SYNTHESES OF (+)- AND (-)-MELLEIN UTILIZING AN ANNELATION REACTION OF ISOXAZOLES WITH DIMETHYL 3-OXOGLUTARATE[1]

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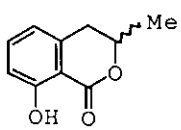
Abstract---Naturally occurring dihydroisocoumarins, (+)- and (-)-mellein (2 and 3), metabolites of fungals, *Cercospora* sp. and *Aspergillus* sp., etc., were synthesized from the isoxazoles (32) and (33) by the annelation reactions with dimethyl 3-oxoglutarate.

Naturally occurring dihydroisocoumarins (+)- and (-)-mellein (2 and 3) are well known as metabolites of fungals, *Cercospora* sp. and *Aspergillus* sp., etc.[2] (-)-Mellein (3) was also isolated from the mandibular gland secretion of carpenter ants[3] and the hairpencils of male oriental fruit moths.[4] A few biological activities of melleins were reported to date, namely, an



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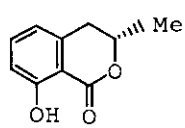

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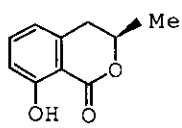

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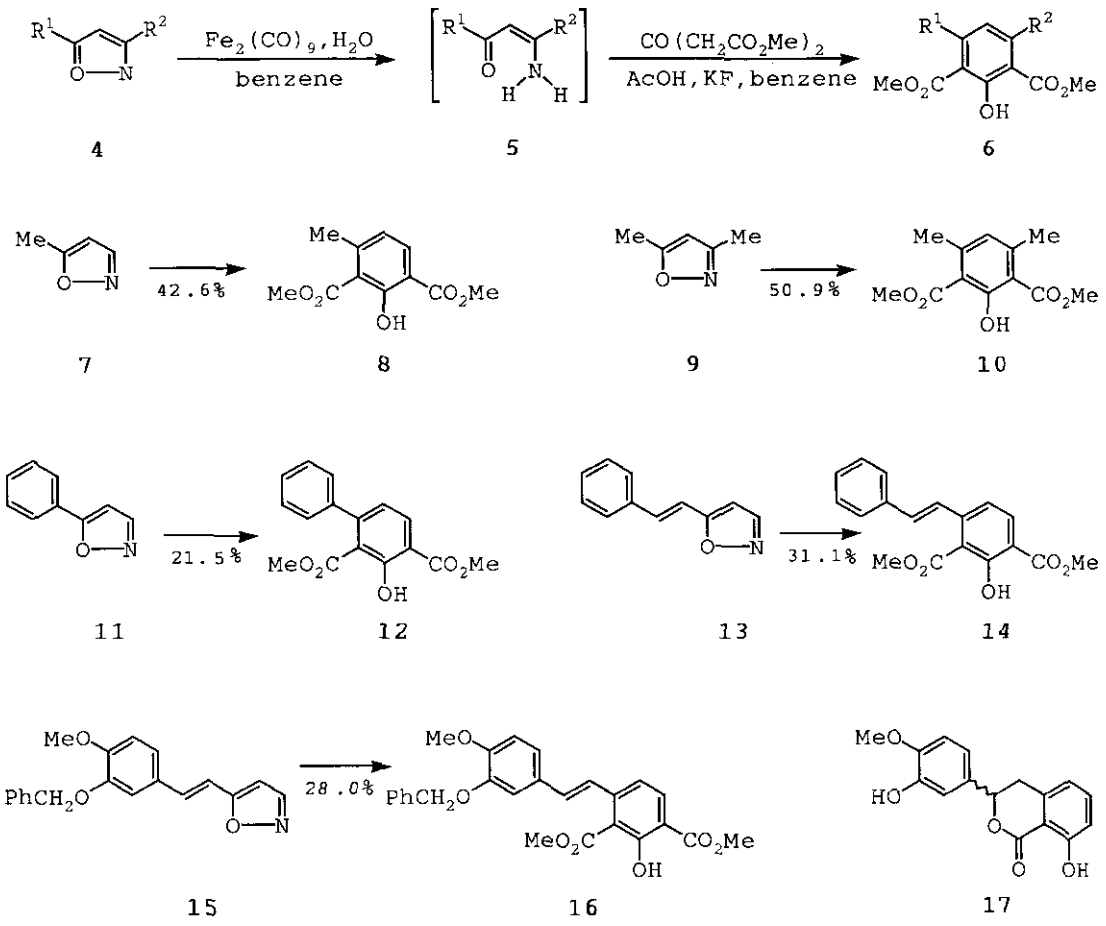
Scheme 1

inhibitory effect on the growth of hypocotyl and root of lettuce seedlings on (+)-mellein,[5] an antibacterial activity and an attraction activity of female carpenter ants on (-)-mellein.[4,6,7] Although various syntheses of melleins[8] including chiral one[9] were reported, we synthesized of (±)-, (+)-, and (-)-mellein (**1**, **2**, and **3**) utilizing an annelation reaction of isoxazoles with dimetyl 3-oxoglutarate in connection with our previous report[10] on the annelation reactions of enaminones with dimethyl 3-oxoglutarate.

It was well established that isoxazole undergoes reductive cleavage to give β-enaminones by catalytic hydrogenation,[11] reduction by Na in alcohol,[11] and reactions with transition metal carbonyls such as $Mo(CO)_6$,[12] $Fe(CO)_5$ with hν,[13] and $Fe_2(CO)_9$ in the presence of water.[13] Therefore, isoxazoles can be considered to be equivalent synthon of β-enaminones or β-diketones in masked form. Though a few attempts for the synthesis of phenols utilizing this property of isoxazoles have been reported already,[14] the reactions of isoxazoles with the metal carbonyls have become of interest because of its *in situ* generation of the enaminones in connection with an aromatic annelation reaction of the enaminones with dimethyl 3-oxoglutarate.[10] Thus, the reactions of dimethyl 3-oxoglutarate with the enaminones (**5**) generated by the reaction of the isoxazoles (**4**) with $Fe_2(CO)_9$ in the presence of water were investigated. Preliminary annelation reactions were investigated on the isoxazoles (**7**,[15] **9**,[15] **11**, **13**, and **15**). Among of these isoxazoles **11**, oil, **13**, mp 39-41°C, and **15**, mp 128-130°C, were synthesized from the corresponding enaminones[10] with $NH_2OH{\cdot}HCl$ and K_2CO_3.

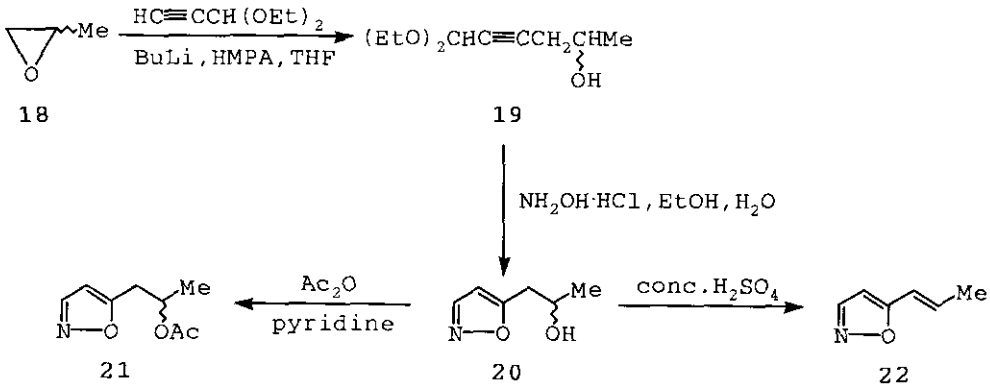
The aromatic annelation reaction was performed successfully in one flask as follows. To a benzene solution of the isoxazole, $Fe_2(CO)_9$ and water were



Scheme 2

added under a nitrogen atmosphere and the whole was stirred at 45°C for 30 min. And then, a solution of dimethyl 3-oxoglutarate, KF, and AcOH in benzene was added to the above solution and refluxed for 12 h removing water with water separator. The dimethyl 2-hydroxy-1,3-benzenedicarboxylates (**8**), mp 53-54°C, (**10**), mp 110-111°C, (**12**), mp 108-109°C, (**14**), mp 151-152°C, and (**16**), mp 128-130°C, were obtained from the corresponding isoxazoles by the standard reaction method in yields shown in Scheme 2. These results provide

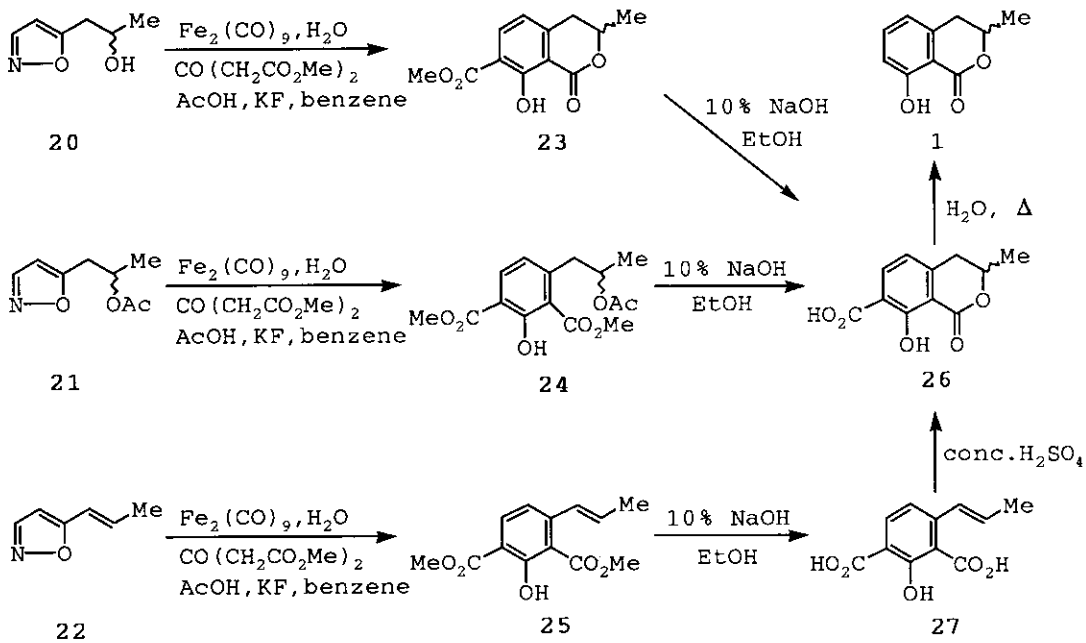
a new aromatic annelation method in the synthesis of β-polyketide derived natural products, in particular, in the synthesis of naturally occurring (±)-phyllodulcin (17)[16] in view of the result of 15 to 16.[10] Further, these results indicate the potential of this method in the synthesis of (±)-mellein (1) from isoxazoles (20, 21, and 22) with dimethyl 3-oxoglutarate.



Scheme 3

The coupling reaction of (±)-propylene oxide (18) with propiolaldehyde diethyl acetal in the presence of butyllithium (BuLi) and hexamethylphosphoric triamide (HMPA) in tetrahydrofuran (THF) gave coupling product (19), oil, in 90.6% yield, which was treated with $NH_2OH·HCl$ in ethanol and water to yield the isoxazole (20), oil, in 86.8% yield. The isoxazole (20) was converted to 21, oil, by acetylation with acetic anhydride in pyridine (63.5%) and to 22, oil, by dehydration with concentrated H_2SO_4 (70.5%). The reaction of isoxazoles (20, 21, and 22) with dimethyl 3-oxoglutarate under the conditions mentioned above, afforded the condensation products (23), mp 144-145°C, (24), oil, and (25), oil, in yields of 36.9%, 30.3%, and 32.5%, respectively. The compounds (23) and (24) were hydrolysed with 10% NaOH in ethanol to give the same acid (26), mp 243-245°C, in 85.5% and 97.9% yield. The compound (25) was hydrolysed with 10% NaOH in ethanol to give the

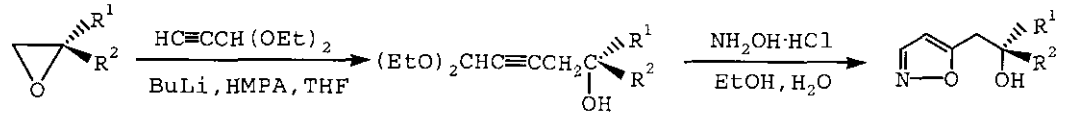
dibasic acid (**27**), mp 247-249°C, in 87.8% yield, which was treated with concentrated H_2SO_4 to yield the acid (**26**) in 80.4% yield. The acid (**26**) was decarboxylated by heating it in a sealed tube in water at 180°C to give (±)-mellein (**1**), mp 35-36°C, in 94.3% yield, which gave the same physical data with those reported for the synthetic (±)-mellein.[8]



Scheme 4

In the next place, we plan to synthesize (+)- and (-)-mellein (**2** and **3**) *via* the isoxazoles (**32**) and (**33**), using (-)- and (+)-propylene oxide (**28** and **29**) as a chiral template. The coupling product (**30**), oil, $[\alpha]_D$ +10° (*c*=0.85, $CHCl_3$), of epoxide (**28**) with propiolaldehyde diethyl acetal, was treated with $NH_2OH{\cdot}HCl$ to yield the isoxazole (**32**), oil, $[\alpha]_D$ +29° (*c*=1.00, $CHCl_3$), followed by condensation with dimethyl 3-oxoglutarate to give the ester (**34**), mp 134-135°C, $[\alpha]_D$ +117° (*c*=1.00, $CHCl_3$). The compound (**34**) was hydrolysed with 10% NaOH in ethanol to give the acid (**36**), mp 232-233°C,

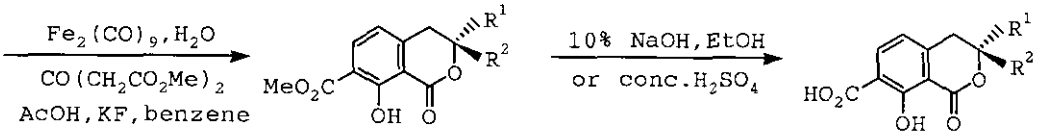
$[\alpha]_D$ +133° (*c*=1.01, MeOH), which was decarboxylated to give (+)-mellein (**2**), mp 38.5-39.5°C, $[\alpha]_D$ +81° (*c*=1.01, $CHCl_3$). Since the value of specific rotation of this synthetic **2** was lower than that of the natural product, the ester (**34**) was hydrolysed with concentrated H_2SO_4 to the acid (**36**), mp 234-235°C, $[\alpha]_D$ +165° (*c*=0.51, MeOH), in 84.2% yield, which was decarboxylated to afford (+)-mellein (**2**), mp 51-52°C, $[\alpha]_D$ +102° (*c*=1.00, $CHCl_3$) (lit.,[17] mp 51.5-52°C, $[\alpha]_D$ +102° (*c*=1.07, $CHCl_3$)). All physical data of synthetic **2** were identical with those of the natural product.[17]



28 R^1=Me, R^2=H
29 R^1=H, R^2=Me

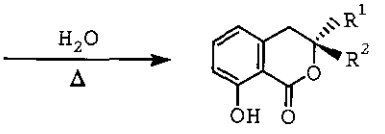
30 R^1=Me, R^2=H
31 R^1=H, R^2=Me

32 R^1=Me, R^2=H
33 R^1=H, R^2=Me



34 R^1=Me, R^2=H
35 R^1=H, R^2=Me

36 R^1=Me, R^2=H
37 R^1=H, R^2=Me



2 R^1=Me, R^2=H
3 R^1=H, R^2=Me

Scheme 5

Similarly, the synthesis of (-)-mellein (**3**), mp 51-52°C, $[\alpha]_D$ -94° (*c*=0.69, $CHCl_3$) (lit.,[18] mp 56°C, $[\alpha]_D$ -103° (*c*=1.00, $CHCl_3$)) was achieved starting from the coupling product (**31**), oil, $[\alpha]_D$ -10° (*c*=0.99, $CHCl_3$), which was obtained from (+)-propylene oxide (**29**) and propiolaldehyde diethyl acetal, through the isoxazole (**33**), oil, $[\alpha]_D$ -31° (*c*=0.60, $CHCl_3$), the ester (**35**), mp 134-135.5°C, $[\alpha]_D$ -117° (*c*=1.00, $CHCl_3$), and the acid (**37**), mp 231-232°C, $[\alpha]_D$ -155° (*c*=0.53, MeOH). All physical data of synthetic **3** were identical with those of the natural product.[18]

These syntheses of (±)-, (+)-, and (-)-mellein (**1**, **2**, and **3**) consist of five steps, including one hydrolysis step, from (±)-, (-), and (+)-propylene oxide (**18**, **28**, and **29**) and give overall yield of *ca*. 23%.

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 or EX-90 spectrometer with tetramethylsilane as an internal standard, ms with a JEOL JMS-D 300 spectrometer, and optical rotations with a JASCO DIP-140 polarimeter. Elemental analyses were done by Mrs. A. Ono, Kissei Pharmaceutical Company Ltd., Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merk Kieselgel G nach Stahl were used for column chromatography and tlc, respectively.

Preparation of isoxazoles 11, 13, and 15 from the corresponding enaminones

NH_2OH·HCl (1.3 g, 18 mmol) and anhydrous K_2CO_3 (1.3 g, 9 mmol) were added to

a solution of corresponding enaminones (7 mmol) in ethanol (23 ml) and the whole was refluxed for 6 h. The reaction mixture was concentrated under a vacuum, poured into water, and extracted with chloroform. The organic layer was washed with dilute HCl and water, then dried over dry Na_2SO_4 and concentrated. A solution of the residue in benzene was subjected to silica gel chromatography.

5-Phenylisoxazole (11)

Enaminone: 3-Dimethylamino-1-phenyl-2-propenone.[10] Colorless oil (88.2%). Ir (film) cm^{-1}: 1604, 1585, 1564. Nmr ($CDCl_3$) δ: 6.36(1H, d, J=2 Hz, olefinic H), 7.10-7.77(5H, m, aromatic H), 8.82(1H, d, J=2 Hz, olefinic H). This product (11) was used in the next step without further investigation.

5-(2-Phenylethenyl)isoxazole (13)

Enaminone: 1-Dimethylamino-5-phenyl-1,4-pentadien-3-one.[10] Colorless crystals (51.5%), mp 39-41°C. Ir (film) cm^{-1}: 1650, 1604, 1587, 1563, 1507. Nmr ($CDCl_3$) δ: 6.08(1H, d, J=2 Hz, olefinic H), 6.74(1H, d, J=16 Hz, olefinic H), 6.98-7.38(6H, m, aromatic and olefinic H), 7.98(1H, d, J=2 Hz, olefinic H). High ms m/z Calcd for $C_{11}H_9NO$ (M^+): 171.0685. Found: 171.0698.

5-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]isoxazole (15)

Enaminone: 5-(3-Benzyloxy-4-methoxyphenyl)-1-dimetylamino-1,4-pentadien-3-one.[10] Colorless crystals (56.8%), mp 128-130°C (MeOH). Ir (KBr) cm^{-1}: 1645, 1600, 1580, 1560, 1510. Nmr ($CDCl_3$) δ: 3.83(3H, s, OMe), 5.08(2H, s, methylene H), 6.08(1H, d, J=1.8 Hz, olefinic H), 6.62(1H, d, J=16 Hz, olefinic H), 6.74(1H, d, J=8.4 Hz, aromatic H), 6.88-7.40(8H, m, aromatic and olefinic H), 8.04(1H, d, J=1.8 Hz, olefinic H). High ms m/z Calcd for $C_{19}H_{17}NO_3$ (M^+): 307.1207. Found: 307.1212. Anal. Calcd for $C_{19}H_{17}NO_3$:

C,74.25; H,5.57; N,4.56. Found: C, 74.15; H, 5.57; N, 4.30.

Reactions of Isoxazoles with Dimethyl 3-Oxoglutarate

$Fe_2(CO)_9$ (3.6 g, 1 mmol) and water (90 mg) were added to a solution of the isoxazole (5 mmol) and the whole was heated at 45°C for 30 min under a nitrogen atmosphere. Dimethyl 3-oxoglutarate (1.74 g, 10 mmol), KF (580 mg, 1 mmol), and AcOH (1.2 g) were then added and the reaction mixture was heated under reflux with water separation by means of a Dean-Stark trap. After reflux for 12 h, the mixture was concentrated under vacuum, poured into water, acidified with dilute HCl, and extracted with chloroform. The organic layer was washed with saturtated $NaHCO_3$ and water, then dried over dry Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography. The benzene eluate gave the condensation product as crystals (ether-hexane).

Dimethyl 2-Hydroxy-4-methyl-1,3-benzenedicarboxylate (8)

Colorless crystals (42.6%), mp 53-54°C. Ir (KBr) cm^{-1}: 1725, 1663, 1620. Nmr ($CDCl_3$) δ: 2.20(3H, s, Me), 3.78(6H, s, CO_2Me), 6.53(1H, d, J=7.8 Hz, aromatic H), 7.56(1H, d, J=7.8 Hz, aromatic H), 10.91(1H, s, OH). This and following compounds (**10**, **12**, **14**, and **16**) were identified with authentic sample[10] by mixed mp and ir, nmr comparisons.

Dimethyl 2-Hydroxy-4,6-dimethyl-1,3-benzenedicarboxylate (10)

Colorless crystals (50.9%), mp 110-111°C. Ir (KBr) cm^{-1}: 1715, 1655, 1608. Nmr ($CDCl_3$) δ: 2.35(6H, s, Me), 3.86(6H, s, CO_2Me), 6.45(1H, s, aromatic H), 11.71(1H, s, OH).

Dimethyl 2-Hydroxy-4-phenyl-1,3-benzenedicarboxylate (12)

Colorless crystals (21.5%), mp 108-109°C. Ir (KBr) cm^{-1}: 1725, 1668, 1610. Nmr ($CDCl_3$) δ: 3.58(3H, s, CO_2Me), 3.88(3H, s, CO_2Me), 6.77(1H, d, J=7.8 Hz, aromatic H), 7.24(5H, s, aromatic H), 7.75(1H, d, J=7.8 Hz, aromatic H), 11.00(1H, s, OH).

Dimethyl 2-Hydroxy-4-(2-phenylethenyl)-1,3-benzenedicarboxylate (14)

Yellow crystals (31.1%), mp 151-152°C. Ir (Nujol) cm^{-1}: 1713, 1664, 1635, 1613. Nmr ($CDCl_3$) δ: 3.93(3H, s, CO_2Me), 3.96(3H, s, CO_2Me), 7.03(2H, s, olefinic H), 7.13-7.43(6H, m, aromatic H), 7.74(1H, d, J=8.0 Hz, aromatic H), 11.00(1H, br, OH).

Dimethyl 4-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]-2-hydroxy-1,3-benzenedicarboxylate (16)

Orange colored crystals (28.0%), mp 128-130°C. Ir (Nujol) cm^{-1}: 1713, 1660, 1620, 1589, 1510. Nmr ($CDCl_3$) δ: 3.92(3H, s, OMe), 3.96(6H, s, OMe), 5.20(2H, s, methylene H), 6.93-7.53(11H, m, aromatic and olefinic H), 7.80(1H, d, J=8 Hz, aromatic H), 11.50(1H, s, OH).

(±)-6,6-Diethoxy-4-hexyn-2-ol (19)

A solution of 1.6 M BuLi in hexane (4.9 ml, 8 mmol) and a solution of 18 (2.3 g, 40 mmol) in THF (5 ml) were successively added dropwise to a stirred solution of propiolaldehyde diethyl acetal (0.97 g, 8 mmol) and HMPA (6.3 ml) in THF (5 ml) at -30°C under a nitrogen atmosphere. After 2 h, the whole was stirred for 30 min at room temperature. The reaction mixture was quenched with saturated NH_4Cl and then extracted with ethyl acetate. The organic layer was washed with saturated NaCl, then dried over dry Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography. The

elution with 25% ethyl acetate in hexane gave 1.28 g (90.6%) of **19**, as a colorless oil. Ir (film) cm^{-1}: 3400, 2230. Nmr ($CDCl_3$) δ: 1.23(6H, t, J=7.3 Hz, Me), 1.28(3H, d, J=6.4 Hz, Me), 1.99(1H, br, OH), 2.42(2H, dd, J=6.6, 1.2 Hz, methylene H), 3.70(5H, m, methylene and methine H), 5.26(1H, t, J=1.7 Hz, methine H). This product (**19**) was used in the next step without further investigation.

The following compounds (**30**) and (**31**) were prepared from **28** and **29** in a similar manner described in **19**.

(+)-6,6-Diethoxy-4-hexyn-2-ol (30)

Colorless oil (90.6%). $[\alpha]_D$ +10° (*c*=0.85, $CHCl_3$).

(-)-6,6-Diethoxy-4-hexyn-2-ol (31)

Colorless oil (90.6%). $[\alpha]_D$ -10° (*c*=0.99, $CHCl_3$).

(±)-5-(2-Hydroxypropyl)isoxazole (20)

$NH_2OH \cdot HCl$ (560 mg, 8 mmol) was added to a solution of **19** (1.25 g, 7 mmol) in ethanol (15 ml) and water (3 ml) and the whole was refluxed for 1 h. The reaction mixture was concentrated under a vacuum and extracted with ether. The organic layer was dried over dry Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography. The elution with 50% ethyl acetate in hexane gave 740 mg (86.8%) of **20**, as a colorless oil. Ir (film) cm^{-1}: 3380, 1600. Nmr ($CDCl_3$) δ: 1.29(3H, d, J=6.1 Hz, Me), 2.95(2H, d, J=6.1 Hz, methylene H), 4.21(1H, sextet, J=6.1 Hz, methine H), 6.11(1H, d, J=1.7 Hz, olefinic H), 8.18(1H, d, J=1.7 Hz, olefinic H). CI ms m/z: 128 (M^++1).

The following compounds (**32**) and (**33**) were prepared from **30** and **31** in a similar manner described in **20**.

(+)-5-(2-Hydroxypropyl)isoxazole (32)

Colorless oil (86.8%). $[\alpha]_D$ +29° (c=1.00, $CHCl_3$).

(-)-5-(2-Hydroxypropyl)isoxazole (33)

Colorless oil (86.8%). $[\alpha]_D$ -31° (c=0.60, $CHCl_3$).

(±)-5-(2-Acetoxypropenyl)isoxazole (21)

Acetic anhydride (3 ml, 32 mmol) was added to a solution of **20** (200 mg, 1.6 mmol) in dry pyridine (1 ml) and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$, dilute HCl, and water, then dried over dry Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography. The elution with 25% ethyl acetate in hexane gave 169 mg (63.5%) of **21** as a colorless oil. Ir (film) cm^{-1}: 1740, 1600. Nmr ($CDCl_3$) δ: 1.29(3H, d, J=6.4 Hz, Me), 2.03(3H, s, OCOMe), 3.06(2H, d, J=6.1 Hz, methylene H), 5.21(1H, sextet, J=6.1, 6.4 Hz, methine H), 6.07(1H, d, J=1.6 Hz, olefinic H), 8.17(1H, d, J=1.6 Hz, olefinic H). CI ms m/z: 170(M^++1).

5-Propenylisoxazole (22)

A mixture of **20** (200 mg, 1.6 mmol) and concentrated H_2SO_4 (1 ml) was stirred at 100°C for 1.5 h. The reaction mixture was poured into ice-water, neutralized with saturated $NaHCO_3$, and extracted with ether. The organic layer was washed with saturated NaCl, dried over dry Na_2SO_4 and concentrated to yield 121 mg (70.5%) of **22** as a colorless oil. Nmr ($CDCl_3$) δ: 1.93(3H, d, J=5.6 Hz, Me), 6.07(1H, d, J=1.3 Hz, olefinic H), 6.39(2H, m, olefinic H), 8.15(1H, d, J=1.3 Hz, olefinic H).

The compound (**22**) was used in the next step without further purification because of its volatility.

The compounds (23, 34, 35, 24, and 25) were prepared from 20, 32, 33, 21, and 22 in a similar manner described in reactions of isoxazoles with dimethyl 3-oxoglutarate.

(±)-3,4-Dihydro-8-hydroxy-7-methoxycarbonyl-3-methylisocoumarin(23)

Colorless flaky crystals (36.9%), mp 144-145°C (ether-hexane). Ir (Nujol) cm^{-1}: 1720, 1655, 1610. Nmr ($CDCl_3$) δ: 1.54(3H, d, J=6.4 Hz, Me), 2.97(2H, d, J=7.1 Hz, methylene H), 3.94(3H, s, CO_2Me), 4.72(1H, m, methine H), 6.75(1H, d, J=7.9 Hz, aromatic H), 8.04(1H, d, J=7.9 Hz, aromatic H), 12.17(1H, s, OH). Ms m/z: 236 (M^+). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.09; H, 5.18.

(+)-3,4-Dihydro-8-hydroxy-7-methoxycarbonyl-3-methylisocoumarin(34)

Colorless flaky crystals (36.9%), mp 134-135°C (ether-hexane). $[\alpha]_D$ +117° (*c*=1.00, $CHCl_3$).

(-)-3,4-Dihydro-8-hydroxy-7-methoxycarbonyl-3-methylisocoumarin(35)

Colorless flaky crystals (36.9%), mp 134-135°C (ether-hexane). $[\alpha]_D$ -117° (*c*=1.00, $CHCl_3$).

(±)-Dimethyl 4-(2-Acetoxypropyl)-2-hydroxy-1,3-benzenedicarboxylate (24)

Colorless oil (30.3%). Ir (film) cm^{-1}: 1740, 1680, 1630, 1580, 1500. Nmr ($CDCl_3$) δ: 1.22(3H, d, J=6.4 Hz, Me), 1.99(3H, s, OCOMe), 2.89(2H, m, methylene H), 3.70(3H, d, J=2.9 Hz, CO_2Me), 3.96(3H, d, J=1.5 Hz, CO_2Me), 5.14(1H, m, methine H), 6.80(1H, d, J=8.3 Hz, aromatic H), 7.81(1H, d, J=8.3 Hz, aromatic H), 11.18(1H, s, OH). High ms m/z Calcd for $C_{15}H_{18}O_5$ (M^+): 310.1053. Found: 310.1076.

Dimethyl 2-Hydroxy-4-propenyl-1,3-benzenedicarboxylate (25)

Red oil (32.5%). Ir (film) cm^{-1}: 1730, 1680, 1650, 1620, 1570. Nmr ($CDCl_3$) δ: 1.90(3H, d, J=4.8 Hz, Me), 3.94(3H, s, CO_2Me), 3.96(3H, s, CO_2Me), 6.38(2H, m, olefinic H), 7.03(1H, d, J=8.3 Hz, aromatic H), 7.78(1H, d, J=8.3 Hz, aromatic H), 11.15(1H, s, OH). High ms m/z Calcd for $C_{13}H_{14}O_5$ (M^+): 250.0842. Found: 250.0853.

2-Hydroxy-4-propenyl-1,3-benzenedicarboxylic Acid (27)

10% NaOH (3 ml, 7.5 mmol) was added to a solution of 25 (50 mg, 0.2 mmol) in ethanol (5 ml) and the whole was refluxed for 2 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was saturated NaCl, and then dried over dry Na_2SO_4 and concentrated. The residue was recrystallized from ethyl acetate to yield 39 mg (87.8%) of 27 as colorless needles, mp 247-249°C. Ir (Nujol) cm^{-1}: 1715, 1665, 1650, 1615. Nmr ($CDCl_3$) δ: 1.90(3H, d, J=5.1 Hz, Me), 6.39(1H, m, olefinic H), 6.48(4H, br, olefinic H, OH, CO_2H), 6.65(1H, d, olefinic H), 7.03(1H, d, J=8.5 Hz, aromatic H), 7.82(1H, d, J=8.5 Hz, aromatic H). Ms m/z: 222 (M^+). Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.31; H, 4.62.

(±)-3,4-Dihydro-8-hydroxy-3-methyl-7-isocoumarincarboxylic Acid (26)

a) The compound 26 was prepared from 23 and 24 in a similar manner described in 27. Colorless needles (85.5% from 23 and 97.9% from 24), mp 243-245°C (ethyl acetate). Ir (film) cm^{-1}: 1680, 1620, 1575, 1505. Nmr ($CDCl_3$) δ: 1.52(3H, d, J=6.5 Hz, Me), 2.97(2H, d, J=7.3 Hz, methylene H), 4.69(1H, m, methine H), 6.08(2H, br, CO_2H and OH), 6.79(1H, d, J=7.8 Hz, aromatic H), 8.08(1H, d, J=7.8 Hz, aromatic H). Ms m/z: 222 (M^+). Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.20; H, 4.56.

b) A mixture of **27** (10 mg, 0.045 mmol) and concentrated H_2SO_4 (0.5 ml) was stirred at 0°C for 3 h. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over dry Na_2SO_4 and concentrated. The residue was recrystallized from ethyl acetate to yield 8 mg (80.4%) of **26**.

(+)-3,4-Dihydro-8-hydroxy-3-methyl-7-isocoumarincarboxylic Acid (36)

a) The compound (**36**) was prepared from **34** in a similar manner described in **27**. Colorless needles (85.5%), mp 232-233°C (ethyl acetate), $[\alpha]_D$ +133° (*c*=1.01, MeOH).

b) A mixture of **34** (80 mg) and cocentrated H_2SO_4 (2.5 ml) was stirred at 70°C for 7 h. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over dry Na_2SO_4 and concentrated. The residue was recrystallized from ethyl acetate to yield 63 mg (84.2%) of **36** as colorless needles, mp 234-235°C. $[\alpha]_D$ +165° (*c*=0.51, MeOH).

The compound (**37**) was prepared from **35** in a similar manner described in b) of **36**.

(-)-3,4-Dihydro-8-hydroxy-3-methyl-7-isocoumarincarboxylic Acid (37)

Colorless needles (84.2%), mp 231-232°C (ethyl acetate), $[\alpha]_D$ -155° (*c*=0.53, MeOH).

(±)-Mellein (1)

A mixture of **26** (1 g) and water (100 ml) was heated at 180°C in a sealed tube for 40 h. The reaction mixture was extracted with ethyl acetate. The

organic layer was washed with saturated $NaHCO_3$, dried over dry Na_2SO_4 and concentrated. The residue was recrystallized from ether-hexane to yield 756 mg (94.3%) of **1** as colorless needles, mp 35-36°C (lit.,[8] mp 37-38°C). Ir (KBr) cm^{-1}: 1680, 1625, 1590, 1500. Nmr ($CDCl_3$) δ: 1.53(3H, d, J=6.4 Hz, Me), 2.93(2H, d, J=7.4 Hz, methylene H), 4.71(1H, m, methine H), 6.69(1H, dd, J=7.3, 1.0 Hz, aromatic H), 6.89(1H, d, J=8.3 Hz, aromatic H), 7.41(1H, dd, J=7.3, 8.3 Hz, aromatic H), 11.03(1H, s, OH). High ms m/z Calcd for $C_{10}H_{10}O_3$ (M^+): 178.0630. Found: 178.0625.

(+)-Mellein (2)

a) The compound (2) was prepared from **36**, synthesized by a) of **36**, in a similar manner described in **1**. Colorless needles (94.3%), mp 38.5-39.5°C (ether-hexane), $[\alpha]_D$ +81° (*c*=1.01, $CHCl_3$).

b) The compound (2) was prepared from **36**, synthesized by b) of **36**, in a similar manner described in **1**. Colorless needles (94.3%), mp 51-52°C (ether-hexane), $[\alpha]_D$ +102° (*c*=1.00, $CHCl_3$). (lit.,[17] mp 51.5-52°C, $[\alpha]_D$ +102° (*c*=1.07, $CHCl_3$)).

The following compound (3) was prepared from **37**, synthesized by b) of **36**, in a similar manner described in **1**.

(-)-Mellein (3)

Colorless needles (94.3%), mp 51-52°C (ether-hexane), $[\alpha]_D$ -94° (*c*=0.69, $CHCl_3$). (lit.,[18] mp 56°C, $[\alpha]_D$ -103° (*c*=1.00, $CHCl_3$)).

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