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Total Synthesis of (±)-Silybin, an Antihepatotoxic Flavonolignan

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The flavonolignan (±)-silybin (**1**), having an antihepatotoxic activity, has been synthesized *via* a key intermediate (**9**), which was prepared from readily available starting materials (**2**) and (**3**). The aldehyde (**9**) was transformed to the methoxymethyl ether (**10**), which was condensed with an acetophenone derivative (**11**) to yield the chalcone (**12**). Oxidation of the chalcone (**12**) with alkaline hydrogen peroxide, followed by treatment of the resulting epoxide (**13**) with hydrochloric acid afforded (±)-**1**.

Keywords——flavonolignan; silybin; *Silybum marianum*; benzodioxane; flavononol; taxifolin

The flavonolignan silybin (**1**) has an interesting antihepatotoxic activity and was isolated from the fruits of *Silybum marianum*, which has been used as a folk medicine in Jammu aur Kashmir[1] and Europe.[2] The structure (**1**) of silybin was established in 1975 on the basis of degradative evidence[3] and a synthesis of dehydrosilybin pentamethyl ether.[4] The absolute configuration at C-2 and C-3 of the flavanonol ring in silybin was established[5a] as 2*R* and 3*R*, and furthermore the *trans* configuration of the benzodioxane ring was also demonstrated. Silybin was shown[5a] to be a diastereoisomeric mixture of *ca.* 1 : 1 composition at C-12 and C-13. Recently, Merlini and co-workers[5b,c] have reported the biomimetic synthesis of natural silybin by silver oxide promoted oxidative coupling of coniferyl alcohol and (2*R*,3*R*)-dihydroquercetin (taxifolin). In this synthesis, it is a disadvantage that silybin was obtained along with a nearly equal amount of isosilybin (**14**), a regioisomer of silybin.

We wish to report here a regiospecific total synthesis of silybin from readily available starting materials (**2** and **3**). Our synthetic design is based upon construction of the substituted benzodioxane ring, followed by formation of the flavanonol moiety.

In order to synthesize silybin, 3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (**9**) is the key intermediate, and this has already been prepared by oxidative coupling of protocatechualdehyde and coniferyl alcohol by Merlini *et al.*[5c] We have synthesized **9** in a different way as follows.

Ethyl 2-bromo-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (**3**), obtained according to the reported procedure,[6] was reacted with 4-hydroxy-3-(methoxymethoxy)benzaldehyde (**2**)[7] in *N*,*N*-dimethylformamide (DMF) containing potassium *tert*-butoxide at room temperature to give a keto ether (**4**). This compound was readily converted into the corresponding acetal (**5**) by heating with trimethoxymethane and ammonium chloride in methanol. Reduction of **5** with sodium borohydride in ethanol at room temperature afforded the diol (**6**) in good yield. The infrared (IR) spectrum of **6** lacked both carbonyl bands (1675 and 1750 cm^{-1}) which were found in the compound (**5**), and showed hydroxyl bands at 3550 and 3500 cm^{-1}. On thin-layer chromatography (TLC), **6** gave a single spot in various solvents, and all signals in the proton nuclear magnetic resonance (^{1}H-NMR)

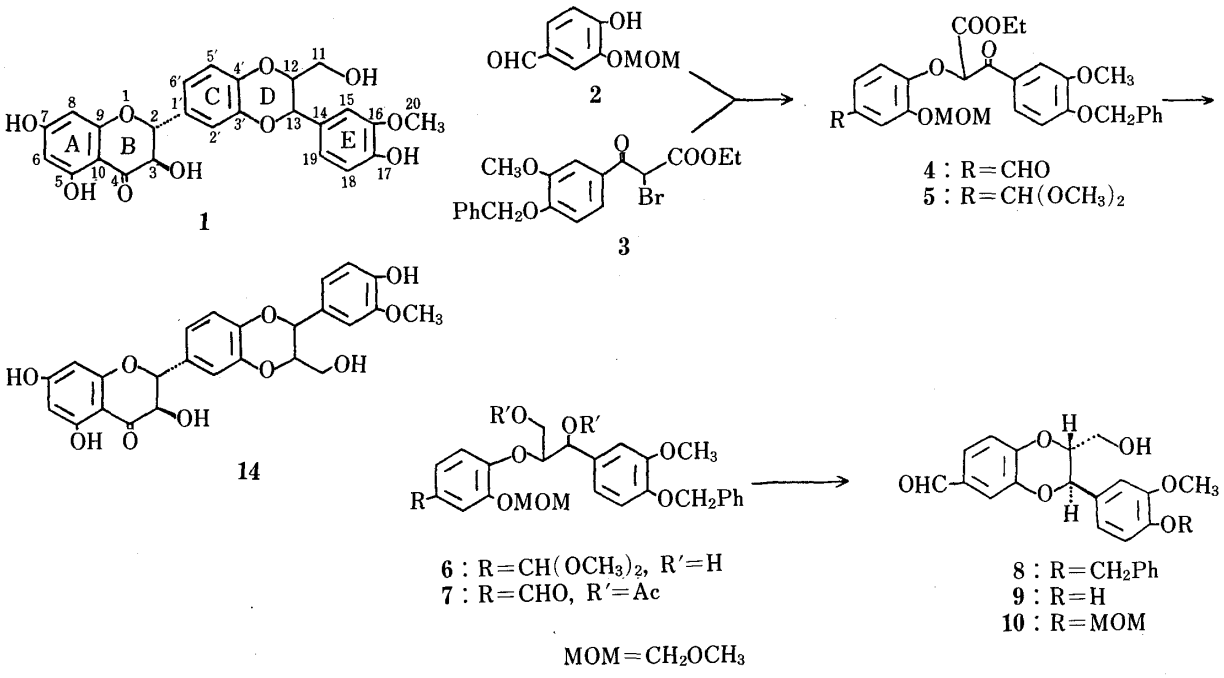

Chart 1

spectrum were readily assignable; doublet signals ($J=6$ Hz) due to the benzyl proton at δ 4.93, hydroxymethyl proton at δ 3.72 (multiplet), and a methine proton at δ 4.20. Its acetyl derivative (**7**) was also homogeneous on the basis of the ^{1}H-NMR spectrum and TLC behavior in various solvents. Thus, the diol (**6**) is considered to be sterically homogeneous, though the relative configuration between the *sec*-hydroxyl and hydroxymethyl groups remains unsolved. Hänsel and co-workers have reported[7] that the similar reduction of ethyl 2-[4-dimethoxymethyl-2-(methoxymethoxy)phenoxy]-3-(3,4-dimethoxyphenyl)-3-oxopropionate afforded ethyl 2-[4-formyl-2-methoxymethoxy)phenoxy]-3-(3,4-dimethoxyphenyl)-3-hydroxypropionate as a sole product in about 80% yield. On treatment with 5% sulfuric acid in acetic acid at 70 °C for 30 min, **6** was cyclized to produce the desired benzodioxane derivative (**8**) in 70% yield. The mass spectrum (MS) of **8** showed the molecular peak at *m/z* 406 and displayed the characteristic fragment ions at *m/z* 136 and 270, which are considered to be formed by a retro Diels–Alder reaction of the dioxane ring.[3] The ^{1}H-NMR spectrum exhibited a benzylic proton signal at δ 4.96 as a doublet ($J=8$ Hz), which is attributed to *trans* configuration[7] of the substituents in the dioxane system. Hänsel *et al.*[7] reported that the similar acid-catalyzed cyclization of ethyl 2-[4-formyl-2-methoxymethoxy)phenoxy]-3-(3,4-dimethoxyphenyl)-3-hydroxypropionate with sulfuric acid gave the *trans*-benzodioxane derivative as a major product together with the *cis*-derivative as a minor product. In our reaction, however, no *cis* product was formed. The benzyl group of **8** was removed by hydrogenolysis under atmospheric pressure of hydrogen in the presence of 5% palladized charcoal in a mixture of ethanol and ethyl acetate to afford **9**, the ^{1}H-NMR spectrum of which was identical with that of an authentic sample.[5c] The overall yield of the aldehyde (**9**) from **2** was 27%.

The final conversion of **9** to silybin (**1**) was accomplished by application of the method for the efficient stereocontrolled synthesis of (2*R**,3*R**)-taxifolin, which was recently reported by Onda *et al.*[8]

The aldehyde (**9**) was easily converted to the methoxymethyl ether (**10**) in 79% yield. Condensation of 2,4,6-trimethoxymethoxyacetophenone (**11**)[9] with **10** in the presence of sodium hydroxide[10] provided the expected chalcone (**12**) in 94% yield. In the ^{1}H-NMR

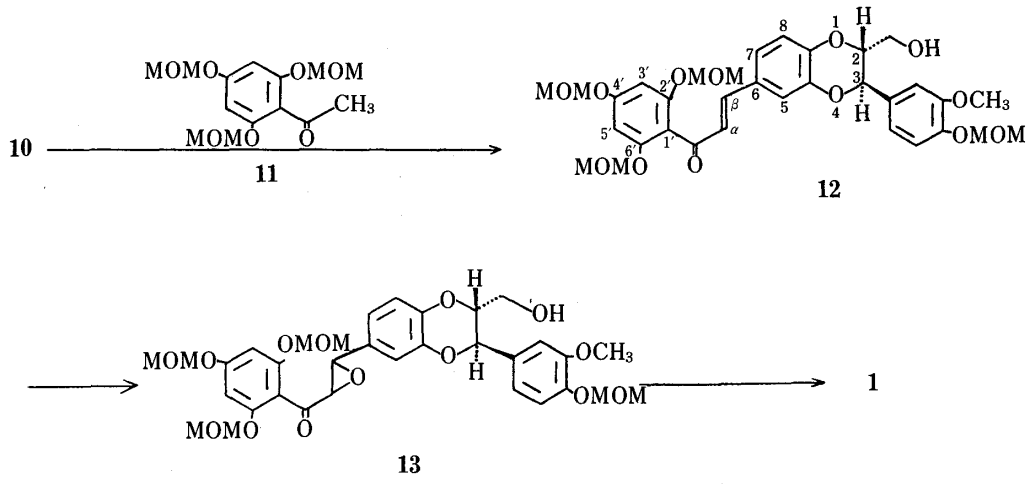

Chart 2

spectrum, the coupling constant between the signals of two vinylic protons newly appearing at δ 6.83 and 7.30 is 16 Hz, which indicates the formation of a *trans* double bond. Alkaline hydrogen peroxide oxidation of **12** gave an epoxide (**13**)[11] in 97% yield. The ^{1}H-NMR spectrum of **13** revealed signals at δ 3.86 and 3.94 due to oxide ring protons as a doublet with vicinal coupling constants of 2 Hz. This clearly showed that the stereochemistry of the epoxide system was *trans*.[12] The obtained epoxide (**13**) underwent deprotection and cyclization upon treatment with hydrochloric acid in methanol at 70 °C to afford racemic silybin[13] in 63% yield.

Experimental

All melting points are uncorrected. Column chromatography was run on Merck Silica gel 60 (70—230 mesh) and TLC was performed on glass plates precoated with Kieselgel 60 F_{254} (Merck). MS were recorded on a Hitachi M-52 spectrometer and high-resolution MS on a Hitachi M-80 spectrometer. IR spectra were obtained on a JASCO IRA-3 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PS-100 nuclear magnetic resonance spectrometer and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad).

Ethyl 2-[4-Formyl-2-(methoxymethoxy)phenoxy]-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (4)——4-Hydroxy-3-(methoxymethoxy)benzaldehyde (**2**)[7] (3.20 g) in DMF (10 ml) was added dropwise to a stirred suspension of *tert*-BuOK (2.07 g) in DMF (20 ml) at room temperature. The mixture was stirred for 1 h, then a solution of ethyl 2-bromo-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (**3**)[6] (7.20 g) in DMF (20 ml) was added dropwise to the reaction mixture under ice-cooling, and stirring was continued for a further 2 h at room temperature. The mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a solid (**4**). This crude solid was recrystallized from EtOH. Colorless needles. mp 108—109 °C (5.93 g) (66%). *Anal.* Calcd for $C_{28}H_{28}O_9$: C, 66.13; H, 5.55. Found: C, 66.02; H, 5.47. MS *m/z*: 508 (M^+), 477, 463, 445, 340, 328, 285. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1695, 1595. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.43 (3H, s, $OCH_2O\underline{CH_3}$), 3.93 (3H, s, OCH_3), 4.28 (2H, q, J=7 Hz, $OCH_2\underline{CH_3}$), 5.20 (2H, s, OCH_2OCH_3 or OCH_2Ph), 5.24 (2H, s, OCH_2OCH_3 or OCH_2Ph), 5.84 (1H, s, $CHCOOEt$), 6.88—7.84 (11H, m, 11 × aromatic protons), 9.88 (1H, s, CHO).

Ethyl 2-[4-Dimethoxymethyl-2-(methoxymethoxy)phenoxy]-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (5)——A mixture of **4** (1.74 g) and NH_4Cl (15 mg) in MeOH (1.4 ml) and trimethoxymethane (1.8 ml) was heated under reflux for 1 h. After cooling, the insoluble material was filtered off. The resulting filtrate was evaporated to produce a solid (**5**). The solid was recrystallized from ether and petroleum ether (60—70 °C). Colorless needles. mp 59—60 °C (1.78 g) (94%). *Anal.* Calcd for $C_{30}H_{34}O_{10}$: C, 64.97; H, 6.18. Found: C, 65.21; H, 5.95. MS *m/z*: 554 (M^+), 523, 508, 478, 405. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1675, 1595. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.24 (6H, s, $CH(O\underline{CH_3})_2$), 3.37 (3H, s, $OCH_2O\underline{CH_3}$), 3.89 (3H, s, OCH_3), 4.25 (2H, q, J=7 Hz, $OCH_2\underline{CH_3}$), 5.13 (2H, s, OCH_2OCH_3 or OCH_2Ph), 5.20 (2H, s, OCH_2OCH_3 or OCH_2Ph), 5.29 (1H, s, $CH(OCH_3)_2$), 5.73 (1H, s, $CHCOOEt$),

6.85—7.84 (11H, m, 11 × aromatic protons).

2-[4-Dimethoxymethyl-2-(methoxymethoxy)phenoxy]-3-(4-benzyloxy-3-methoxyphenyl)-propane-1,3-diol (6)——$NaBH_4$ (0.38 g) was added portionwise to a stirred solution of **5** (1.66 g) in EtOH (40 ml) at room temperature. After standing for 8 h at the same temperature, the reaction mixture was evaporated under reduced pressure. Water was added to the resulting residue and the mixture was extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. The resulting oil was purified by column chromatography on silica gel using $CHCl_3$–acetone (10 : 1, v/v) as an eluent to provide an oil (**6**). Colorless oil (1.50 g) (97%). TLC (silica gel/$CHCl_3$–acetone 3 : 1 (v/v), Rf=0.21). High-resolution MS m/z: 514.2201 Calcd for $C_{28}H_{34}O_9$ (M^+). Found: 514.2209. MS m/z: 514 (M^+), 496, 483, 452, 421, 361. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3500, 1605, 1595. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (6H, s, $CH(OC\underline{H}_3)_2$), 3.50 (3H, s, $OCH_2OC\underline{H}_3$), 3.90 (3H, s, OCH_3), 3.72 (2H, m, $C\underline{H}_2OH$), 4.20 (1H, m, $C\underline{H}CH_2OH$), 4.93 (1H, d, J=6 Hz, $C\underline{H}OH$), 5.10 (2H, s, $OC\underline{H}_2OCH_3$ or $OC\underline{H}_2Ph$), 5.17 (2H, s, $OC\underline{H}_2OCH_3$ or $OC\underline{H}_2Ph$), 5.30 (1H, s, $C\underline{H}(OCH_3)_2$), 6.80—7.44 (11H, m, 11 × aromatic protons).

Acetylation of 6——Compound **6** (257 mg) was acetylated with acetic anhydride (1 ml) and pyridine (1 ml) at room temperature for 5 h. The resulting mixture was evaporated under reduced pressure to give an oil (**7**). Colorless oil (260 mg) (94%). TLC (silica gel/$CHCl_3$–acetone 5 : 1 (v/v), Rf=0.68). High-resolution MS m/z: 552.1994 Calcd for $C_{30}H_{32}O_{10}$ (M^+). Found: 552.2001. MS m/z: 552 (M^+), 448, 285, 243, 179, 137. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1695, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, $OCOCH_3$), 2.07 (3H, s, $OCOCH_3$), 3.48 (3H, s, $OCH_2OC\underline{H}_3$), 3.92 (3H, s, OCH_3), 4.36 (2H, m, $C\underline{H}_2OCOCH_3$), 4.95 (1H, m, $C\underline{H}CH_2OCOCH_3$), 5.20 (4H, s, $OC\underline{H}_2Ph$ and $OC\underline{H}_2OCH_3$), 6.06 (1H, d, J= 6 Hz, $C\underline{H}OCOCH_3$), 6.80—7.64 (13H, m, 13 × aromatic protons), 9.88 (1H, s, CHO).

3-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (8)——A stirred mixture of **6** (1.45 g) in acetic acid (40 ml) in the presence of 5% sulfuric acid (4 ml) was heated at 70 °C for 30 min. After cooling, the reaction mixture was poured into water and extracted with AcOEt. The extract was washed, dried over Na_2SO_4, and evaporated. The resulting oil was purified by column chromatography on silica gel using $CHCl_3$–acetone (10 : 1, v/v) as an eluent to yield an oil (**8**). Colorless oil (0.80 g), (70%). TLC (silica gel/$CHCl_3$–acetone 5 : 1 (v/v), Rf=0.48). High-resolution MS m/z: 406.1415 Calcd for $C_{24}H_{22}O_6$ (M^+). Found: 406.1428. MS m/z: 406 (M^+), 388, 315, 308, 270, 244, 136. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1695, 1605, 1595. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (2H, m, $C\underline{H}_2OH$), 3.91 (3H, s, OCH_3), 4.09 (1H, m, $OC\underline{H}CH_2OH$), 4.96 (1H, d, J=8 Hz, $OC\underline{H}Ph$), 5.14 (2H, s, $OC\underline{H}_2Ph$), 6.92—7.48 (11H, m, 11 × aromatic protons), 9.80 (1H, s, CHO).

3-(4-Hydroxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (9)——A solution of **8** (0.812 g) in AcOEt (25 ml) and EtOH (25 ml) was subjected to catalytic reduction over 5% Pd–C (100 mg) at ambient temperature. After absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was evaporated. The resulting oil was purified by column chromatography on silica gel using $CHCl_3$–acetone (10 : 1, v/v) as an eluent to afford an oil (**9**). Colorless oil (398 mg) (63%). TLC (silica gel/$CHCl_3$–acetone 5 : 1 (v/v), Rf=0.30). High-resolution MS m/z: 316.0946 Calcd for $C_{17}H_{16}O_6$ (M^+). Found: 316.0947. MS m/z: 316 (M^+), 298, 283, 270, 229, 180. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3550, 1695, 1605, 1595. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (2H, m, $C\underline{H}_2OH$), 3.91 (3H, s, OCH_3), 4.12 (1H, m, $C\underline{H}CH_2OH$), 4.97 (1H, d, J=8 Hz, $OC\underline{H}Ph$), 6.04 (1H, s, OH), 6.96—7.50 (6H, m, 6 × aromatic protons), 9.88 (1H, s, CHO).

The ^{1}H-NMR spectrum was completely superimposable on that of a sample provided by Merlini.[5c]

Condensation of 10 and 11 (Formation of 12)——A solution of **9** (316 mg) in tetrahydrofuran (THF) (3 ml) was added dropwise to a suspension of NaH (containing 40% mineral oil) (50 mg) in THF (3 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 30 min and then chloromethyl methyl ether (0.112 ml) was added gradually. The stirred mixture was allowed to stand at room temperature for 2 h, then the reaction mixture was poured into water. The resulting mixture was extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated to yield an oil (**10**). Colorless oil. (285 mg) (79%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1695, 910. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, $OCH_2OC\underline{H}_3$), 3.78 (2H, m, $C\underline{H}_2OH$), 3.85 (3H, s, OCH_3), 3.99 (1H, m, $C\underline{H}CH_2OH$), 5.02 (1H, d, J=8 Hz, $OC\underline{H}Ph$), 5.19 (2H, s, $OC\underline{H}_2OCH_3$), 6.90—7.23 (6H, m, 6 × aromatic protons), 9.80 (1H, s, CHO). The following reaction was carried out without purification of the oil (**10**).

A mixture of **10** (250 mg), 2,4,6-trimethoxymethoxyacetophenone (**11**)[9] (215 mg), and sodium hydroxide (20 mg) in dry EtOH (8 ml) was stirred for 8 h under a nitrogen atmosphere. The mixture was poured into ice-water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residual oil was purified by column chromatography on silica gel using benzene–acetone (9 : 1, v/v) as an eluent to give an oil (**12**). Yellowish oil (421 mg) (94%). TLC (silica gel/benzene–acetone 7 : 3 (v/v), Rf=0.33). High-resolution MS m/z: 642.2309 Calcd for $C_{33}H_{38}O_{13}$ (M^+). Found: 642.2255. MS m/z: 642 (M^+), 597, 503, 416, 360. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3595, 1635, 1605, 910. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (6H, s, 2 × $OCH_2OC\underline{H}_3$), 3.52 (6H, s, 2 × $OCH_2OC\underline{H}_3$), 3.80 (2H, m, $C\underline{H}_2OH$), 3.91 (3H, s, OCH_3), 4.06 (1H, m, $OC\underline{H}CH_2OH$), 5.01 (1H, d, J=8 Hz, $OC\underline{H}Ph$), 5.10 (4H, s, 2 × $OC\underline{H}_2OCH_3$), 5.17 (2H, s, $OC\underline{H}_2OCH_3$), 5.24 (2H, s, $OC\underline{H}_2OCH_3$), 6.55 (2H, s, 2 × aromatic protons), 6.83 (1H, d, J=16 Hz, α-H), 7.30 (1H, d, J=16 Hz, β-H), 6.90—7.30 (6H, m, 6 × aromatic protons).

Reaction of 12 with Alkaline Hydrogen Peroxide (Formation of 13)——An aqueous 5% NaOH (0.50 ml) was added to a solution of **12** (400 mg) in MeOH (10 ml) containing 30% H_2O_2 (0.50 ml) under ice-cooling and the whole was stirred for 4 h at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The

extract was washed with water, dried over Na_2SO_4, and evaporated to give an oil (**13**). Colorless oil (396 mg) (97%). TLC (silica gel/benzene–acetone 7 : 3 (v/v), $Rf=0.32$). High-resolution MS m/z: 658.2258 Calcd for $C_{33}H_{38}O_{14}$ (M^+). Found: 658.2211. MS m/z: 658 (M^+), 440, 360, 258. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 1695, 1600, 910. ^{1}H-NMR ($CDCl_3$) δ: 3.38 (6H, s, $2\times OCH_2OC\underline{H}_3$), 3.40 (3H, s, $OCH_2OC\underline{H}_3$), 3.46 (3H, s, $OCH_2OC\underline{H}_3$), 3.70 (2H, m, $C\underline{H}_2OH$), 3.85 (3H, s, OCH_3), 3.86 (1H, d, $J=2$ Hz, α-H or β-H), 3.94 (1H, d, $J=2$ Hz, α-H or β-H), 4.10 (1H, m, $C\underline{H}CH_2OH$), 4.92 (1H, d, $J=8$ Hz, $OC\underline{H}Ph$), 5.07 (4H, s, $2\times OC\underline{H}_2OCH_3$), 5.16 (2H, s, $OC\underline{H}_2OCH_3$), 5.25 (2H, s, $OC\underline{H}_2OCH_3$), 6.52 (2H, s, $2\times$ aromatic protons), 6.80—7.20 (6H, m, $6\times$ aromatic protons).

(±)-Silybin (1)——A mixture of MeOH (5 ml) and conc. HCl (1 ml) was added dropwise to a solution of **13** (360 mg) in MeOH (4 ml) and THF (1 ml) and the reaction mixture was heated at 70 °C for 5 min. After cooling, the mixture was poured into ice-water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residual oil was purified by column chromatography on silica gel using $CHCl_3$–acetone–AcOEt–HCOOH (8 : 1 : 1 : 0.01, v/v) as an eluent to afford a solid (**1**). The solid was recrystallized from AcOEt. Colorless needles. mp 160—162 °C (166 mg) (63%). *Anal.* Calcd for $C_{25}H_{22}O_{10}\cdot H_2O$: C, 60.00; H, 4.83. Found: C, 60.01; H, 5.15. MS m/z: 482 (M^+), 464, 301, 180, 162. IR ν_{max}^{KBr} cm^{-1}: 3435, 1625. IR ν_{max}^{DMSO} cm^{-1}: 1660. ^{1}H-NMR (DMSO-d_6) δ: 3.10—3.70 (2H, m, $C\underline{H}_2OH$), 3.77 (3H, s, OCH_3), 4.05—4.15 (1H, m, $OC\underline{H}CH_2OH$), 4.57 (1H, q, $J=6$, 11 Hz, $COC\underline{H}OH$ (ring B)), 4.90 (1H, d, $J=8$ Hz, $ArOC\underline{H}Ph$ (ring D)), 5.03 (1H, d, $J=11$ Hz, $ArOC\underline{H}Ar$ (ring B)), 5.74 (1H, d, $J=6$ Hz, OH (ring B)), 5.83 (1H, d, $J=2$ Hz, aromatic proton (ring A)), 5.88 (1H, d, $J=2$ Hz, aromatic proton (ring A)), 6.80—7.25 (6H, m, $6\times$ aromatic protons), 9.15 (1H, s, OH). ^{13}C-NMR (DMSO-d_6) δ: 197.56 (s, C-4), 166.67 (s, C-7), 163.22 (s, C-5), 162.35 (s, C-9), 147.54 (s, C-16), 146.90 (s, C-17), 143.57 (s, C-4′), 143.16 (s, C-3′), 129.93 (s, C-1′), 127.42 (s, C-14), 121.16 (d, C-6′), 120.40 (d, C-19), 116.25 (d, C-2′), 116.08 (d, C-5′), 115.25 (d, C-18), 111.62 (d, C-15), 100.39 (s, C-10), 96.00 (d, C-6), 94.95 (d, C-8), 82.49 (d, C-2), 78.04 (d, C-12), 75.76 (d, C-13), 71.37 (d, C-3), 60.08 (t, C-11), 55.64 (q, C-20).

This compound was found to be identical with natural silybin[5c] by comparison of their IR (DMSO), ^{1}H-NMR (DMSO-d_6), ^{13}C-NMR (DMSO-d_6), and mass spectra.

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11) The compound was homogeneous on TLC in various solvent systems. The ^{1}H-NMR spectral measurement in chloroform in the presence of Sievers' reagent (2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione europium) revealed that the methoxyl signal was split into two peaks of equal intensity. Hence, the ratio of the diastereoisomeric mixture was about 1 to 1.
12) A. Guademer, "Stereochemistry," Vol. 1, ed. by H. B. Kagan, Georg Thieme Publishers, Stuttgart, 1977, p. 77.
13) The ^{1}H-NMR spectrum of this racemic silybin in a mixture of benzene and pyridine showed double signals of the methoxyl group (see ref. 5*a*); These appeared to be equal intensity, suggesting that the product is a *ca.* 1 : 1 mixture of diastereomers.