Total Synthesis of Silychristin, an Antihepatotoxic Flavonolignan[1)]

Hitoshi TANAKA, Masaru HIROO, Kazuhiko ICHINO, and Kazuo ITO*

Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468, Japan. *Received September 9, 1988*

The total synthesis of silychristin, an antihepatotoxic flavonolignan, is described. The key intermediate, the *trans*-dihydrobenzofuran (15) was synthesized as follows. Treatment of the chalcone epoxide (9) with boron trifluoride etherate and subsequent reduction with sodium borohydride gave exclusively the *erythro*-1,2-diaryl-1,3-propanediol (10). Hydrogenolysis of 10 with hydrogen over a palladium catalyst followed by cyclization of the debenzylation product (13) with boron trifluoride etherate in acetic acid afforded 15 as a single product.

Keywords silychristin; *Silybum marianum*; Compositae; flavonolignan; flavanonol; dihydrobenzofuran; antihepatotoxic activity; acid rearrangement; chalcone epoxide

Flavonolignans have been found in the seed extract of *Silybum marianum* (Compositae) which has been widely used as a folk medicine in Jammu and Kashmir[2)] and Europe.[3)] The flavonolignans consist of a flavanonol moiety and a C_6—C_3 unit (lignan). Silychristin,[4)] a component of the flavonolignans, has a unique skeleton (highly substituted *trans*-dihydrobenzofuran) and exhibits biological (antihepatotoxic) activity.[5)] Concerning the structure of silychristin, Wagner *et al.*[6)] and Zanarotti[7)] reported the structure to be as shown by formula **1** on the basis of spectroscopic analysis and the structural elucidation of degradation products of silychristin. Further, the absolute configurations at C-2 and C-3 of the flavanonol ring were established as 2*R* and 3*R*, and *trans* configuration (α-*R* and β-*S* configuration) of the dihydrobenzofuran ring was also demonstrated.

We wish to describe an efficient total synthesis of silychristin having the *trans*-dihydrobenzofuran ring, which was readily prepared by acid rearrangement of a chalcone epoxide (**9**) according to the procedure developed by Brunow and Lundquist.[8)]

The starting material, a chalcone epoxide (**9**) was prepared as follows. Benzylation of 5-bromo-3,4-dihydroxybenzaldehyde (**2**)[9)] with benzyl chloride followed by acetalization of the resulting benzyl ether (**3**) gave a dimethyl acetal (**4**) in good yield. The compound (**4**) reacted with *n*-butyl lithium in ether at −78 °C to yield a lithio derivative which, on addition of *N*,*N*-dimethylformamide (DMF), was converted into an aldehyde (**5**) in 94% yield. Condensation of the aldehyde (**5**) with 4-benzyloxy-3-methoxyacetophenone (**6**)[10)] in the presence of potassium hydroxide provided the corresponding chalcone (**7**) in 93%

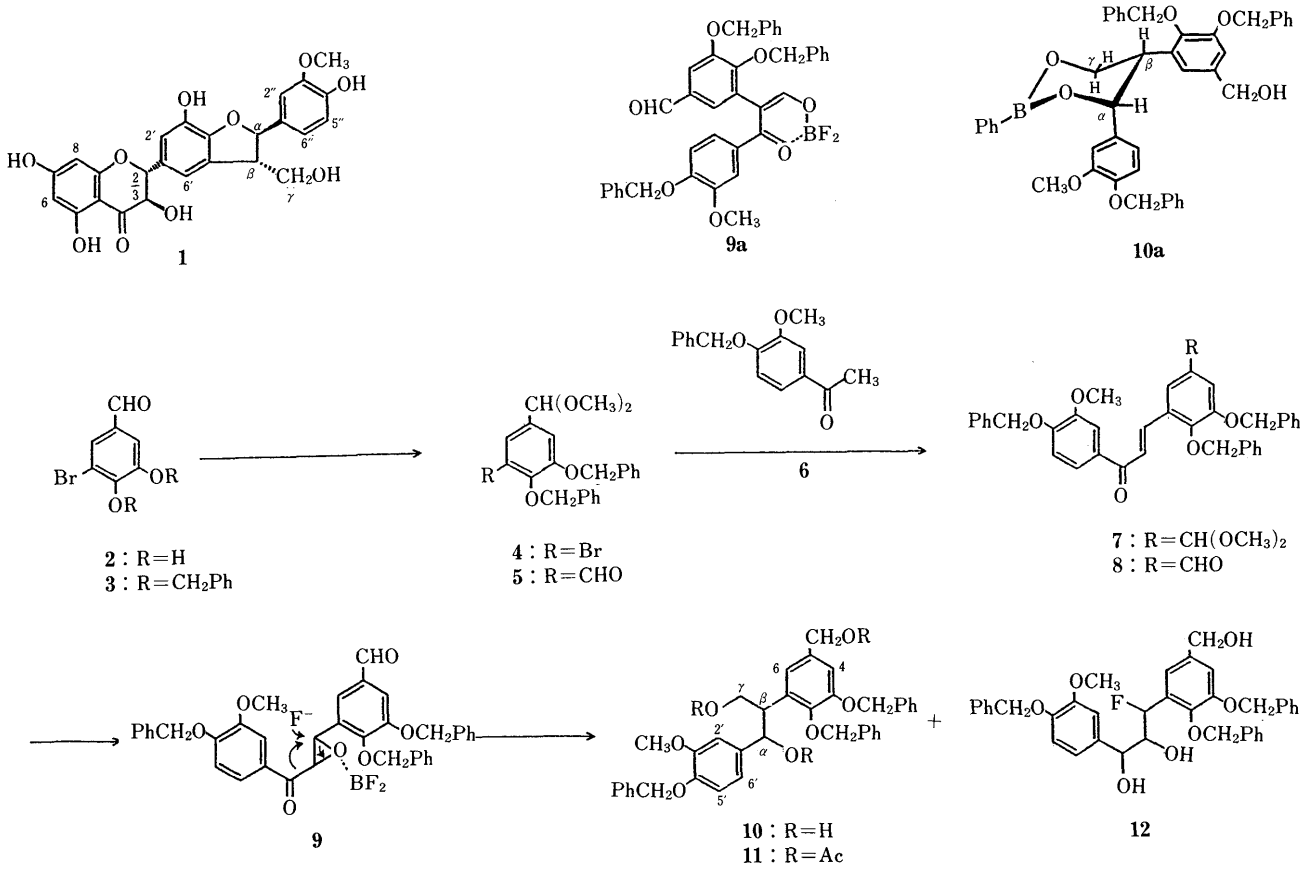

Chart 1

yield. As the acetal group in **7** partially decomposed in alkaline hydrogen peroxide, removal of the acetal group by treatment with hydrochloric acid prior to epoxidation was carried out to give **8**. This compound (**8**) was oxidized with hydrogen peroxide in the presence of sodium hydroxide to yield the desired chalcone epoxide (**9**) in 92% yield. On treatment with boron trifluoride etherate in benzene under ice-water, the chalcone epoxide (**9**) underwent rearrangement, giving the corresponding boron fluoride complex (**9a**), which without purification was reduced with sodium borohydride to afford a 1,2-diaryl-1,3-propanediol (**10**) as a stereochemically sole product (39% yield). In this rearrangement reaction, a fluorohydrin (**12**) was obtained in 27% yield. The structure of **10** was determined as follows. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **10** showed the disappearance of signals in the oxirane proton region. The α-proton signal was observed at δ4.87 as a doublet (J=6.4 Hz) and the β- and γ-proton signals (δ3.52—3.60) appeared as multiplets. The compound (**10**) was acetylated by a normal procedure to give a triacetate (**11**). In the ^{1}H-NMR spectrum of **11**, the signals of the acetoxyl groups were observed as three singlets at δ1.89, 1.92, and 2.11.[11] Further, the triacetate revealed signals of an α-proton (δ6.06, d, J=7.8 Hz), β-proton (δ4.04, m), and γ-protons (δ3.89, dd, J=7.1, 11.1 Hz; δ4.22, dd, J=6.1, 11.1 Hz), indicating a 1,2-disubstituted-1,3-propanediol moiety. In order to clarify the stereochemistry of **10**, a phenylboronate (**10a**) with a stable six-membered ring structure (chair form) was prepared by refluxing **10** with phenylboronic acid. The ^{1}H-NMR spectrum of **10a** displayed a α-proton signal at δ5.30 as a doublet with a vicinal coupling constant of 4.0 Hz, which corresponds to a dihedral angle of about 45°. Furthermore, the β-proton gave a double double doublet signal at δ4.01 and the coupling constant between the β- and γ-protons is 10.4 Hz, indicating the axial orientation of the β-proton. Therefore, the equatorial orientation of α-proton was suggested. From these results, the configuration of **10** was confirmed to be *erythro* form. Hydride reduction of the boron fluoride complex (**9a**) proceeds highly stereoselectively to generate the *erythro* form (**10**) exclusively, and this outcome was compatible with the result reported by Kristersson and Lundquist.[13] Further, the expected structure of the minor product (**12**) was consistent with the spectral data (infrared (IR) spectrum, mass spectrum (MS), and ^{1}H-NMR spectrum). Namely, the ^{1}H-NMR spectrum displayed characteristic large coupling constants between fluorine and hydrogen, corresponding to one geminal coupling constant (46.1 Hz) and one vicinal coupling constant (26.2 Hz). The plane structure was therefore represented by formula (**12**), but the stereochemistry remains unsolved. In the similar rearrangement reaction of chalcone epoxides, House and Ryerson[14] reported that fluorohydrins were also found as by-products among the reaction products.

Next, catalytic hydrogenation of **10** with 10% palladium on carbon provided a debenzylation product (**13**) which cyclized with boron trifluoride etherate in acetic acid at 5 °C to afford a dihydrobenzofuran (**15**) as a single product (77% yield). The ^{1}H-NMR spectrum of the tetraacetate (**16**), obtained from **15** by acetylation, revealed signals of two aromatic acetoxyl groups (δ2.31) and two aliphatic acetoxyl groups (δ2.08 and 2.09). Further, the α-, β-, and γ-proton signals of the dihydrobenzofuran ring were observed at δ5.59 (H_α, d, J=5.7 Hz), 3.74 (H_β, m), and 4.30 (H_γ, dd, J=7.7, 11.1 Hz) and 4.45 (H_γ, dd, J=5.7, 11.1 Hz), respectively. Since the γ-proton signals did not appear at an unusually high field position, as is characteristic for *cis*-2-aryl-3-substituted dihydrobenzofurans,[15] the *trans* configuration of the primary alcohol group and the aryl substituent, as in silychristin,[6] and silyhermin,[16] was assigned.

Protection of **15** with methoxymethyl chloride afforded a methoxymethyl ether (**17**) which was readily hydrolyzed with sodium hydroxide to yield a benzyl alcohol derivative (**18**). On mild oxidation with active manganese dioxide in dichloromethane, **18** was converted into an aldehyde (**19**) in an excellent yield. Reaction of **19** with an acetophenone derivative (**20**), readily obtainable by methoxymethylation of 2,4,6-trihydroxyacetophenone, in the presence of sodium hydroxide afforded the corresponding chalcone (**21**) in 94% yield. The ^{1}H-NMR spectrum exhibited two olefinic proton

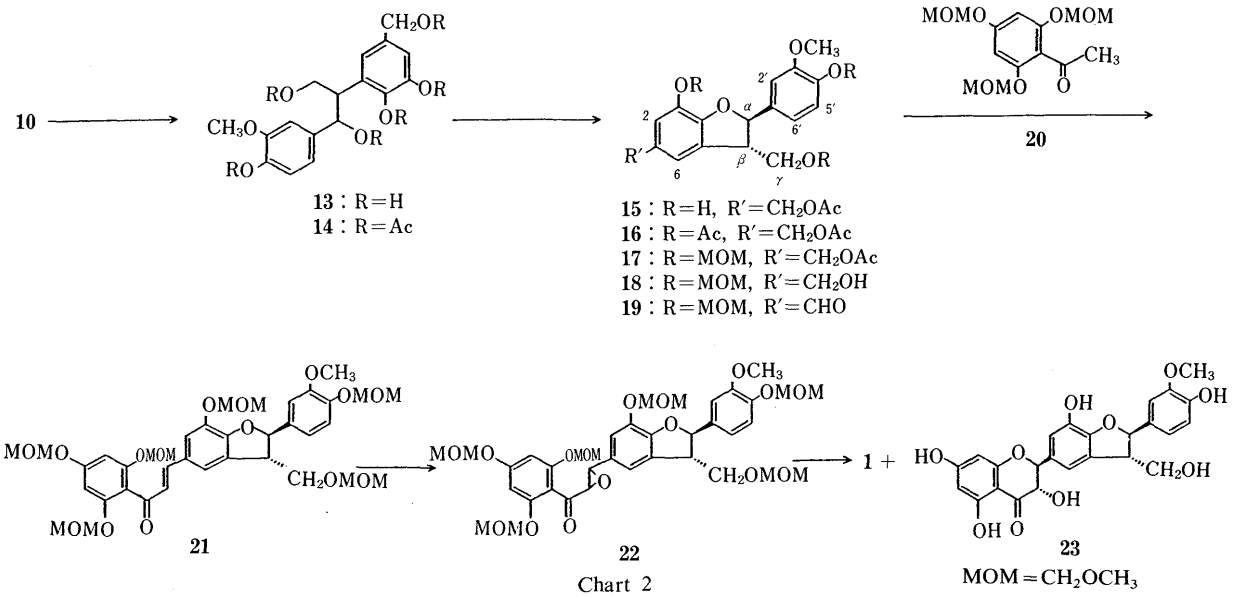

Chart 2

signals at δ 6.85 and 7.28 as a doublet whose coupling constant was 16.1 Hz, indicating the formation of a *trans* double bond. Oxidation of **21** with alkaline hydrogen peroxide provided an unstable epoxide (**22**) in an excellent yield. This, in the ^{1}H-NMR spectrum, showed oxirane proton signals at δ 3.90 and 3.94 as a doublet (J = 2.0 Hz), in accordance with a *trans* orientation of the epoxide system.

Finally, brief heating of **22** with concentrated hydrochloric acid at 70 °C resulted in deprotection (removal of the methoxymethyl groups) and simultaneous cyclization to give a mixture of silychristin (**1**) and its diastereoisomer (**23**) which, after separation by column chromatography on silica gel followed by preparative high-performance liquid chromatography (HPLC), furnished racemic silychristin in 19% yield and its isomer (**23**) in 16% yield. Silychristin, in the ^{1}H-NMR spectrum, revealed signals of the C-2 proton (δ 4.64) and C-3 proton (δ 5.05) as doublets (J = 11.4 Hz), demonstrating a *trans* configuration of the flavanonol nucleus. This synthetic silychristin was identical with a natural authentic sample[7] on the basis of direct comparisons of spectroscopic data (MS and ^{1}H-NMR spectra) and chromatographic behavior (thin layer chromatography (TLC) and HPLC). The other compound (**23**) also had a *trans* orientation (J = 11.4 Hz) of the flavanonol moiety, as in silychristin (**1**). The IR and mass spectra of **23** were closely similar to those of silychristin (**1**) and, in a comparison of the ^{1}H-NMR spectra, all coupling constants of **23** had the same values as those of **1**, but the chemical shifts were often found to have very small differences. Therefore, compound **23** is a stereoisomer of **1** at the C-2 and C-3 positions and can be represented by formula **23**.

This is the first synthesis of a member of the flavonolignans, having a *trans*-dihydrobenzofuran ring.

Experimental

All melting points are uncorrected. Column chromatography was run on Merck Silica gel 60 (70—230 mesh). TLC was performed on glass plates precoated with Kieselgel 60 F_{254} (Merck). Electron impact mass spectrum (EI-MS) were recorded on a Hitachi M-52 spectrometer, and high-resolution MS and secondary ion mass spectrometry (SIMS) on a Hitachi M-80 spectrometer. Fast atom bomberdment mass spectrum (FAB-MS) were recorded on JEOL JMS-DX300 and JEOL JMA-DA5000 spectrometers. IR spectra were obtained on a JASCO IR-810 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GX-270 and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra on a JEOL JNM-FX-100 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). HPLC was conducted on a JASCO TRI-ROTAR-II instrument.

5-Bromo-3,4-dibenzyloxybenzaldehyde (3) A mixture of (**2**)[9] (165 g), benzyl chloride (231 g), and anhydrous potassium carbonate (367 g) in DMF (1.5 l) was refluxed for 3 h. After cooling, potassium carbonate was filtered off. The filtrate was evaporated and the resulting residue was dissolved in AcOEt. The AcOEt solution was washed with a good deal of water, dried over Na_2SO_4, and evaporated to give a solid. The solid was recrystallized from MeOH to afford **3** (260 g) (86%) as colorless needles, mp 105—106 °C. *Anal.* Calcd for $C_{21}H_{17}BrO_3$: C, 63.63; H, 4.33. Found: C, 63.57; H, 4.30. IR ($CHCl_3$): 1690, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.16, 5.18 (4H, 2×s, 2×OC$\underline{H}_2$Ph), 7.25—7.48 (11H, m, 11×aromatic protons), 7.67 (1H, d, J = 1.7 Hz, aromatic proton), 9.82 (1H, s, CHO).

5-Bromo-3,4-dibenzyloxybenzaldehyde Dimethyl Acetal (4) A mixture of **3** (255 g), trimethyl orthoformate (328 g), and ammonium chloride (2.75 g) in MeOH (600 ml) was refluxed for 4 h under a nitrogen atmosphere. After cooling, excess $NaHCO_3$ was added to the reaction mixture and $NaHCO_3$ was removed by filtration. The filtrate was poured into a good deal of water and then extracted with AcOEt. The AcOEt layer was washed with brine, dried over Na_2SO_4, and evaporated to give a pale yellow solid. The solid was recrystallized from petroleum ether to afford **4** (260 g, 91%) as colorless prisms. mp 72—73 °C. *Anal.* Calcd for $C_{23}H_{23}BrO_4$: C, 62.43; H, 5.24. Found: C, 62.29; H, 5.18. IR ($CHCl_3$): 1600, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (6H, s, CH(OC$\underline{H}_3$)$_2$), 5.04, 5.13 (4H, 2×s, 2×OC$\underline{H}_2$Ph), 5.29 (1H, s, C$\underline{H}$(OCH$_3$)$_2$), 7.06 (1H, d, J = 1.7 Hz, aromatic proton), 7.25—7.49 (11H, m, 11×aromatic protons).

3,4-Dibenzyloxy-5-formylbenzaldehyde Dimethyl Acetal (5) A solution of *n*-butyl lithium (1.56 M solution in *n*-hexane) (33.8 ml) was added dropwise to **4** (14.6 g) in dry ether (700 ml) cooled to −78 °C under a nitrogen atmosphere. Stirring was continued at the same temperature for 10 min and dry DMF (10.2 ml) was added dropwise. The reaction mixture was slowly warmed to room temperature over 3 h, and then quenched with a solution of saturated aqueous ammonium chloride (20 ml). The organic layer was separated and washed with brine, dried over Na_2SO_4, and evaporated to give a solid. The solid was recrystallized from EtOH to afford **5** (12.1 g, 94%) as colorless needles. mp 98—99 °C. *Anal.* Calcd for $C_{24}H_{24}O_5$: C, 73.44; H, 6.17. Found: C, 73.65; H, 6.21. IR ($CHCl_3$): 1690, 1610, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (6H, s, CH(OC$\underline{H}_3$)$_2$), 5.19 (4H, s, 2×OC$\underline{H}_2$Ph), 5.32 (1H, s, C$\underline{H}$(OCH$_3$)$_2$), 7.31—7.50 (12H, m, 12×aromatic protons), 10.24 (1H, s, CHO).

1-(4-Benzyloxy-3-methoxyphenyl)-3-(2,3-dibenzyloxy-5-dimethoxymethylphenyl)-2-propen-1-one (7) A mixture of **5** (50 g), **6**[10] (32.7 g), and potassium hydroxide (100 g) in absolute EtOH (2.5 l) was stirred for 4 h under a nitrogen atmosphere. The reaction mixture was poured into ice-water. The resulting precipitate was collected by filtration and dissolved in AcOEt. The AcOEt solution was washed with water, dried over Na_2SO_4, and evaporated to give a yellow solid. The solid was recrystallized from MeOH to afford **7** (75 g, 93%) as yellow needles. mp 117—119 °C. *Anal.* Calcd for $C_{40}H_{38}O_7$: C, 76.17; H, 6.07. Found: C, 75.91; H, 6.02. MS m/z: 630 (M^+), 584, 523, 493, 477, 304, 267, 241, 213, 181, 151. IR ($CHCl_3$): 1660, 1600, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (6H, s, CH(OC$\underline{H}_3$)$_2$), 3.94 (3H, s, OCH$_3$), 5.06, 5.17, 5.24 (6H, 3×s, 3×OC$\underline{H}_2$Ph), 5.35 (1H, s, C$\underline{H}$(OCH$_3$)$_2$), 6.84 (1H, d, J = 8.4 Hz, aromatic proton), 7.17—7.60 (19H, m, 19×aromatic protons), 7.58 (1H, d, J = 16.1 Hz, olefin H$_\alpha$), 8.02 (1H, d, J = 16.1 Hz, olefin H$_\beta$).

1-(4-Benzyloxy-3-methoxyphenyl)-3-(2,3-dibenzyloxy-5-formylphenyl)-2-propen-1-one (8) A mixture of dioxane (100 ml) and concentrated HCl (150 ml) was added to a solution of **7** (42 g) in dioxane (300 ml) and MeOH (200 ml). The whole was stirred at room temperature for 1.5 h. The reaction mixture was neutralized with 10% NaOH. The resulting precipitate was collected by filtration and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried over Na_2SO_4, and evaporated to give a yellow solid. The solid was recrystallized from AcOEt to afford **8** (33.8 g, 87%) as yellow prisms. mp 170—171 °C. *Anal.* Calcd for $C_{38}H_{32}O_6$: C, 78.05; H, 5.52. Found: C, 78.12; H, 5.51. MS m/z: 584 (M^+), 493, 477, 304, 241. IR ($CHCl_3$): 1700, 1660, 1600, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.94 (3H, s, OCH$_3$), 5.18, 5.21, 5.24 (6H, 3×s, 3×OC$\underline{H}_2$Ph), 6.85 (1H, d, J = 8.4 Hz, aromatic proton), 7.23—7.74 (19H, m, 19×aromatic protons), 7.61 (1H, d, J = 16.1 Hz, olefin H$_\alpha$), 8.00 (1H, d, J = 16.1 Hz, olefin H$_\beta$), 9.92 (1H, s, CHO).

1-(4-Benzyloxy-3-methoxyphenyl)-3-(2,3-dibenzyloxy-5-formylphenyl)-2,3-epoxy-1-propanone (9) A solution of 30% H_2O_2 (150 ml) and 5% NaOH (150 ml) was added to a mixture of **8** (20 g) in MeOH (400 ml) and dioxane (800 ml). The whole was stirred at room temperature for 3 h. The mixture was poured into ice-water. The resulting precipitate was collected by filtration and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried over Na_2SO_4, and evaporated to give a solid. The solid was recrystallized from AcOEt to afford **9** (18.9 g, 92%) as colorless needles, mp 158—160 °C. *Anal.* Calcd for $C_{38}H_{32}O_7$: C, 75.97; H, 5.37. Found: C, 75.92; H, 5.35. MS m/z: 600 (M^+), 584, 582, 509, 493, 492, 481, 477, 331, 304, 255, 242, 213, 181, 151. IR ($CHCl_3$): 1690, 1600, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.94 (3H, s, OCH$_3$), 4.12 (1H, d, J = 2.0 Hz, epoxy H$_\alpha$ or epoxy H$_\beta$), 4.26 (1H, d, J = 2.0 Hz, epoxy H$_\alpha$ or epoxy H$_\beta$), 5.15 (2H, d, J = 3.0 Hz, OC$\underline{H}_2$Ph), 5.22, 5.23 (4H, 2×s, 2×OC$\underline{H}_2$Ph), 6.84 (1H, d, J = 8.4 Hz, aromatic proton), 7.10—7.57 (19H, m, 19×aromatic protons), 9.88 (1H, s, CHO).

Treatment of 9 with $BF_3 \cdot Et_2O$ Followed by Reduction with $NaBH_4$ (Formation of 10) Freshly distilled boron trifluoride etherate (5.32 ml) was added dropwise to a solution of **9** (20 g) in dry benzene (1.6 l) chilled with ice-cold water under a nitrogen atmosphere. The mixture was stirred at the same temperature for 20 min and the reaction was then stopped by addition of water. The organic layer was separated and washed with water, dried over Na_2SO_4, and evaporated to give a yellow oil. This oil was dissolved in tetrahydrofuran (THF) (500 ml) and then sodium borohydride (6.7 g) was added gradually with stirring at room temperature. After stirring for 2 h, the reaction mixture was poured into ice-water and then

extracted with AcOEt. The AcOEt layer was washed with brine, dried over Na_2SO_4, and evaporated to yield a pale yellow oil. The oil was purified by column chromatography on silica gel using $CHCl_3$–acetone (1 : 1) to give a colorless oil **10** (7.9 g, 39%) and a crude solid. The solid was recrystallized from benzene to afford **12** (5.6 g, 27%) as colorless prisms.

10: FAB-MS *m/z*: 607 ($M^+ + H$). IR ($CHCl_3$): 3600, 3425, 1610, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52—3.60 (3H, m, H_β and 2 × H_γ), 3.64 (3H, s, OCH_3), 4.51 (2H, s, CH_2OH), 4.53 (1H, d, J=11.1 Hz, OCH_2Ph), 4.87 (1H, d, J=6.4 Hz, H_α), 4.91 (1H, d, J=11.1 Hz, OCH_2Ph), 5.05, 5.06 (4H, 2 × s, 2 × OCH_2Ph), 6.63 (1H, dd, J=1.7, 8.4 Hz, $H_{6'}$), 6.67 (1H, d, J=1.7 Hz, $H_{2'}$), 6.72 (1H, d, J=8.4 Hz, $H_{5'}$), 6.90 (1H, d, J=1.7 Hz, H_4 or H_6), 6.97 (1H, d, J=1.7 Hz, H_4 or H_6), 7.20—7.42 (15H, m, 15 × aromatic protons).

12: mp 119—121 °C. *Anal.* Calcd for $C_{38}H_{37}FO_7$: C, 73.04; H, 5.97. Found: C, 72.94; H, 5.92. MS *m/z*: 624 (M^+), 604, 586, 570, 513, 495, 362, 271, 254, 242, 226, 213, 191. IR ($CHCl_3$): 3600, 3425, 1610, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.76 (3H, s, OCH_3), 4.02 (1H, ddd, J=2.4, 7.1, 26.2 Hz, ArCH(OH)CH(OH)), 4.54 (2H, s, CH_2OH), 4.71 (1H, d, J=7.1 Hz, ArCH(OH)CH(OH)), 4.94 (1H, d, J=11.1 Hz, OCH_2Ph), 5.02 (1H, d, J=11.1 Hz, OCH_2Ph), 5.07, 5.10 (4H, 2 × s, 2 × OCH_2Ph), 5.98 (1H, dd, J=2.4, 46.1 Hz, ArCH(F)), 6.76 (2H, s, 2 × aromatic protons), 6.86 (1H, s, aromatic proton), 6.98 (1H, d, J=1.7 Hz, aromatic proton), 7.01 (1H, d, J=1.7 Hz, aromatic proton), 7.25—7.47 (15H, m, 15 × aromatic protons).

Acetylation of 10 (Formation of 11) A mixture of **10** (200 mg), acetic anhydride (1.4 ml), and pyridine (1.2 ml) was stirred at room temperature overnight. Ice-water was poured into the reaction mixture and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give an oil. The oil was purified by column chromatography on silica gel using AcOEt–benzene (1 : 5) to afford **11** (235 mg, 97%) as a colorless oil. High resolution MS *m/z*: 732.2932 Calcd for $C_{44}H_{44}O_{10}$ (M^+). Found: 732.2893. MS *m/z*: 732 (M^+), 672, 612, 582, 522, 521, 431, 285, 243. IR ($CHCl_3$): 1735, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89, 1.92, 2.11 (9H, 3 × s, 3 × OAc), 3.70 (3H, s, OCH_3), 3.89 (1H, dd, J=7.1, 11.1 Hz, H_γ), 4.04 (1H, m, H_β), 4.22 (1H, dd, J=6.1, 11.1 Hz, H_γ), 4.60 (1H, d, J=11.1 Hz, OCH_2Ph), 4.96 (1H, d, J=11.1 Hz, OCH_2Ph), 5.05 (2H, d, J=2.0 Hz, CH_2OAc), 5.10, 5.11 (4H, 2 × s, 2 × OCH_2Ph), 6.06 (1H, d, J=7.8 Hz, H_α), 6.66 (1H, d, J=1.7 Hz, $H_{2'}$), 6.72 (1H, dd, J=1.7, 8.4 Hz, $H_{6'}$), 6.78 (1H, d, J=8.4 Hz, $H_{5'}$), 6.94 (1H, d, J=1.7 Hz, H_4 or H_6), 7.02 (1H, d, J=1.7 Hz, H_4 or H_6), 7.23—7.46 (15H, m, 15 × aromatic protons).

The Phenylborate (10a) A mixture of **10** (35 mg) and phenylboronic acid (7.0 mg) in anhydrous dioxane (0.5 ml) and anhydrous benzene (5 ml) was refluxed for 4 h, collecting the water in a Dean–Stark head. After cooling, the solvent was removed. The resulting oil was purified by preparative TLC on silica gel using $CHCl_3$–MeOH (20 : 1) to give a colorless oil (31 mg, 81%). ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, OCH_3), 3.92 (1H, dd, J=4.0, 10.4 Hz, H_γ), 4.01 (1H, ddd, J=4.0, 4.0, 10.4 Hz, H_β), 4.18 (1H, dd, J=10.4, 10.4 Hz, H_γ), 4.29 (2H, s, CH_2OH), 4.99 (1H, d, J=11.1 Hz, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.11 (1H, d, J=11.1 Hz, OCH_2Ph), 5.15 (2H, s, OCH_2Ph), 5.30 (1H, d, J=4.0 Hz, H_α), 5.72 (1H, d, J=1.7 Hz, H_4 or H_6), 6.10 (1H, d, J=2.0 Hz, $H_{2'}$), 6.46 (1H, dd, J=2.0, 8.4 Hz, $H_{6'}$), 6.75 (1H, d, J=8.4 Hz, $H_{5'}$), 6.96 (1H, d, J=1.7 Hz, H_4 or H_6), 7.23—7.50 (18H, m, aromatic protons), 7.90 (2H, dd, J=1.4, 7.7 Hz, aromatic protons).

***erythro*-1-(4-Hydroxy-3-methoxyphenyl)-2-(2,3-dihydroxy-5-hydroxymethylphenyl)-1,3-propanediol (13)** A solution of **10** (4.5 g) in MeOH (300 ml) was subjected to catalytic reduction over 10% Pd–C (900 mg). After absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was evaporated to give a brown oil. The oil was purified by column chromatography on silica gel using $CHCl_3$–MeOH (5 : 1) to afford **13** (1.65 g, 66%) as a colorless oil. SIMS *m/z*: 335 ($M^+ + H$). IR (KBr): 3925, 3350, 1600 cm^{-1}.

Acetylation of 13 (Formation of 14) A mixture of **13** (30 mg), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was treated by a similar procedure to that described for **11**. The resulting oil was purified by preparative TLC on silica gel using AcOEt–benzene (1 : 3) to afford **14** (45 mg, 86%) as a colorless oil. High-resolution MS *m/z*: 588.1840 Calcd for $C_{29}H_{32}O_{13}$ (M^+). Found: 588.1826. MS *m/z*: 588 (M^+), 546, 486, 444, 426, 384, 342, 292, 283, 250, 237, 208, 195, 190, 165, 153, 147, 137. IR ($CHCl_3$): 1765, 1740, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.94, 1.97, 2.10, 2.26, 2.29, 2.33 (18H, 6 × s, 6 × OAc), 3.70 (3H, s, OCH_3), 3.78 (1H, m, H_β), 4.10 (1H, dd, J=7.1, 11.1 Hz, H_γ), 4.37 (1H, dd, J=6.1, 11.1 Hz, H_γ), 5.03 (2H, d, J=2.0 Hz, CH_2OAc), 6.04 (1H, d, J=7.8 Hz, H_α), 6.65 (1H, d, J=1.7 Hz, $H_{2'}$), 6.84 (1H, dd, J=1.7, 8.4 Hz, $H_{6'}$), 6.98 (1H, d, J=8.4 Hz, $H_{5'}$), 7.05 (1H, d, J=1.7 Hz, H_4 or H_6), 7.15 (1H, d, J=1.7 Hz, H_4 or H_6).

3-Hydroxymethyl-2-(4-hydroxy-3-methoxyphenyl)-7-hydroxy-5-acetoxymethyl-2,3-dihydrobenzofuran (15) Boron trifluoride etherate (1.1 ml) was added dropwise to a stirred solution of **13** (1.65 g) in AcOH (150 ml) cooled to 5 °C. Stirring was continued at the same temperature for 15 min. The reaction mixture was poured into ice-water and then extracted with AcOEt. The AcOEt layer was washed with brine, dried over Na_2SO_4, and evaporated to give a brown oil. The oil was purified by column chromatography on silica gel using $CHCl_3$–MeOH (15 : 2) to afford **15** (1.37 g, 77%) as a colorless oil. High resolution MS *m/z*: 360.1207 Calcd for $C_{19}H_{20}O_7$ (M^+). Found: 360.1216. MS *m/z*: 360 (M^+), 342, 330, 292, 270, 251, 239, 181, 152, 137, 116. IR ($CHCl_3$): 3550, 3400, 1740, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, OAc), 3.57 (1H, m, H_β), 3.78 (3H, s, OCH_3), 3.85 (1H, dd, J=4.7, 11.1 Hz, H_γ), 3.92 (1H, dd, J=6.1, 11.1 Hz, H_γ), 4.96 (2H, d, J=1.7 Hz, CH_2OAc), 5.52 (1H, d, J=6.7 Hz, H_α), 6.75—6.84 (5H, m, 5 × aromatic protons).

Acetylation of 15 (Formation of 16) A mixture of **15** (5 mg), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was treated by a similar procedure to that described for **11**. The resulting oil was purified by preparative TLC on silica gel using AcOEt–benzene (1 : 10) to afford **16** (6.2 mg, 92%) as a colorless oil. High-resolution MS *m/z*: 486.1524 Calcd for $C_{25}H_{26}O_{10}$ (M^+). Found: 486.1505. MS *m/z*: 486 (M^+), 444, 426, 384, 342, 324, 310, 282, 269, 251, 195. IR ($CHCl_3$): 1760, 1740, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08, 2.09 (6H, 2 × s, 2 × OAc), 2.31 (6H, s, 2 × OAc), 3.74 (1H, m, H_β), 3.83 (3H, s, OCH_3), 4.30 (1H, dd, J=7.7, 11.1 Hz, H_γ), 4.45 (1H, dd, J=5.7, 11.1 Hz, H_γ), 5.03 (2H, s, CH_2OAc), 5.59 (1H, d, J=5.7 Hz, H_α), 6.89 (1H, dd, J=2.0, 8.4 Hz, $H_{6'}$), 7.01 (1H, d, J=1.7 Hz, H_2 or H_6), 7.02 (1H, d, J=8.4 Hz, $H_{5'}$), 7.03 (1H, d, J=2.0 Hz, $H_{2'}$), 7.09 (1H, d, J=1.7 Hz, H_2 or H_6).

Methoxymethylation of 15 (Formation of 17) A solution of methoxymethyl chloride (7.6 ml) in dry CH_2Cl_2 (20 ml) was added dropwise to a mixture of **15** (2 g) in dry CH_2Cl_2 (150 ml) containing diisopropylethylamine (14.7 ml) with stirring. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into ice-water. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to give a brown oil. The oil was purified by column chromatography on silica gel using AcOEt–benzene (1 : 5) to afford **17** (1.81 g, 66%) as a colorless oil. High-resolution MS *m/z*: 492.1993 Calcd for $C_{25}H_{32}O_{10}$ (M^+). Found: 492.1992. MS *m/z*: 492 (M^+), 430, 385, 357, 326, 313, 281. IR ($CHCl_3$): 1740, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, OAc), 3.36, 3.50, 3.52 (9H, 3 × s, 3 × CH_2OCH_3), 3.69 (1H, m, H_β), 3.79 (1H, dd, J=7.1, 9.6 Hz, H_γ), 3.85 (1H, m, H_γ), 3.86 (3H, s, OCH_3), 4.67, 5.22 (4H, 2 × s, 2 × CH_2OCH_3), 5.02 (2H, d, J=1.7 Hz, CH_2OAc), 5.24 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.28 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.57 (1H, d, J=6.7 Hz, H_α), 6.92 (1H, dd, J=2.0, 8.4 Hz, $H_{6'}$), 6.94 (1H, d, J=1.7 Hz, H_2 or H_6), 6.98 (1H, d, J=2.0 Hz, $H_{2'}$), 7.06 (1H, d, J=1.7 Hz, H_2 or H_6), 7.12 (1H, d, J=8.4 Hz, $H_{5'}$).

Hydrolysis of 17 (Formation of 18) A solution of 1 N NaOH (7.5 ml) was added to a solution of **17** (1.1 g) in MeOH (20 ml) and the whole was stirred at room temperature for 1 h. The reaction mixture was neutralized with 1 N HCl, poured into water, and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give an oil. The oil was purified by column chromatography on silica gel using AcOEt–benzene (1 : 3) to afford **18** (920 mg, 91%) as a colorless oil. High-resolution MS *m/z*: 450.1887 Calcd for $C_{23}H_{30}O_9$ (M^+). Found: 450.1867. MS *m/z*: 450 (M^+), 388, 375, 343, 326, 313, 299, 281, 181. IR ($CHCl_3$): 3600, 3020, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.36, 3.50, 3.52 (9H, 3 × s, 3 × CH_2OCH_3), 3.68 (1H, m, H_β), 3.79 (1H, dd, J=7.1, 9.6 Hz, H_γ), 3.84 (1H, dd, J=6.1, 9.6 Hz, H_γ), 3.85 (3H, s, OCH_3), 4.61 (2H, s, CH_2OH), 4.67, 5.21 (4H, 2 × s, 2 × CH_2OCH_3), 5.24 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.28 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.57 (1H, d, J=6.7 Hz, H_α), 6.92 (1H, dd, J=2.0, 8.4 Hz, $H_{6'}$), 6.94 (1H, d, J=1.7 Hz, H_2 or H_6), 6.97 (1H, d, J=2.0 Hz, $H_{2'}$), 7.06 (1H, d, J=1.7 Hz, H_2 or H_6), 7.11 (1H, d, J=8.4 Hz, $H_{5'}$).

Oxidation of 18 (Formation of 19) Freshly prepared manganese dioxide (2.0 g) was added gradually to a solution of **18** (700 mg) in CH_2Cl_2 (20 ml). The suspension was vigorously stirred for 30 min. The reaction mixture was filtered and the filtrate was evaporated to give an oil. The oil was purified by column chromatography on silica gel using AcOEt–benzene (1 : 5) to afford **19** (660 mg, 95%) as a colorless oil. High-resolution MS *m/z*: 448.1731 Calcd for $C_{23}H_{28}O_9$ (M^+). Found: 448.1717. MS *m/z*: 448 (M^+), 418, 416, 385, 373, 341, 312, 297, 181. IR ($CHCl_3$): 1690, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.32, 3.51, 3.53 (9H, 3 × s, 3 × CH_2OCH_3), 3.76 (1H, m, H_β), 3.82 (1H, m, H_γ), 3.86 (3H, s, OCH_3), 3.87 (1H, m, H_γ), 4.68, 5.22 (4H, 2 × s, 2 × CH_2OCH_3), 5.28 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.32 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.67 (1H, d, J=

6.7 Hz, H_α), 6.91 (1H, d, J=2.0, 8.4 Hz, $H_{6'}$), 6.95 (1H, d, J=2.0 Hz, $H_{2'}$), 7.14 (1H, d, J=8.4 Hz, $H_{5'}$), 7.52 (1H, d, J=1.7 Hz, H_2 or H_6), 7.60 (1H, d, J=1.7 Hz, H_2 or H_6), 9.83 (1H, s, CHO).

2,4,6-Tris(methoxymethoxy)acetophenone (20) A solution of 2,4,6-trihydroxyacetophenone (8 g) in DMF (40 ml) was added dropwise to a suspension of NaH (60% dispersion in mineral oil) (11 g) in DMF (400 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 15 min and then methoxymethyl chloride (22 ml) was added. Stirring was continued for 2 h, then the reaction mixture was poured into ice-water. The resulting mixture was extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give a solid. The solid was recrystallized from ether to afford **20** (10.3 g, 72%) as colorless needles, mp 39—41 °C (lit.[17] mp 40—42 °C).

Condensation of 19 with 20 under Alkaline Conditions (Formation of 21) A mixture of **19** (618 mg), **20** (414 mg), and sodium hydroxide (600 mg) in absolute EtOH (15 ml) was stirred for 4 h under a nitrogen atmosphere. The mixture was poured into ice-water and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated to give a yellow oil. The oil was purified by column chromatography on silica gel using $CHCl_3$–acetone (1 : 4) to afford **21** (950 mg, 94%) as a yellow oil. High-resolution MS m/z: 730.2833 Calcd for $C_{37}H_{46}O_{15}$ (M^+). Found: 730.2893. MS m/z: 730 (M^+), 685, 623, 591, 547, 477, 285, 271, 181. IR ($CHCl_3$): 1640, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.35 (3H, s, CH_2OCH_3), 3.40 (6H, s, $2\times CH_2OCH_3$), 3.50 (3H, s, CH_2OCH_3), 3.51 (6H, s, $2\times CH_2OCH_3$), 3.69 (1H, m, H_β), 3.81 (2H, m, H_γ), 3.86 (3H, s, OCH_3), 4.67 (2H, s, CH_2OCH_3), 5.12 (4H, s, $2\times CH_2OCH_3$), 5.20, 5.22 (4H, $2\times$s, $2\times CH_2OCH_3$), 5.23 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.27 (1H, d, J=6.7 Hz, CH_2OCH_3), 5.60 (1H, d, J=6.7 Hz, H_α), 6.57 (2H, s, H_3 and H_5), 6.85 (1H, d, J=16.1 Hz, olefin H_α), 6.91 (1H, dd, J=2.0, 8.4 Hz, $H_{6''}$), 6.95 (1H, d, J=2.0 Hz, $H_{2''}$), 7.12 (1H, d, J=8.4 Hz, $H_{5''}$), 7.16 (1H, s, $H_{2'}$ or $H_{6'}$), 7.25 (1H, s, $H_{2'}$ or $H_{6'}$), 7.28 (1H, d, J=16.1 Hz, olefin H_β).

Reaction of 21 with Alkaline Hydrogen Peroxide (Formation of 22) A solution of 30% H_2O_2 (10 ml) and 5% NaOH (10 ml) was added to a solution of **21** (950 mg) in MeOH (50 ml) and the whole was stirred at room temperature for 4 h. The reaction mixture was poured into ice-water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give **22** (930 mg, 96%) as a colorless oil. MS m/z: 746 (M^+), 719, 508, 448, 418, 386, 341, 312, 297, 285, 181, 151. IR ($CHCl_3$): 1730, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.35 (3H, s, CH_2OCH_3), 3.40 (6H, s, $2\times CH_2OCH_3$), 3.47, 3.49, 3.50 (9H, $3\times$s, $3\times CH_2OCH_3$), 3.66 (1H, m, H_β), 3.78 (2H, m, H_γ), 3.85 (3H, s, OCH_3), 3.90 (1H, d, J=2.0 Hz, epoxy H_α or epoxy H_β), 3.94 (1H, d, J=2.0 Hz, epoxy H_α or epoxy H_β), 4.65 (2H, s, CH_2OCH_3), 5.12, 5.13, 5.16, 5.21 (8H, $4\times$s, $4\times CH_2OCH_3$), 5.56 (1H, d, J=6.7 Hz, H_α), 6.52 (2H, s, H_3 and H_5), 6.88 (1H, d, J=1.7 Hz, $H_{2'}$ or $H_{6'}$), 6.92 (1H, dd, J=2.0, 8.4 Hz, $H_{6''}$), 6.98 (1H, d, J=1.7 Hz, $H_{2'}$ or $H_{6'}$), 7.00 (1H, d, J=2.0 Hz, $H_{2''}$), 7.11 (1H, d, J=8.4 Hz, $H_{5''}$).

Silychristin (1) and Its Isomer (23) A mixture of MeOH (8 ml) and concentrated HCl (2 ml) was added dropwise to a solution of **22** (450 mg) in MeOH (30 ml) and the reaction mixture was heated at 70 °C for 15 min. After cooling, the reaction mixture was poured into ice-water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give a yellow oil. The oil was chromatographed on a silica gel column using $CHCl_3$–MeOH (15 : 2) to provide a mixture (270 mg) of **1** and **23**. A portion of the mixture (200 mg) was separated into two peaks at t_R (min) 28.0 (**1**) and 40.0 (**23**) by HPLC. Conditions: column, Develosil pack ODS-5, 10 × 250 mm; eluent, H_2O–MeOH–AcOH (70 : 30 : 5); flow rate, 5.0 ml/min; detector, ultraviolet (UV) detector (280 nm). Each peak of **1** and **23** was collected by repeated HPLC under the above-mentioned conditions, yielding **1** (41 mg, 19%) as a colorless amorphous powder and **23** (35 mg, 16%) as a colorless amorphous powder.

1: FAB-MS m/z: 483.1301 (Calcd for $C_{25}H_{22}O_{10}$+H: 483.1291). IR (KBr): 3400, 1650 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.61 (1H, m, H_β), 3.84 (3H, s, OCH_3), 3.86 (1H, m, H_γ), 3.92 (1H, dd, J=5.7, 11.1 Hz, H_γ), 4.64 (1H, d, J=11.4 Hz, H_2), 5.05 (1H, d, J=11.4 Hz, H_3), 5.59 (1H, d, J=6.7 Hz, H_α), 5.96 (1H, d, J=2.0 Hz, H_6), 6.00 (1H, d, J=2.0 Hz, H_8), 6.83 (1H, d, J=8.4 Hz, $H_{5''}$), 6.93 (1H, dd, J=2.0, 8.4 Hz, $H_{6''}$), 7.00 (1H, d, J=1.7 Hz, $H_{2'}$ or $H_{6'}$), 7.03 (1H, d, J=1.7 Hz, $H_{2'}$ or $H_{6'}$), 7.10 (1H, d, J=2.0 Hz, $H_{2''}$). ^{13}C-NMR (CD_3OD) δ: 198.2 (s, C-4), 168.7 (s, C-7), 165.2 (s, C-5), 164.4 (s, C-9), 149.1 (s, C-3′′), 147.5 (s, C-3′ and C-4′′), 142.1 (s, C-4′), 134.7 (s, C-1′′), 131.5 (s, C-5′), 130.1 (s, C-1′), 119.8 (d, C-6′′), 117.0 (d, C-6′), 116.6 (d, C-2′), 116.2 (d, C-5′′), 110.7 (d, C-2′′), 101.8 (s, C-10), 97.4 (d, C-6), 96.3 (d, C-8), 89.1 (d, C-α), 85.2 (d, C-2), 73.7 (d, C-3), 64.8 (t, C-γ), 56.4 (q, OCH_3), 55.4 (d, C-β).

The synthetic silychristin (**1**) was shown to be identical with an authentic sample[7] by comparison of the spectroscopic data (MS, ^{1}H-NMR, and ^{13}C-NMR) and the retention time in HPLC.

23: FAB-MS m/z: 483.1328 (Calcd for $C_{25}H_{22}O_{10}$+H: 483.1291). IR (KBr): 3400, 1650 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.61 (1H, m, H_β), 3.84 (1H, s, OCH_3), 3.85 (1H, m, H_γ), 3.92 (1H, dd, J=5.7, 11.1 Hz, H_γ), 4.67 (1H, d, J=11.4 Hz, H_2), 5.05 (1H, d, J=11.4 Hz, H_3), 5.60 (1H, d, J=6.7 Hz, H_α), 5.96 (1H, d, J=2.0 Hz, H_6), 6.00 (1H, d, J=2.0 Hz, H_8), 6.83 (1H, d, J=8.4 Hz, $H_{5''}$), 6.93 (1H, dd, J=2.0, 8.4 Hz, $H_{6''}$), 6.99 (1H, d, J=1.7 Hz, $H_{2'}$ or $H_{6'}$), 7.04 (1H, d, J=1.7 Hz, $H_{2'}$ or $H_{6'}$), 7.10 (1H, d, J=2.0 Hz, $H_{2''}$). ^{13}C-NMR (CD_3OD) δ: 198.2 (s, C-4), 168.7 (s, C-7), 165.2 (s, C-5), 164.4 (s, C-9), 149.0 (s, C-3′′), 147.5 (s, C-3′ and C-4′′), 142.1 (s, C-4′), 134.8 (s, C-1′′), 131.5 (s, C-5′), 130.0 (s, C-1′), 119.7 (d, C-6′′), 116.9 (d, C-6′), 116.6 (d, C-2′), 116.2 (d, C-5′′), 110.6 (d, C-2′′), 101.8 (s, C-10), 97.4 (d, C-6), 96.3 (d, C-8), 89.1 (d, C-α), 85.2 (d, C-2), 73.8 (d, C-3), 64.8 (t, C-γ), 56.4 (q, OCH_3), 55.5 (d, C-β).

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