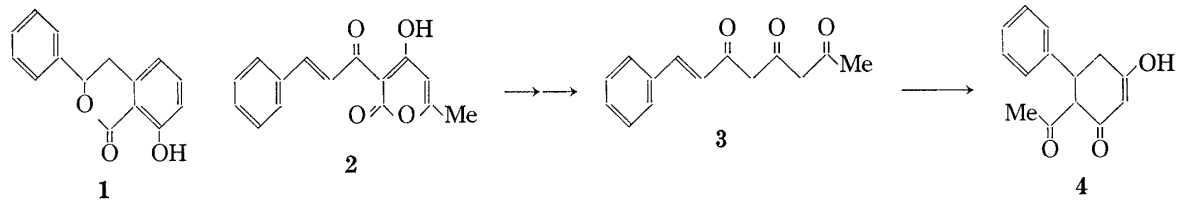

Chart 1

In the vegetable kingdom, phyllodulcin (**11**), a sweet constituent of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto,[3] and hydrangenol (**12**), a constituent of *Hydrangea hortensia* DC. var. *otakusa* Maxim.,[3] are well-known isocoumarins. These dihydroisocoumarins are thought to be biosynthesized through the shikimate-malonate route, as shown in Chart 2.[4] Presumably the *trans*-cinnamic acid **5** or **6** yields the triketo acid **7** or **8** after condensation with 3 molecules of malonic acid, followed by aromatization to yield **9** or **10** and lactonization to give the dihydroisocoumarin **11** or **12**, respectively.

The design for the biogenetic-type synthesis of a dihydroisocoumarin, 3,4-dihydro-8-hydroxy-3-phenylisocoumarin (**1**), is shown in Chart 3. Two possible problems arise. One is whether the triketone **17** derived from *trans*-cinnamaldehyde (**13**) and dehydroacetic acid (**14**) gives the cyclization product **18** by intramolecular condensation, and the other is whether the cyclotriketone **18** can afford the diketone **19** by regiospecific reduction.

The reaction of *trans*-cinnamaldehyde (**13**) with dehydroacetic acid (**14**) in pyridine in the presence of piperidine gave the condensation product **15**, mp 182—184°, in 89% yield. **15**

1) Part IV: N. Takeuchi, H. Nakagawa, and S. Tobinaga, *Chem. Pharm. Bull.*, **28**, 3002 (1980).
2) Location: *Tsurumaki, Setagaya-ku, Tokyo, 154, Japan.*
3) Y. Asahina and J. Asano, *Yakugaku Zasshi*, **51**, 595, 749 (1913); *idem*, *Chem. Ber.*, **62**, 171 (1929); **63**, 429, 2049 (1930); **64**, 1252 (1931).
4) D.E. Hathway, *Biochem. J.*, **71**, 553 (1959); T.A. Geissman, "Biogenesis of Natural Compounds," ed. P. Bernfeld, Pergamon, Oxford, 1967, p. 743.

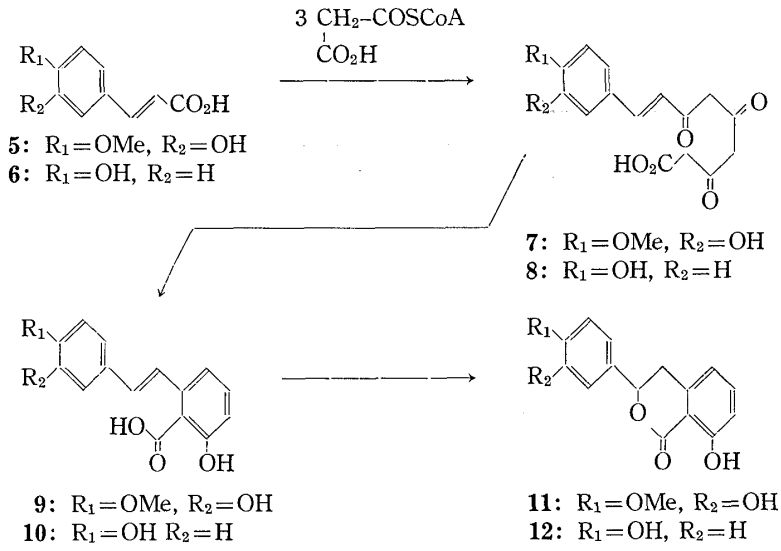

Chart 2

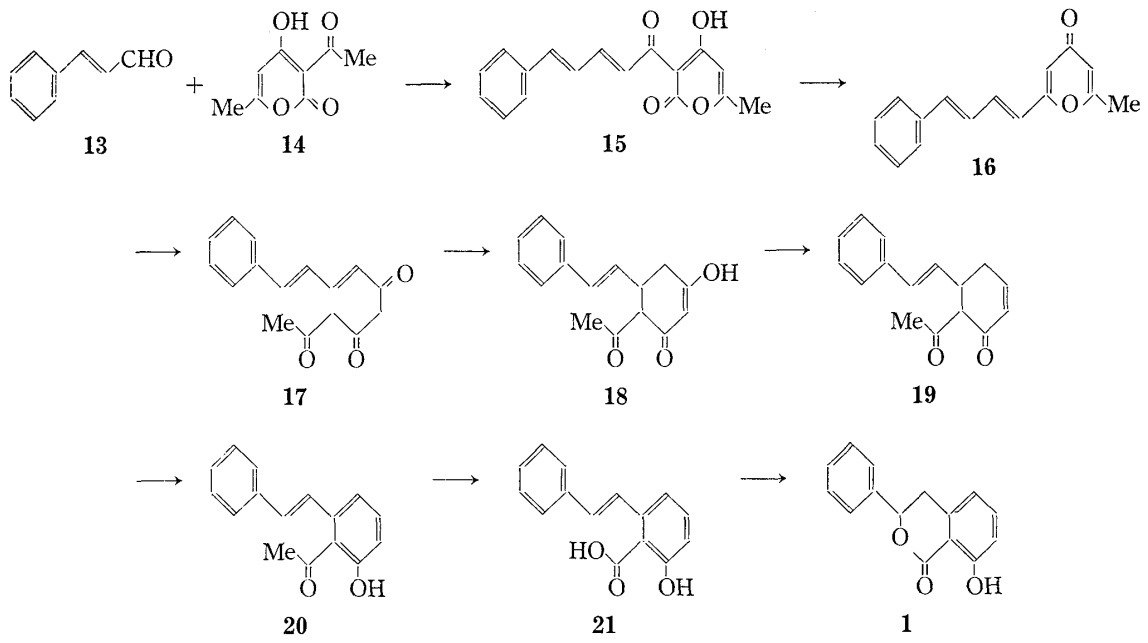

Chart 3

was transformed into the 4-pyrone **16**, mp 139—141° (75% yield), by treatment with conc. HCl, and the subsequent treatment of **16** with aqueous $Ba(OH)_2$ gave the triketone **17**, mp 135—136.5°, in 90% yield. When the triketone **17** was heated in 10% K_2CO_3–EtOH (1: 1), an acidic compound **18**, mp 136—138°, was obtained in 25% yield.

The following chemical transformations were investigated to confirm the structure of **18**. That is, **18** gave the acetate **22** on acetylation with CH_3CO–H_2PO_4[5] and the dichloride **23** on chlorination with $CuCl_2 \cdot 2H_2O$–LiCl in dimethylformamide (DMF). Further, the dichloride **23** gave the acetate **24** on acetylation with Ac_2O–H_2SO_4, and the phenol **25**, mp 159—160°, on dehydrochlorination with LiCl in DMF. The nuclear magnetic resonance (NMR) spectrum of the acetate **24** shows the presence of two methylene protons centered at 2.72 (1H, q, J=5 Hz, J=18 Hz) and 3.18 (1H, q, J=18 Hz, J=9 Hz), one methine proton centered at 3.85 (1H, m,

5) J.S. Fritzand and G.H. Schenk, *Anal. Chem.*, **31**, 1308 (1959).

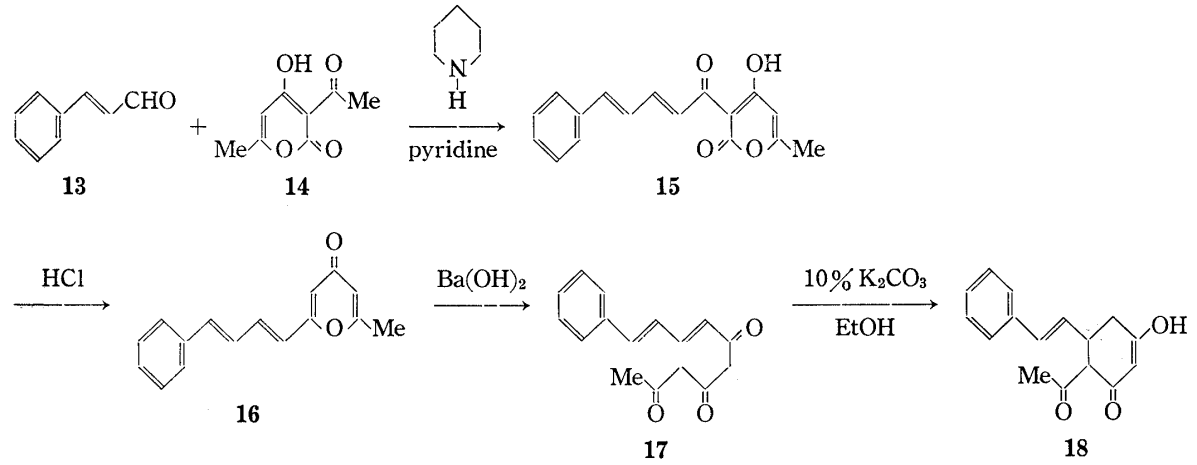

Chart 4

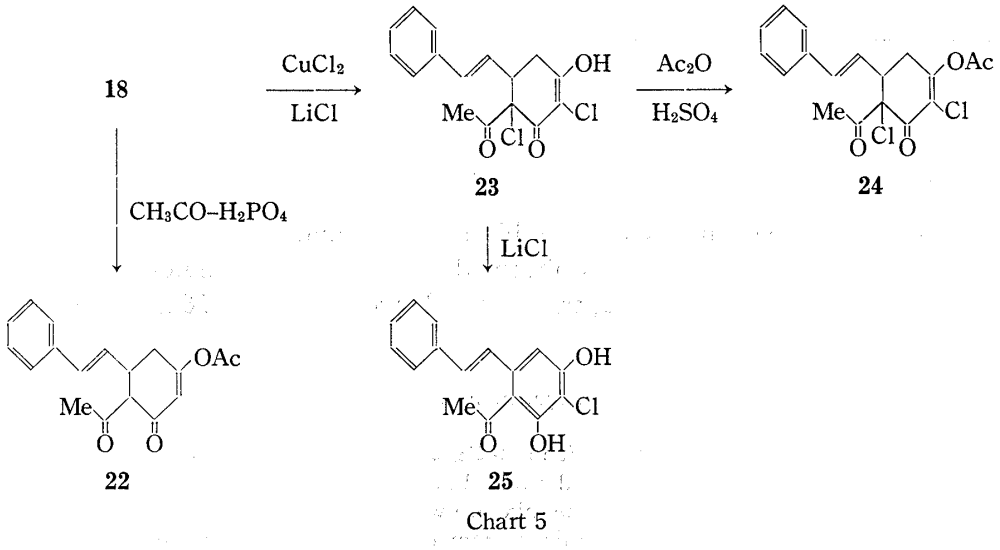

Chart 5

J=7.5 Hz, J=5 Hz, J=9 Hz), and two olefinic protons centered at 6.10 (1H, q, J=7.5 Hz, J=16 Hz) and 6.60 (1H, d, J=16 Hz), in good agreement with the proposed structure of the acetate **24**.

The successful conversion of the cyclotriketone **18** to the diketone **19** by partial reduction was achieved as follows. First, **18** was transformed into the enaminones **26** by reaction with pyrrolidine in toluene; The product was a mixture in two spots on thin-layer chromatography (TLC) and may correspond to the structures **26** (75% yield). Partial reduction of the enaminones **26** to the ketoalcohol **27** was performed using $LiAlH_4$–$AlCl_3$[6] in tetrahydrofuran (THF) in 46% yield, and **27** was transformed into the methylketone **19** by oxidation with Jones' reagent, mp 98.5—99.5°, in 76% yield. Subsequently, the methylketone **19** was converted to the chloride **28** (92% yield), and then **28** gave the expected phenol **20** on dehydrochlorination with LiCl in DMF, in 72% yield.

Finally, the conversion of the phenol to the dihydroisocoumarin **1** was carried out in the following fashion. The phenol **20** was transformed into the pyridinium salt by reaction with pyridine-I_2, followed by treatment with 10% KOH–EtOH (1: 1) to afford the acid **21**, mp 147.5—149°, in 50% yield. The lactonization of **21** to the dihydroisocoumarin **1**, mp 108—109.5°, proceeded smoothly on treatment with cold conc. H_2SO_4, in 75% yield.

6) J.M. Coulter, J.W. Lewis, and P.P. Lynch, *Tetrahedron*, **24**, 4489 (1968).

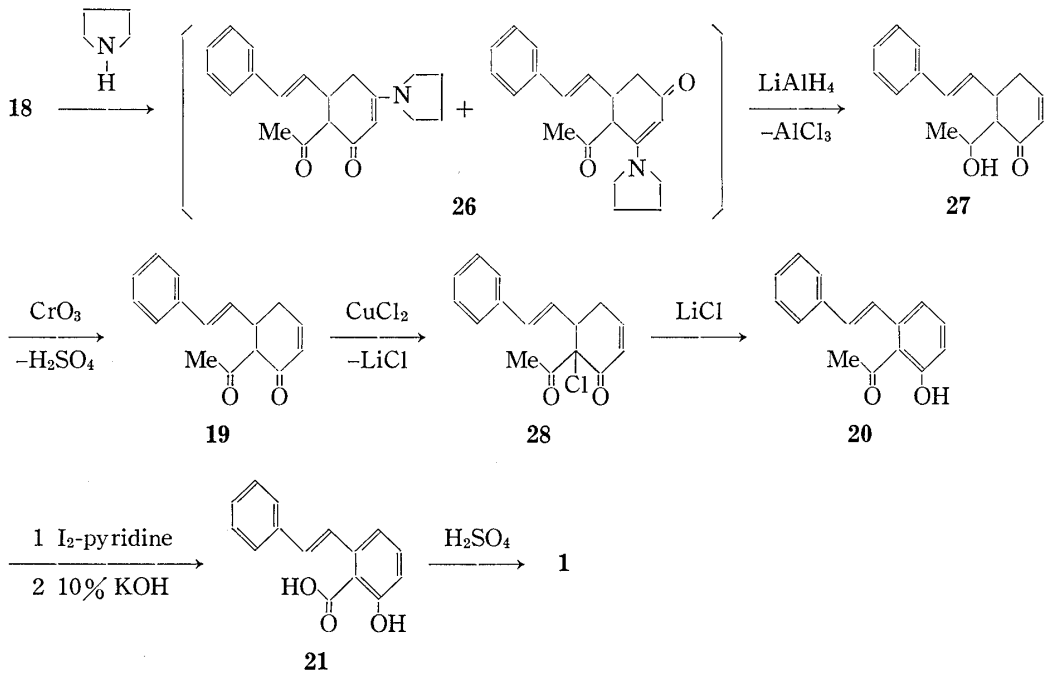

Chart 6

Thus, a biogenetic-type synthesis of the dihydroisocoumarin **1** was achieved starting from the condensation product **15**, which was obtained from *trans*-cinnamaldehyde and dehydroacetic acid (**14**), through the 4-pyrone **16**, triketone **17**, cyclotriketone **18** and the partial reduction product **19**, successively.

Experimental[7]

4-Hydroxy-6-methyl-3-(5-phenyl-2,4-pentadienoyl)-2H-2-pyranone (15)——A mixture of dehydroacetic acid **14** (10 g), *trans*-cinnamaldehyde (7.8 g) and piperidine (0.1 ml) in dry pyridine (47.6 ml) was heated at 45° for 45 min, and then at 100° for 1 hr. The mixture was allowed to stand at room temperature. The separated crystals were collected and recrystallized from ether–chloroform to yield 15 g (89%) of **15** as orange-colored crystals, mp 182—184°. *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.30; H, 5.01. IR ν_{max}^{Nujol} cm^{-1}: 1715, and 1610. NMR ($CDCl_3$) δ: 2.25 (3H, s, $-CH_3$), 5.98 (1H, s, olefinic H), 7.12 (2H, m, olefinic H×2), 7.48 (5H, m, aromatic H×5), 7.86 (2H, m, olefinic H×2), and 18.00 (1H, s, –OH).

2-Methyl-6-(4-phenyl-1,3-butadienyl)-4H-4-pyranone (16)——Conc. HCl (40 ml) was added to a solution of **15** (6.3 g) in acetic acid (60 ml), and refluxed for 2 hr. The solution was concentrated under a vacuum, made basic with 10% K_2CO_3 and then extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether–chloroform to yield 4 g (75%) of **16** as yellow crystals, mp 139—141°. IR ν_{max}^{Nujol} cm^{-1}: 1655. NMR ($CDCl_3$) δ: 2.32 (3H, s, $-CH_3$), 6.15 (1H, d, J=2 Hz, olefinic H), 6.23 (1H, d, J=2 Hz, olefinic H), 6.43 (1H, t, J=3 Hz, olefinic H), 7.02 (3H, m, olefinic H×3), and 7.50 (5H, m, aromatic H×5).

10-Phenyl-7,9-decadiene-2,4,6-trione (17)——A saturated solution of $Ba(OH)_2$ (2.1 g) was added to a solution of **16** (1.6 g) in ethanol (10 ml), and the mixture was refluxed on a water bath for 30 min. The precipitated Ba salts were separated from the solution by filtration, acidified with 5% HCl and extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether–chloroform to yield 1.5 g (90%) of **17** as yellow crystals, mp 135—136.5°. *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.94; H, 6.27. IR ν_{max}^{Nujol} cm^{-1}: 1610.

7) All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 215 spectrometer, ultraviolet (UV) spectra with a Hitachi 124 spectrometer, NMR spectra with a Varian T-60 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ soln.), and MS spectra with a Hitachi RMS-4 spectrometer at 70 eV using the direct insertion technique. Elementary analyses were done by Mrs. K. Sasaki, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel G nach Stahl were used for column chromatography and TLC, respectively.

6-Acetyl-3-hydroxy-5-styryl-2-cyclohexenone (18)——A solution of **17** (20 g) in ethanol (150 ml) was refluxed with 10% K_2CO_3 (150 ml) on a water bath for 2 hr. The solution was concentrated under a vacuum, acidified with 10% HCl and then extracted with chloroform. The organic layer was extracted with sat. $NaHCO_3$. The aqueous layer was acidified with 10% HCl and then extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether–chloroform to yield 5 g (25%) of **18** as colorless crystals, mp 136—138°. *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.96; H, 6.38. MS *m/e*: 256 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1715, and 1612. NMR ($CDCl_3$) δ: 2.23 (3H, s, $-COCH_3$), 5.40 (2H, m, olefinic H×2), 5.50 (1H, m, –OH, D_2O-exchangeable), 5.55 (1H, s, olefinic H, D_2O-exchangeable), and 7.35 (5H, s, aromatic H×5).

3-Acetoxy-6-acetyl-5-styryl-2-cyclohexenone (22)——Compound **18** (50 mg) was heated with acetic-phosphoric anhydride[5] (3 ml) at 50° for 15 min. The reaction mixture was poured into ice-water and then extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was purified by preparative TLC (with chloroform as a developing solvent) to yield 34 mg (59%) of **22** as a colorless oil. MS *m/e*: 298 (M^+). IR $\nu_{max}^{liq.}$ cm^{-1}: 1765, 1720, and 1670. NMR ($CDCl_3$) δ: 2.15 (3H, s, $-OCOCH_3$), 2.21 (3H, s, $-COCH_3$), and 7.38 (5H, s, aromatic H×5).

6-Acetyl-2,6-dichloro-3-hydroxy-5-styryl-2-cyclohexenone (23)——A mixture of $CuCl_2 \cdot 2H_2O$ (200 mg) and LiCl (16.6 mg) in DMF (1 ml) was heated at 80°, and then **18** (100 mg) was added and the whole was heated at 80° for 3 hr. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with H_2O, dried and concentrated to yield 109 mg (86%) of **23** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1720, and 1660. The compound **23** was used in the next step without further purification.

3-Acetoxy-6-acetyl-2,6-dichloro-5-styryl-2-cyclohexenone (24)——A solution of **23** (100 mg) in acetic anhydride (1.5 ml) was treated with 0.2 ml of a mixture of conc. H_2SO_4 (0.2 ml) and acetic anhydride (5 ml), and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 83.6 mg (74%) of **24** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1780, 1720, 1687, and 1625. NMR ($CDCl_3$) δ: 2.32 (3H, s, $-COCH_3$), 2.43 (3H, s, $-COCH_3$), 2.72 (1H, q, J=5 Hz, J=18 Hz, $-CH_2-$), 3.18 (1H, q, J=18 Hz, J=9 Hz, $-CH_2-$), 3.85 (1H, m, J=7.5 Hz, J=5 Hz, J=9 Hz, methine H), 6.10 (1H, q, J=7.5 Hz, J=16 Hz, olefinic H), 6.60 (1H, d, J=16 Hz, olefinic H), and 7.38 (5H, s, aromatic H×5).

4-Acetyl-2-chloro-5-styryl-1,3-benzenediol (25)——LiCl (60 mg) was added to a solution of **23** (100 mg) in DMF (3 ml), and the mixture was heated at 100° for 2 hr. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was extracted with 10% NaOH. The aqueous layer was acidified with conc. HCl and extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 68 mg (79%) of **25** as colorless crystals, mp 159—160°. MS *m/e*: 288 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1580. NMR ($CDCl_3$) δ: 2.50 (3H, s, $-COCH_3$), 6.75 (1H, s, aromatic H), 12.10 (1H, s, –OH).

The Mixture 26——A mixture of **18** (2.18 g), pyrrolidine (1 g) and *p*-toluenesulfonic acid (0.1 g) in ab. toluene (5 ml) was heated under reflux with water separation by means of a Dean-Stark trap. After reflux for 3 hr, the mixture was concentrated under a vacuum. The residue was subjected to silica gel chromatography. The chloroform eluate yielded 2.4 g (75%) of **26** as an oil, giving two spots on TLC. IR $\nu_{max}^{liq.}$ cm^{-1}: 1712, 1600, and 1550. NMR ($CDCl_3$) δ: 2.00 (4H, m, $-CH_2CH_2-$), 2.30 (3H, s, $-COCH_3$), 2.46—2.94 (2H, broad, $-CH_2-$), 3.07—3.70 (6H, broad, $-CH_2NCH_2-$ and $\geqslant CH \times 2$), 5.16 (1H, s, olefinic H), 6.45 (2H, m, olefinic H×2), and 6.37 (5H, s, aromatic H×5). The mixture **26** was used in the next step without separation.

6-(1-Hydroxyethyl)-5-styryl-2-cyclohexenone (27)——A solution of $AlCl_3$ (0.67 g) in THF (4 ml) was added to a solution of $LiAlH_4$ (0.7 g) in THF (18 ml) at 0° and the whole was stirred at 0° for 1 hr. To this mixture, a solution of **26** (1 g) in THF (5 ml) was added. The whole was stirred overnight at 0° then poured into ice-water and 10% HCl, and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 0.36 g (46%) of **27** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1664. NMR ($CDCl_3$) δ: 1.22 (3H, d, J=6.4 Hz, $-CH_3$), 3.90 (1H, m, =CH–O–), 6.95 (1H, broad, –OH), and 7.27 (5H, s, aromatic H×5).

6-Acetyl-5-styryl-2-cyclohexenone (19)——A solution of **27** (121 mg) in acetone (5 ml) was treated with 0.5 ml of Jones' reagent [obtained by adding 6 ml of H_2O to a mixture of CrO_3 (2.67 g) and conc. H_2SO_4 (2.3 ml)]. The mixture was allowed to stand at room temperature for 15 min, then poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 91 mg (76%) of **19** as colorless crystals, mp 98.5—99.5°. *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.03; H, 6.67. IR ν_{max}^{Nujol} cm^{-1}: 1720, and 1660. NMR ($CDCl_3$) δ: 2.07 (3H, s, $-COCH_3$), 2.52 (2H, m, $-CH_2-$), 3.46 (2H, m, $\geqslant CH \times 2$), 5.93—6.70 (4H, m, olefinic H×4), and 7.17 (5H, s, aromatic H×5).

6-Acetyl-6-chloro-5-styryl-2-cyclohexenone (28)——A mixture of $CuCl_2 \cdot 2H_2O$ (541 mg) and LiCl (51.4 mg) in DMF (10 ml) was heated at 80°, and then **19** (240 mg) was added and the whole was heated at 80° for 3 hr. The mixture was poured into ice-water and extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated to yield 252 mg (91.8%) of **28** as an oil. The

compound **28** was used in the next step without further purification.

2-Acetyl-3-styrylphenol (20)——LiCl (63 mg) was added to a solution of **28** (252 mg) in DMF (10 ml), and the mixture was heated at 100° for 2 hr, then poured into ice-water and extracted with ether. The ether layer was extracted with 10% NaOH. The aqueous layer was acidified with conc. HCl and then extracted with ether. The resulting ether layer was washed with sat. $NaHCO_3$ and H_2O, dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 158 mg (72.3%) of **20** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1635, 1600, and 1500. NMR ($CDCl_3$) δ: 2.62 (3H, s, $-COCH_3$), 6.80—7.63 (8H, m, aromatic H×8), and 11.90 (1H, s, –OH).

6-Styrylsalicylic Acid (21)——I_2 (190 mg) was added to a solution of **20** (238 mg) in dry pyridine (500 mg), and the mixture was heated on a water bath for 1 hr. The reaction mixture was allowed to stand overnight at room temperature and the separated crystals were collected. A solution of these crystals in 3 ml of ethanol was treated with 10% KOH (3 ml) and the mixture was heated on a water bath for 1 hr, then acidified with conc. HCl and extracted with chloroform. The organic layer was extracted with sat. $NaHCO_3$. The aqueous layer was acidified with conc. HCl and extracted with chloroform. The resulting organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 120 mg (50%) of **21** as colorless crystals, mp 147—149°. MS *m/e*: 240 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1640, and 1593.

3,4-Dihydro-8-hydroxy-3-phenylisocoumarin (1)——A solution of **21** (40 mg) in conc. H_2SO_4 (1 ml) was stirred at 0° for 5 min. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 30 mg (75%) of **1** as colorless crystals, mp 108—109.5°. *Anal.* Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.14; H, 5.01. MS *m/e*: 240 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1670, 1615, and 1580. NMR ($CDCl_3$) δ: 3.13 (2H, m, $-CH_2-$), 5.58 (1H, q, $J=10$ Hz, $J=6$ Hz, =CH–O–), and 7.35 (5H, s, aromatic H×5).