SYNTHESES OF *DIHYDROISOCOUMARINS*, (±)-*HYDRANGENOL* AND (±)-PHYLLODULCIN, UTILIZING AN ANNELATION REACTION OF ENAMINONES WITH ETHYL ACETOACETATE. STUDIES ON THE β-CARBONYL COMPOUNDS CONNECTED WITH THE β-POLYKETIDES XIII[1]

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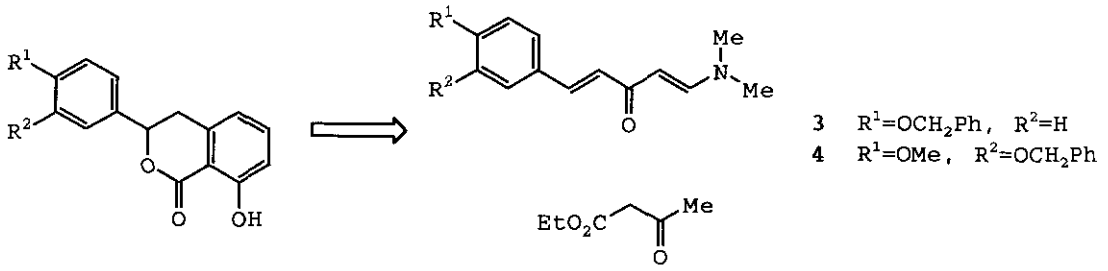
Abstract---Naturally occurring dihydroisocoumarins, (±)-hydrangenol (1) and (±)-phyllodulcin (2) were synthesized from the enaminones (3) and (4) by the annelation reactions with ethyl acetoacetate (5).

Naturally occurring dihydroisocoumarins, hydrangenol (1)[2,3] and phyllodulcin (2)[2-5] are known as a constituent of *Hydrangea opuloides* Stend var. *otakusa* Maxim (Japanese name: Ajisai) and a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto (Japanese name: Amacha), respectively. Although chemical syntheses of 1[6-11] and 2[9,10,12-14] have already been reported, we describe herein a new synthetic method, applying the aromatic annelation reaction reported in the proceeding paper,[15] by the reactions of enaminones with ethyl acetoacetate. The present synthetic strategy consists of aromatic annelation with two synthons, namely, the enaminones (3) and (4) and ethyl acetoacetate (5), as shown in Scheme 1.



1 R^1=OH, R^2=H
2 R^1=OMe, R^2=OH

3 R^1=OCH_2Ph, R^2=H
4 R^1=OMe, R^2=OCH_2Ph

5

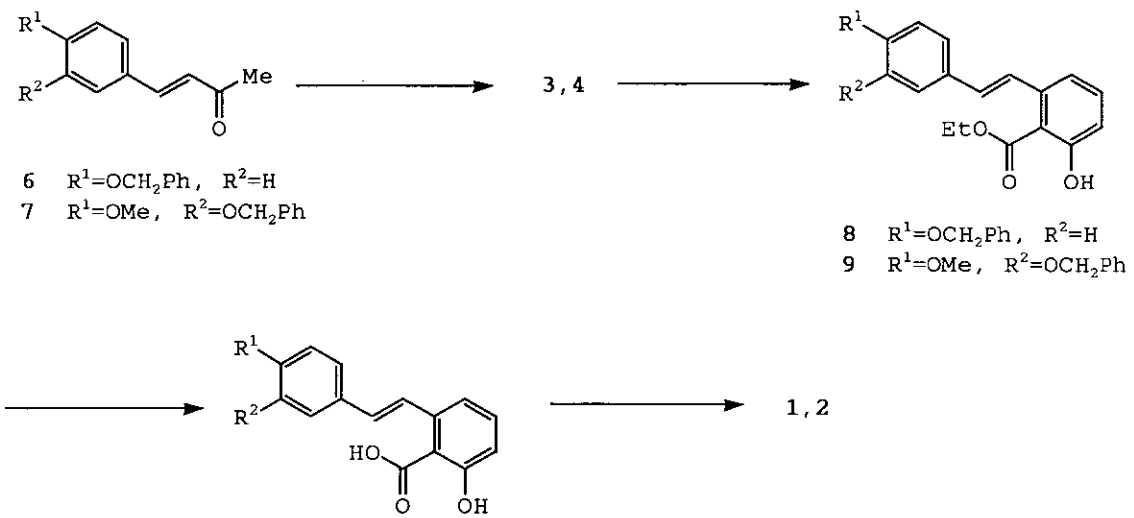
Scheme 1

First, the synthesis of (±)-hydrangenol (**1**) was investigated. The enaminone, 1-(4-benzyloxyphenyl)-5-dimethylamino-1,4-pentadien-3-one (**3**), mp 123-125 °C, was prepared by condensing *p*-benzyloxybenzaldehyde with acetone in the presence of 10% NaOH (68.2% yield), followed by the treatment of the resulting 4-(4-benzyloxyphenyl)-3-buten-2-one (**6**), mp 87-89 °C, with bis-dimethylaminomethoxymethane in dimethylformamide (DMF) (78.0% yield).

The reaction of **3** with the dianion prepared from the reaction of **5** with NaH and butyllithium (BuLi) in tetrahydrofuran (THF), in the presence of BF_3·OEt_2, followed by treatment with KF in toluene afforded the condensation product (**8**), mp 92-94 °C, in 22.2% yield. Analytical data show that the condensation product is ethyl 6-[2-(4-benzyloxyphenyl)ethenyl]salicylate (**8**).

The ester (**8**) was hydrolyzed with 10% KOH in ethanol to give the acid, 6-[2-(4-benzyloxyphenyl)ethenyl]salicylic acid (**10**), mp 153-155 °C, in 90.0% yield. Lactonization and debenzylation of **10** with concentrated HCl in methanol afforded (±)-hydrangenol (**1**), mp 177-179 °C (lit.,[6] mp 178-180 °C)

in 81.0% yield. All physical data for this synthetic hydrangenol (1) were identical with those of an authentic sample[6] except for its optical rotation.



6 R^1=OCH_2Ph, R^2=H
7 R^1=OMe, R^2=OCH_2Ph

8 R^1=OCH_2Ph, R^2=H
9 R^1=OMe, R^2=OCH_2Ph

10 R^1=OCH_2Ph, R^2=H
11 R^1=OMe, R^2=OCH_2Ph

Scheme 2

Similarly, we planed to synthesize (±)-phyllodulcin (2) *via* the reaction of the enaminone, 1-(3-benzyloxy-4-methoxyphenyl)-5-dimethylamino-1,4-pentadien-3-one (**4**)[14] using ethyl acetoacetate (5). The reaction of **4** with the dianion of **5** afforded the condensation product, ethyl 6-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]salicylate (**9**), mp 105-107 °C, in 23.0% yield. The ester (**9**) was hydrolyzed to give the acid, 6-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]salicylic acid (**11**), mp 133-135 °C (88.0% yield), which was treated with concentrated HCl to afford (±)-phyllodulcin (2), mp 130-132 °C

(lit.,[14] mp 128-130 °C) in 74.0% yield. All physical data for this synthetic phyllodulcin (2) were identical with those of an authentic sample[14] except for its optical rotation.

EXPERIMENTAL

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Ir spectra were recorded with a Hitachi 260-10 spectrophotometer, nmr spectra with a JEOL JNM-FX 100 spectrometer with tetramethylsilane as an internal standard, ms with a JEOL JMS-D 300 spectrometer. Elemental analyses were done by Miss. K. Nakamura, Kissei Pharmaceutical Company Ltd., Matsumoto, Japan. Wakogel C-200 (silica gel) and Merck Kieselgel G nach stahl (silica gel) were used for column chromatography and tlc, respectively.

4-(4-Benzyloxyphenyl)-3-buten-2-one (6)

Water (25 ml) and 10% NaOH (25 ml) were added to a solution of *p*-benzyloxybenzaldehyde (5 g, 23.6 mmol) in acetone (120 ml) and the whole was stirred at room temperature for 14 h. The reaction mixture was poured into water and the separated crystals were collected, then dried and recrystallized from ethanol to yield 4.0 g (68.2%) as colorless needles, mp 87-89 °C. Ir (nujol) cm^{-1}: 1650, 1620, 1595, 1565, 1495. Nmr ($CDCl_3$) δ: 2.28 (3H, s, Me), 5.04 (2H, s, $OC\underline{H}_2Ph$), 6.52 (1H, d, J=16.8 Hz, olefinic H), 6.92 (2H, d, J=9 Hz, aromatic H), 7.33 (5H, s, aromatic H), 7.42 (1H, d, J=16.8 Hz, olefinic H), 7.44 (2H, d, J=9 Hz, aromatic H). High ms m/z Calcd for $C_{17}H_{16}O_2$ (M^+): 252.1151. Found: 252.1184. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.89; H, 6.39.

1-(4-Benzyloxyphenyl)-5-dimethylamino-1,4-pentadien-3-one (3)

Bisdimethylaminomethoxymethane (1.3 g, 9.8 mmol) was added to a solution of 6 (18.2 g, 72.2 mmol) in DMF (4.5 ml) and the whole was heated at 80 °C for 4 h. The reaction mixture was poured into water and the separated crystals were collected, then dried and recrystallized from ethanol to yield 1.7 g (78.0%) as light yellow needles, mp 123-125 °C. Ir (nujol) cm^{-1}: 1600, 1570, 1540, 1500. Nmr ($CDCl_3$) δ: 2.98 (6H, s, NMe_2), 5.08 (2H, s, $OC\underline{H}_2Ph$), 5.25 (1H, d, J=12.6 Hz, olefinic H), 6.55 (1H, d, J=15.6 Hz, olefinic H), 6.94 (2H, d, J=8.4 Hz, aromatic H), 7.38 (5H, s, aromatic H), 7.50 (2H, d, J=8.4 Hz, aromatic H), 7.55 (1H, d, J=15.6 Hz, olefinic H), 7.73 (1H, d, J=12.6 Hz, olefinic H). High ms m/z: Calcd for $C_{20}H_{21}NO_2$ (M^+): 307.1572. Found: 307.1594. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.15; H, 6.86; N, 4.55.

Ethyl 6-[2-(4-Benzyloxyphenyl)ethenyl]salicylate (8)

NaH (55%, 66 mg, 1.5 mmol) was added to a solution of ethyl acetoacetate (5, 325 mg, 2.5 mmol) in dry THF (3 ml) with stirring at 0 °C under a nitrogen atmosphere and the whole was stirred similarly for an additional 10 min. A solution of 1.38 M BuLi in hexane (2.2 ml, 3 mmol) was added to the mixture and the whole was stirred at 0 °C for 10 min under the same conditions. To the resultant solution, a solution of the 3 (92 mg, 0.3 mmol) and $BF_3 \cdot OEt_2$ (0.4 ml) in dry THF (2 ml) was added at -78 °C. After 10 min, the reaction temperature was raised 0 °C over 1 h. The reaction mixture was poured into ice-water, acidified with 10% HCl, and extracted with ether. The organic layer was washed with brine, dried over dry Na_2SO_4 and concentrated. The residue was dissolved in dry toluene (5 ml), KF (100 mg, 1.7 mmol) was added to the solution, and then the whole was refluxed overnight. The reaction mixture was concentrated under a vacuum, poured into ice-water, and extracted with chloroform. The organic layer was washed with water, then

dried over dry Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography. The eluate with 25% hexane in benzene gave 25 mg (22.2%) of **8** as colorless needles (hexane-ether), mp 92-94 °C. Ir (nujol) cm^{-1}: 1668, 1645, 1600, 1570, 1500. Nmr ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz, $OCH_2\underline{CH_3}$), 4.38 (2H, q, J=7.2 Hz, $OC\underline{H_2}CH_3$), 5.04 (2H, s, $OC\underline{H_2}Ph$), 6.67 (2H, d, J=15.6 Hz, aromatic H), 7.34 (5H, s, aromatic H), 6.89-7.50 (5H, m, olefinic H and aromatic H), 7.59 (2H, d, J=15.6 Hz, aromatic H), 9.58 (1H, s, OH). High ms m/z: Calcd for $C_{24}H_{22}O_4$ (M^+): 374.1518. Found: 374.1496. Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.90; H, 5.93.

The compound (**9**) was prepared from enaminone (**4**)[14] in a similar manner described in **8**.

Ethyl 6-[2-(3-Benzyloxy-4-methoxyphenyl)ethenylsalicylate (9)

Colorless needles (23.0%), mp 105-107 °C (hexane-ether). Ir (nujol) cm^{-1}: 1655, 1600, 1580, 1515. Nmr ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz, $OCH_2\underline{CH_3}$), 3.90 (3H, s, OMe), 4.39 (2H, q, J=7.2 Hz, $OC\underline{H_2}CH_3$), 5.18 (2H, s, $OC\underline{H_2}Ph$), 6.55-7.84 (13H, m, aromatic H and olefinic H), 9.61 (1H, s, OH). High ms m/z: Calcd for $C_{25}H_{24}O_5$ (M^+): 404.1623. Found: 404.1658. Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.16; H, 5.99.

6-[2-(4-Benzyloxyphenyl)ethenyl]salicylic Acid (10)

10% KOH (7 ml) was added to a solution of **8** (100 mg, 0.27 mmol) in ethanol (10 ml) and the whole was refluxed for 3 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was washed with brine, then dried over dry Na_2SO_4 and concentrated. The residue was recrystallized from ether to yield 83 mg (90.0%) of **10** as colorless needles, mp 153-155 °C. Ir (nujol) cm^{-1}: 1650, 1598, 1510. Nmr ($CDCl_3$) δ: 5.00 (2H, s, $OC\underline{H_2}Ph$), 6.00 (2H, br, CO_2H and OH), 6.71 (2H, d,

J=16.8 Hz, aromatic H), 7.30 (5H, s, aromatic H), 6.90-7.55 (5H, m, olefinic H and aromatic H), 7.63 (2H, d, J=16.8 Hz, aromatic H). High ms m/z: Calcd for $C_{22}H_{18}O_4$ (M^+): 346.1205. Found: 346.1220. This product (10) was used in the next step without further purification.

The compound (11) was prepared from 9 in a similar manner described in 10.

6-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]salicylic Acid (11)

Colorless needles (88.0%), mp 133-135 °C (ether-chloroform). Ir (nujol) cm^{-1}: 1640, 1595, 1505. Nmr ($CDCl_3$) δ: 3.88 (3H, s, OMe), 5.17 (2H, br, CO_2H and OH), 5.17 (2H, s, $OC\underline{H}_2Ph$), 6.73 (1H, d, J=16.8 Hz, olefinic H), 6.55-7.55 (11H, m, aromatic H), 7.76 (1H, d, J=16.8 Hz, olefinic H). High ms m/z: Calcd for $C_{23}H_{20}O_5$ (M^+): 376.1311. Found: 376.1342. This product (11) was used in the next step without further purification.

(±)-Hydrangenol (1)

Concentrated HCl (3.5 ml) was added to a solution of 10 (70 mg, 0.2 mmol) in methanol (3.5 ml) and the whole was refluxed for 4 h. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over dry Na_2SO_4 and concentrated. The residue was recrystallized from ethyl acetate to yield 42 mg (81.0%) of 1 as colorless prisms, mp 177-179 °C (lit.,[6] mp 178-180 °C). Ir (nujol) cm^{-1}: 1675, 1610, 1595, 1580, 1515, 1490. Nmr ($CDCl_3$+DMSO-d_6) δ: 3.30 (2H, m, methylene H), 5.40 (1H, dd, J=10.2, 4.2 Hz, methine H), 5.28-5.52 (1H, br, OH), 6.36-7.44 (7H, m, aromatic H), 9.00 (1H, s, OH). This compound (1) was identical with authentic sample[6] by mixed mp and ir, nmr comparisons.

The compound (2) was prepared from 11 in a similar manner described in 1.

(±)-Phyllodulcin (2)

Colorless prisms (74.0%), mp 130-132 °C (hexane-ether), (lit.,[14] mp 128-130 °C). Ir (KBr) cm^{-1}: 1665, 1615, 1595, 1501. Nmr ($CDCl_3$) δ: 3.30 (2H, m, methylene H), 3.91 (3H, s, OMe), 5.50 (1H, dd, J=11.4, 5.4 Hz, methine H), 5.73 (1H, br, OH), 6.66-7.46 (6H, m, aromatic H), 9.71 (1H, s, OH). This compound (2) was identical with authentic sample[14] by mixed mp and ir, nmr comparisons.

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Received, 14th October, 1992