Arylnaphthalene Lignans as Novel Series of Hypolipidemic Agents Raising High-Density Lipoprotein Level[1)]

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A series of arylnaphthalene lignans were synthesized and tested for hypolipidemic activity. The most potent compound (4b) (TA-7552) not only reduced serum cholesterol, but also increased high-density lipoproteins cholesterol in rats. The effective dose of 4b is 100 times less than that of cholestyramine. Structure–activity relationships are discussed.

Key words lignan; hypolipidemic activity; high-density lipoprotein

Hypercholesterolemia is a major risk factor in the development of atherosclerosis and related disease.[2)] The lowering of abnormally elevated levels of atherogenic lipoproteins, very low-density and low-density lipoproteins (VLDL and LDL), is now accepted as the first line of approach to the treatment of hypercholesterolemic patients.[3)] Since high-density lipoproteins (HDL) have been reported to be antiatherogenic,[4)] elevation of HDL cholesterol levels would also be expected to retard the progression of atherosclerosis.[5)] Hence, a substantial effort has been devoted to finding agents that increase HDL cholesterol, and decrease VLDL and LDL cholesterols.[6)]

Lignans, known as plants constituents, have aroused considerable interest in recent years, because they show a broad range of biological activities.[7)] Several lignans have been found in human and animal urine,[8)] and the biological roles of the endogenous lignans have been the subject of extensive investigation.[9)]

During the course of screening for hypolipidemic agents of novel structure, we discovered that 2,3-bis(methoxy-

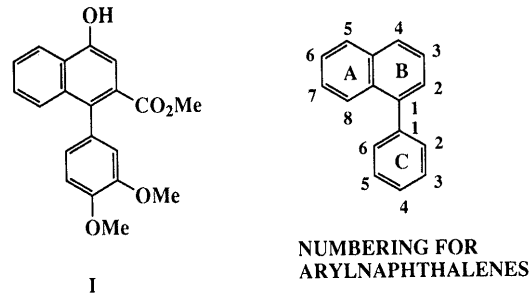

Chart 1

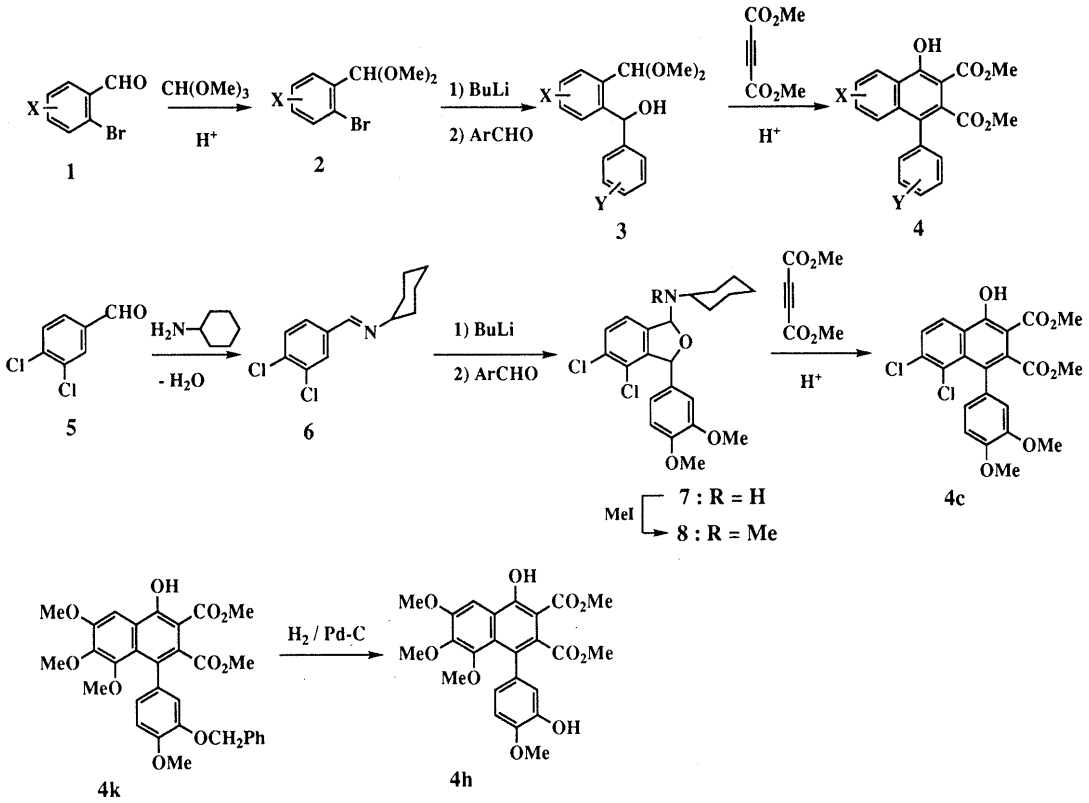

Chart 2

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carbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7-methylenedioxynaphthalene (**4a**), a lignan of the arylnaphthalene series, exhibits marked hypolipidemic and HDL cholesterol-elevating activities. Since this compound is structurally distinct from known agents, we synthesized a series of analogs to examine their biological activity. The following report describes the synthesis and structure–activity relationships of the arylnaphthalene lignans.

Chemistry

The compounds employed in this study were synthesized according to published procedures (Charts 2—4).[10] The dimethyl esters of 1-aryl-4-hydroxynaphthalene-2,3-dicarboxylic acid **4** were synthesized as shown in Chart 2. The key intermediate hydroxy-acetals **3** were prepared by acetalization of the bromoaldehydes **1**,[11] followed by bromine–lithium exchange and quenching with aldehydes. The resultant hydroxy-acetals **3**, or cyclic-acetal **8**, which was prepared from the imine **6**, were converted to the desired diesters **4** in a one-pot manner *via* the Diels–Alder reaction of the *in situ*-generated isobenzofurans followed by aromatization.[12] The 1-arylmethyl derivative **9**, the monoester **10** and the dicarboxlic acid derivative **13** were prepared in a similar manner. Preparation of the lactone **11** was performed by selective reduction of the ester proximate to the hydroxy group of the diester **4a** with borane (Chart 3).[12a] The 4-methoxy derivative **12** was prepared by the methylation of the 4-hydroxy group of **4b**. The 4-hydroxytetralin derivative **16** was prepared by reacting the cyclic acetal **14** with dimethyl maleate followed by hydrogenolysis (Chart 4).[13]

Biological Results

The test compounds were evaluated for hypolipidemic activity in diet-induced hypercholesterolemic rats. Plasma total cholesterol and HDL cholesterol were measured and the percent change *vs.* the control was determined (Table 1).

It is evident from Table 1 that optimal activity, both in hypolipidemic properties and in HDL cholesterol-raising ability, was found in compounds which contained 1-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-4-hydroxynaphthalene (I, Chart 1) as a core structure (**4a**—**d**, **4i**, **10**, **11**). Introduction of a methoxycarbonyl group at the C-3 position of **10** led to an increase in activity (**4b**). Conversion of the 2,3-dimethoxycarbonyl groups of **4a** to a lactone diminished the activity (**11**). Replacement of the 6,7,8-trimethoxy groups of **4b** by two chlorine atoms retained the activity (**4c**), whereas dimethoxy substitution decreased the activity (**4j**). The C-4 hydroxy group of the B-ring is required for activity, because replacement with a methoxy group in compound **4b** led to an inactive compound, **12**. The B-ring needs to be aromatic on the basis of the complete loss of activity of the tetralin **16**. Replacement of the methoxycarbonyl groups in **4b** by carboxyl groups (**13**) considerably diminished the activity. Modification of the 3,4-dimethoxy groups of the C-ring (**4e**—**h**) generally resulted in dramatic reduction of the activity, except for the 3,4-diethoxy derivative **4i**. Introduction of a spacer methylene group between the

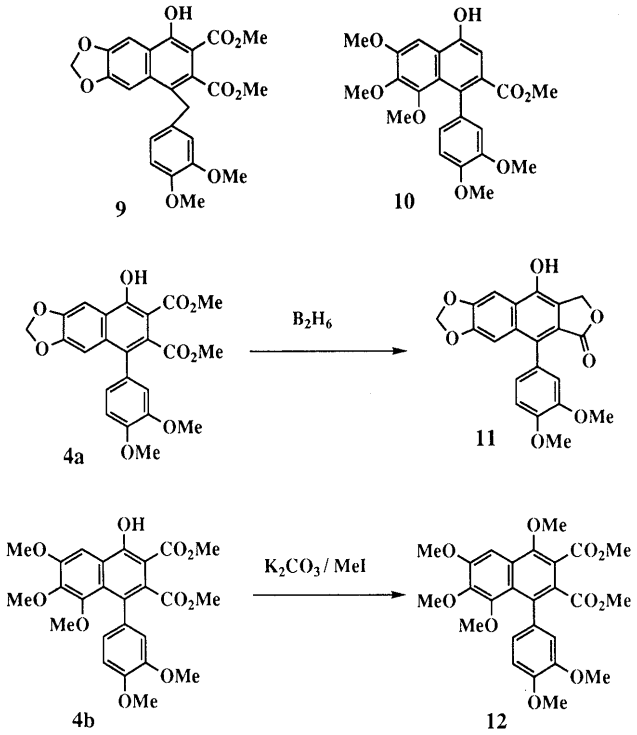


Chart 3

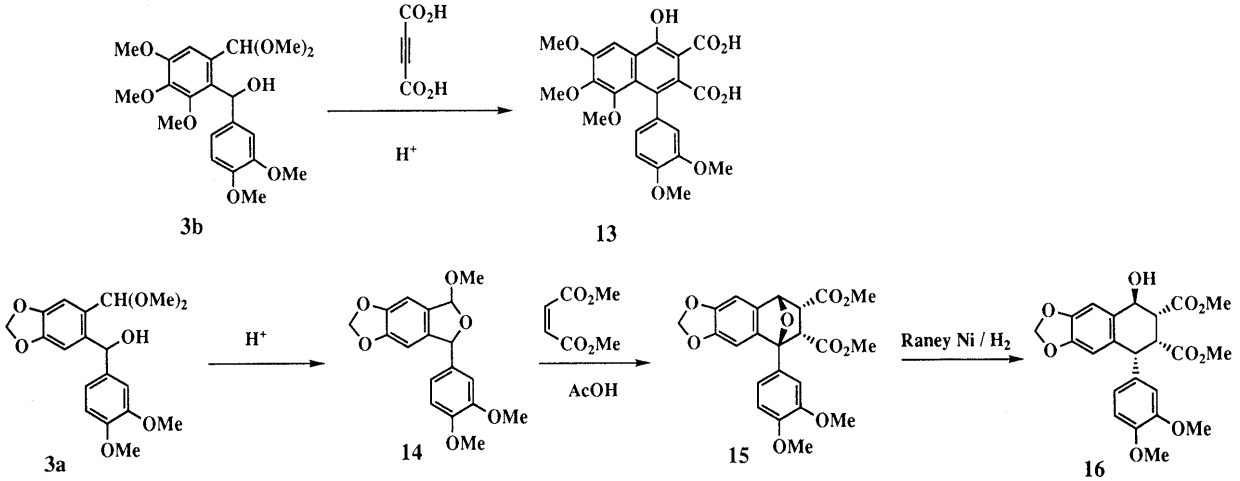
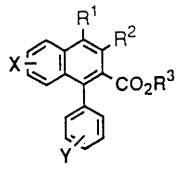
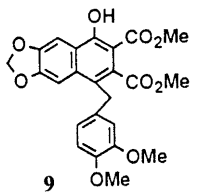


Chart 4

Table 1. Hypolipidemic Results on Cholesterol-Fed Rats[a]



	R^1	R^2	R^3
4	OH	CO_2Me	Me
10	OH	H	Me
11	OH	$-CH_2-$	
12	OMe	CO_2Me	Me
13	OH	CO_2H	H



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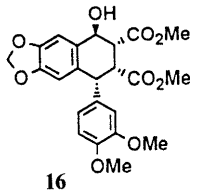

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Compd.	X	Y	Serum cholesterol[b]	HDL-cholesterol[b]
4a	6,7-OCH_2O–	3,4-$(OMe)_2$	−60	+79
4b	6,7,8-$(OMe)_3$	3,4-$(OMe)_2$	−52	+98
4c	7,8-Cl_2	3,4-$(OMe)_2$	−42	+94
4d	H	3,4-$(OMe)_2$	−61	+101
4e	6,7-OCH_2O–	4-MeO	−27	+35
4f	6,7,8-$(OMe)_3$	3,4-OCH_2O–	+4	+17
4g	6,7,8-$(OMe)_3$	3,4,5-$(OMe)_3$	−36	+44
4h	6,7,8-$(OMe)_3$	3-OH, 4-MeO	+22	−2
4i	6,7-OCH_2O–	3,4-$(OEt)_2$	−60	+67
4j	6,7-$(OMe)_2$	3,4-$(OMe)_2$	−38	+24
9	6,7-OCH_2O–	3,4-$(OMe)_2$	+1	+9
10	6,7,8-$(OMe)_3$	3,4-$(OMe)_2$	−44	+70
11	6,7-OCH_2O–	3,4-$(OMe)_2$	−51	+60
12	6,7,8-$(OMe)_3$	3,4-$(OMe)_2$	−10	−4
13	6,7,8-$(OMe)_3$	3,4-$(OMe)_2$	−21	−5
16	6,7-OCH_2O–	3,4-$(OMe)_2$	−14	−3

a) Groups of 5 or 6 male Sprague–Dawley rats were fed a diet containing 2% cholesterol and 0.5% sodium cholate for 7 d. All compounds were dosed at 0.1% of the diet for the last 3 d. The value in the table was determined on the 8th day. *b*) % change *vs.* control. +, increase of cholesterol; −, decrease of cholesterol.

B-ring and the C-ring (**9**) led to complete loss of activity.

On the basis of structural novelty and ease of synthesis, as well as hypolipidemic activity, compound **4b** was selected for further evaluation as a hypolipidemic drug. In direct comparison studies, **4b** demonstrated hypolipidemic activity greater than that of the known agents, cholestyramine, bezafibrate and probucol, in cholesterol-fed rats. Compound **4b** was roughly 100 times more potent than cholestyramine in lowering serum and liver cholesterol, and elevating HDL cholesterol. The results of a mechanistic study indicated that compound **4b** inhibits intestinal absorption of both cholesterol and bile acids. The details of these studies have been reported in a separate paper.[1)]

In conclusion, we have discovered a novel class of hypolipidemic agents having a lignan structure. The most interesting compound in this series, compound **4b**, has greater activity than cholestyramine. The results of further studies on the biological activities of compound **4b** (TA-7552) will be reported at a later date.

Experimental

Melting points were determined in open capillary tubes on a Yamato MP-21 melting point apparatus, without correction. Infrared (IR) spectra were obtained using a Perkin Elmer 1640 IR spectrometer. NMR spectra were recorded on a Hitachi R-90 or a Bruker AC-200 instrument using Me_4Si as an internal standard. Mass spectra (MS) were obtained on a Hitachi M-60 or Hitachi M-2000A spectrometer.

Preparation of the Bromoacetals (2a, b, d) The bromoacetals (**2a, b, d**) were prepared according to the reported method.[10)] 2-Bromo-4,5-methylenedioxybenzaldehyde dimethylacetal (**2a**): 94% yield, bp 130 °C (0.2 mmHg). 2-Bromo-3,4,5-trimethoxybenzaldehyde dimethylacetal (**2b**): 95% yield, bp 140 °C (0.2 mmHg). 2-Bromobenzaldehyde dimethylacetal (**2d**): 93% yield, bp 120°C (1 mmHg).

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7-methylenedioxynaphthalene (4a) BuLi (15% hexane solution) (43 ml, 69 mmol) was added to a solution of 2-bromo-4,5-methylenedioxybenzaldehyde dimethylacetal (**2a**) (20.4 g, 69 mmol) in 80 ml of tetrahydrofuran (THF) at −70 °C. The mixture was stirred at the same temperature for 15 min, then a solution of 3,4-dimethoxybenzaldehyde (10.4 g, 69 mmol) in 30 ml of THF was added at −70 °C. The reaction mixture was stirred at the same temperature for 15 min, diluted with water (200 ml) and extracted with AcOEt. The organic extract was washed with water and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure to give 26.6 g of 2-(3,4-dimethoxy-α-hydroxybenzyl)-4,5-methylenedioxybenzaldehyde dimethylacetal (**3a**) as a yellow oil. The crude product was used without purification in the next step. A mixture of the hydroxy-acetal **3a** (26.6 g) and dimethyl acetylenedicarboxylate (9.5 ml, 83 mmol) was heated under reflux in 10 ml of benzene in the presence of 30 mg of *p*-toluenesulfonic acid monohydrate. After 2 h, the mixture was cooled and concentrated under reduced pressure. To the residue was added 60 ml of methanol, and the mixture was allowed to stand at −30 °C overnight. Crystalline precipitates were collected by filtration and recrystallized from AcOEt to give **4a** (26.4 g, 87%) as colorless prisms, mp 130—133 °C. IR (Nujol): 1730, 1672, 1595, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.55 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 6.03 (s, 2H), 6.77 (s, 1H), 6.85—6.95 (m, 3H), 7.75 (s, 1H), 12.20 (s, 1H). MS *m/z*: 440 (M^+). *Anal.* Calcd for $C_{23}H_{20}O_9$: C, 62.93; H, 4.58. Found: C, 62.78; H, 4.62.

Compounds **4b, d, e, f, g** and **h** were prepared by the same procedure as described above.

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (**4b**): 83% yield. Colorless prisms, mp 178—179 °C. IR (Nujol): 1730, 1660, 1595, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.21 (s, 3H), 3.45 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 4.00 (s, 3H), 6.50—7.10 (m, 3H), 7.60 (s, 1H), 12.50 (br, 1H). MS *m/z*: 486 (M^+). *Anal.* Calcd for $C_{25}H_{26}O_{10}$: C, 61.72; H, 5.39. Found: C, 61.9; H, 5.35.

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-naphthalene (**4d**): 78% yield. Colorless crystals, mp 182—184 °C. IR (Nujol): 1740, 1660, 1620, 1590, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.58 (s, 3H), 3.76 (s, 3H), 3.90 (s, 3H), 3.99 (s, 3H), 6.70—7.20 (m, 3H), 7.40—7.90 (m, 3H), 8.30—8.36 (m, 1H), 12.00 (br, 1H). MS *m/z*: 396 (M^+). *Anal.* Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.47; H, 5.12.

2,3-Bis(methoxycarbonyl)-4-hydroxy-1-(4-methoxyphenyl)-6,7-methylenedioxynaphthalene (**4e**): 81% yield. Colorless prisms, mp 169—171 °C. IR (Nujol): 1740, 1660, 1610, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.55 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 6.03 (s, 2H), 6.72 (s, 1H), 7.00 (d, J=8.0 Hz, 2H), 7.20 (d, J=8.0 Hz, 2H), 7.75 (s, 1H), 12.00 (s, 1H). MS *m/z*: 410 (M^+). *Anal.* Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.46; H, 4.31.

2,3-Bis(methoxycarbonyl)-4-hydroxy-6,7,8-trimethoxy-1-(3,4-methylenedioxyphenyl)naphthalene (**4f**): 53% yield. Colorless prisms, mp 188—189 °C. IR (Nujol): 1730, 1670, 1590, 1490 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.21 (s, 3H), 3.42 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 5.85 (s, 2H), 6.60—6.70 (m, 3H), 7.50 (s, 1H), 12.12 (s, 1H). MS *m/z*: 470 (M^+). *Anal.* Calcd for $C_{24}H_{22}O_{10}$: C, 61.28; H, 4.71. Found: C, 61.17; H, 4.92.

2,3-Bis(methoxycarbonyl)-4-hydroxy-6,7,8-trimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (**4g**): 51% yield. Colorless needles, mp 162—163 °C. IR (Nujol): 1740, 1660, 1620, 1600, 1580, 1500 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.46 (s, 3H), 3.60 (s, 3H), 3.81 (s, 3H), 3.86 (s, 6H), 3.99 (s, 6H), 6.10 (s, 2H), 6.56 (s, 2H), 6.75 (s, 1H), 6.85 (s, 1H), 12.25 (s, 1H). MS *m/z*: 516 (M^+). *Anal.* Calcd for $C_{26}H_{28}O_{11}$: C, 60.46; H, 5.46. Found: C, 60.56; H, 5.37.

2,3-Bis(methoxycarbonyl)-4-hydroxy-1-(3-hydroxy-4-methoxyphenyl)-6,7,8-trimethoxynaphthalene (**4h**): 1-(3-Benzyloxy-4-methoxyphenyl)-2,3-bis(methoxycarbonyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (**4k**) was prepared by the same procedure as used for the preparation of **4a** from **2b** and 3-benzyloxy-4-methoxybenzaldehyde. 38% yield.

Colorless needles, mp 166—167 °C. IR (Nujol): 1730, 1665, 1610, 1590, 1510 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.10 (s, 3H), 3.40 (s, 3H), 3.83 (s, 3H), 3.90 (s, 6H), 4.00 (s, 3H), 5.11 (s, 3H), 6.80—7.00 (m, 3H), 7.10—7.50 (m, 4H), 7.61 (s, 1H), 12.34 (s, 1H). MS *m/z*: 562 (M^+). *Anal.* Calcd for $C_{31}H_{30}O_{10}$: C, 66.19; H, 5.38. Found: C, 66.28; H, 5.33.

A solution of **4k** (2.5 g, 4.4 mmol) in THF (100 ml) and MeOH (30 ml) was hydrogenated over 10% Pd–C (2.5 g) at 50 psi at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and crystallized from hexane to give **4h** (2.1 g, 99%) as colorless needles, mp 204 °C. IR (Nujol): 3300, 1740, 1670, 1600, 1590 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 3.53 (s, 3H), 3.71 (s, 3H), 3.73, (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.02 (s, 3H), 6.70—7.10 (m, 4H), 11.50 (br, 1H), 12.10 (br, 1H). MS *m/z*: 472 (M^+). *Anal.* Calcd for $C_{24}H_{24}O_{10}$: C, 61.01; H, 5.12. Found: C, 61.13; H, 5.09.

2,3-Bis(methoxycarbonyl)-1-(3,4-diethoxyphenyl)-4-hydroxy-6,7-methylenedioxynaphthalene (**4i**): 54% yield. Colorless needles, mp 158—159 °C. IR (Nujol): 1750, 1660, 1620, 1600, 1590, 1580 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 1.30 (t, J=7.0 Hz, 3H), 1.40 (t, J=7.0 Hz, 3H), 3.50 (s, 3H), 3.90 (s, 3H), 4.00 (q, J=7.0 Hz, 2H), 4.10 (q, J=7.0 Hz, 2H), 6.18 (s, 2H), 6.60—6.86 (m, 3H), 7.03 (d, J=6.0 Hz, 1H), 7.40 (s, 1H), 11.40 (s, 1H), 11.40—12.00 (br, 1H). MS *m/z*: 468 (M^+). *Anal.* Calcd for $C_{25}H_{24}O_9$: C, 64.10; H, 5.16. Found: C, 64.03; H, 5.31.

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7-dimethoxynaphthalene (**4j**): 63% yield. mp 208—209 °C. IR (Nujol): 1730, 1660, 1620, 1600, 1590, 1510 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): 3.55 (s, 3H), 3.68 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 6.82 (s, 1H), 6.85 (d, J=7.0 Hz, 1H), 6.87 (s, 1H), 7.10 (d, J=7.0 Hz, 1H), 7.65 (s, 1H), 11.40 (s, 1H). MS *m/z*: 456 (M^+). *Anal.* Calcd for $C_{24}H_{24}O_9$: C, 63.15, H, 5.30. Found: C, 63.03; H, 5.41.

2,3-Bis(methoxycarbonyl)-7,8-dichloro-1-(3,4-dimethoxyphenyl)-4-hydroxynaphthalene (**4c**): 3,4-Dichlorobenzaldehyde cyclohexylimine (**6**) was prepared from 3,4-dichlorobenzaldehyde (**5**) (1.0 eq) and cyclohexylamine (1.2 eq) in benzene solution by azeotropic removal of water. The mixture was concentrated under reduced pressure to give **6**. 98% yield. Yellow oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.00—2.20 (m, 10H), 3.00—3.40 (m, 1H), 7.20—7.90 (m, 3H), 8.15 (s, 1H). To a solution of the imine **6** (10.24 g, 40 mmol) in 100 ml of THF, BuLi (15% hexane solution, 27 ml, 42 mmol) was added at −70 °C. The mixture was stirred at the same temperature for 10 min, then 3,4-dimethoxybenzaldehyde (6.65 g, 40 mmol) in 20 ml of THF was added. After 15 min, the reaction mixture was diluted with saturated aqueous NH_4Cl (100 ml) and extracted with Et_2O. The organic extract was washed with water and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and crystallized from hexane to give **7** (8.6 g, 51%) as colorless crystals, mp 68—69 °C. IR (Nujol): 3300, 1595, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.80—2.30 (m, 11H), 2.70—3.10 (m, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 5.90—6.40 (m, 2H), 6.60—7.00 (m, 3H), 7.22 (d, J=6.0 Hz, 1H), 7.45 (d, J=6.0 Hz, 1H). MS *m/z*: 422 (M^+). A mixture of the amine **7** (2.1 g, 5 mmol) and K_2CO_3 (0.76 g, 5.5 mmol) in 3 ml of hexamethylphosphoramide (HMPA) was treated with MeI (0.38 ml, 6 mmol) at room temperature. After 16 h, the mixture was diluted with water and extracted with AcOEt. The organic extract was washed with water and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated under reduced pressure to give **8** (2.2 g) as a yellow oil. The amine **8** thus obtained was used in the next step without purification. A mixture of the amine **8** (2.2 g) and dimethyl acetylenedicarboxylate (1.0 ml, 8 mmol) was heated under reflux in 2 ml of benzene in the presence of 0.46 ml of methanesulfonic acid. After 2 h, 100 ml of methanol was added, and the mixture was allowed to stand at −30 °C overnight. Crystalline precipitates were collected by filtration and recrystallized from AcOEt to give **4c** (1.9 g, 56%) as colorless prisms, mp 209—210 °C. IR (Nujol); 1730, 1660, 1605, 1580, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.50 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 6.60—7.10 (m, 3H), 7.80 (d, J=9.0 Hz, 1H), 8.40 (d, J=9.0 Hz, 1H), 11.98 (s, 1H). MS *m/z*: 465 (M^+). *Anal.* Calcd for $C_{22}H_{18}Cl_2O_7$: C, 56.79; H, 3.90; Cl, 15.24. Found: C, 56.83; H, 3.78; Cl, 15.31.

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxybenzyl)-4-hydroxy-6,7-methylenedioxynaphthalene (9) This compound was prepared by the same procedure as used for the preparation of **4a** from **2a** and 3,4-dimethoxyphenyl acetaldehyde, 35% yield. Colorless needles, mp 181—183 °C. IR (Nujol): 1730, 1660, 1610, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.79 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 4.11 (s, 2H), 6.02 (s, 2H), 6.60—6.80 (m, 3H), 7.16 (s, 1H), 7.72 (s, 1H), 12.16 (s, 1H). MS *m/z*: 454 (M^+). *Anal.* Calcd for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88. Found: C, 63.57; H, 4.71.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxy-2-methoxycarbonylnaphthalene (10) This compound was prepared by the same procedure as used for the preparation of **4a** from 2-(3,4-dimethoxy-α-hydroxybenzyl)-3,4,5-trimethoxybenzaldehyde dimethylacetal (**3b**) and methyl propiolate, 14% yield. Colorless prisms, mp 217—219 °C. IR (Nujol): 3400, 1730, 1700, 1610 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.20 (s, 3H), 3.41 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.92 (s, 3H), 6.70—6.90 (m, 4H), 7.35 (s, 1H), 9.05 (s, 1H). MS *m/z*: 428 (M^+). *Anal.* Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.62; H, 5.51.

9-(3,4-Dimethoxyphenyl)-4-hydroxy-6,7-methylenedioxynaphtho-[2,3-*c*]furan-1(3*H*)-one (11) Borane–methylsulfide complex (10 M, 0.24 ml, 2.4 mmol) was added to a solution of **4a** (700 mg, 1.8 mmol) in 30 ml of THF, and the mixture was heated under reflux for 4 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 300 ml of methanol containing trifluoroacetic acid (100 mg), and this solution was allowed to stand at room temperature for 12 h. The crystalline precipitates were collected by filtration to afford **11** (560 mg, 1.5 mmol) as colorless needles, 87% yield, mp 297 °C (dec.). IR (Nujol): 3150, 1720, 1620, 1540, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.73 (s, 3H), 3.89 (s, 3H), 5.39 (s, 2H), 6.18 (s, 2H), 6.85 (s, 1H), 7.00—7.40 (m, 4H), 7.65 (s, 1H). MS *m/z*: 380 (M^+). *Anal.* Calcd for $C_{21}H_{16}O_7$: C, 66.32; H, 4.24. Found: C, 66.19; H, 4.31.

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4,6,7,8-tetramethoxynaphthalene (12) A solution of **4b** (4.7 g, 10 mmol) in *N*,*N*-dimethylformamide (DMF, 10 ml) and THF (20 ml) was added to a suspension of NaH (63.6%, 490 mg, 13 mmol) in DMF (10 ml) at 10 °C. The mixture was stirred at room temperature for 1 h, then MeI (2.1 g, 15 mmol) was added. The whole was stirred at room temperature for 18 h, and concentrated under reduced pressure. The residue was diluted with water (100 ml) and extracted with AcOEt (200 ml). The organic extract was washed with water, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The residue was crystallized from Et_2O to give crystalline precipitates, which were recrystallized from AcOEt–hexane to give **12** as colorless prisms, 89% yield, mp 150—151 °C. IR (Nujol): 1720, 1620, 1540, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.24 (s, 3H), 3.46 (s, 3H), 3.55 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 4.02 (s, 3H), 6.50—7.10 (m, 3H), 7.62 (s, 1H). MS *m/z*: 500 (M^+). *Anal.* Calcd for $C_{26}H_{28}O_{10}$: C, 62.39; H, 5.64. Found: C, 62.53; H, 5.55.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene-2,3-dicarboxylic Acid (13) This compound was prepared by the same procedure as used for the preparation of **4a** from the acetal alcohol **3b** and acetylenedicarboxylic acid, 22% yield, mp 157 °C. IR (Nujol): 3150, 1720, 1620, 1540, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 2.73 (s, 3H), 2.89 (s, 3H), 3.17 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 6.60—7.00 (m, 3H), 7.55 (s, 1H), 10.00—13.00 (br, 3H). MS *m/z*: 458 (M^+). *Anal.* Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 60.19; H, 4.91.

***c*-2, *c*-3-Bis(methoxycarbonyl)-*r*-1-(3,4-dimethoxyphenyl)-*t*-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (16)** A solution of **3a** (36 g, 100 mmol) in 30 ml of methanol was treated with AcOH (12 ml) and the mixture was heated under reflux. After 15 min, the mixture was concentrated under reduced pressure and the residue was crystallized from Et_2O to give crystalline precipitates, which were recrystallized from diisopropyl ether to give **14** (20.1 g, 61%) as colorless prisms, mp 132—134 °C. IR (Nujol): 1612, 1500 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.55 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 5.90 (s, 2H), 5.96 (s, 1H), 6.11 (s, 1H), 6.49—6.91 (m, 5H). MS *m/z*: 330 (M^+), 329 (M−H), 299 (M−MeO). *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.46; H 5.49. Found: C, 65.46; H, 5.42. A solution of **14** (3.3 g, 10 mmol) in 20 ml of THF was added to a stirred solution of lithium diisopropylamide in THF [prepared from 4.0 g (40 mmol) of diisopropylamine and BuLi (15% hexane solution, 26 ml, 40 mmol) in 20 ml of THF] at −70 °C. The reaction mixture was stirred at the same temperature for 0.5 h, then AcOH (2.4 ml) in 5 ml of THF was added, followed by dimethyl maleate (7.2 ml, 50 mmol) and AcOH (2.4 ml). The whole was allowed to warm to room temperature for 2 h, diluted with water and extracted with AcOEt. The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography to give **15** (10.6 g, 46%) as a yellow oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.54 (s, 6H), 3.82 (s, 3H), 3.88 (s, 3H), 3.50—4.10 (m, 2H), 5.50 (d, J=6.0 Hz, 1H), 5.90 (s, 2H), 6.50—7.40 (m, 5H). MS m/z: 442 (M^+), 424 ($M-H_2O$), 411 ($M-MeO$). A solution of the oxabicyclo diester **15** (6.5 g, 15 mmol) in 300 ml of ethanol was heated under reflux for 0.5 h, under an atmosphere of hydrogen with freshly prepared W-2 Raney Ni (20 g). The reaction mixture was cooled and filtered. The ethanol was removed from the filtrate under reduced pressure and the residue was purified by silica gel column chromatography to give **16** (1.5 g, 23%) as a yellow foam. IR (Nujol): 1730, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40—3.00 (m, 1H), 3.42 (s, 3H), 3.60—4.20 (m, 2H), 3.63 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.07 (s, 1H), 4.30 (s, 1H), 5.00 (d, J=6.0 Hz, 1H), 5.85 (d, J=6.0 Hz, 1H), 6.50—7.00 (m, 5H). MS m/z: 444 (M^+). *Anal.* Calcd for $C_{23}H_{24}O_9$: C, 62.16; H, 5.44. Found: C, 62.08; H, 5.49.

Biological Method Male Sprague–Dawley rats (4 weeks of ages) were purchased from Clea Japan and maintained on commercial laboratory chow (Clea CE-2 pellets) for at least 1 week before the experiment. Groups of 5 or 6 male rats were fed a diet containing 2% cholesterol and 0.5% sodium cholate for 7 d. For the experimental group, a test compound was added to the diet in a concentration of 0.1% for the last 3 d. On the 8th day, blood was withdrawn from the abdominal aorta under light ether anesthesia. Total cholesterol in serum was measured by the enzymatic method using a kit (Cholestezyme-Eiken). The whole HDL fraction was obtained as the soluble fraction after precipitating VLDL and LDL fractions with dextran sulfate. HDL cholesterol was measured according to the above-mentioned method.

References and Notes

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