Synthesis and Hypolipidemic Activity of Diesters of Arylnaphthalene Lignan and Their Heteroaromatic Analogs[1)]

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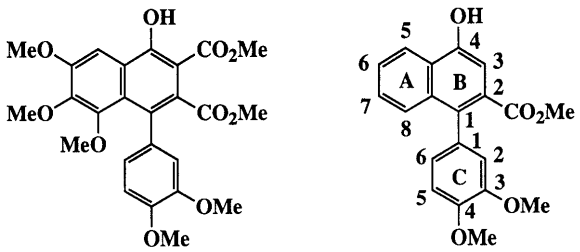
A series of diesters of arylnaphthalene lignan and their heteroaromatic analogs were synthesized and evaluated for hypolipidemic activity. The diesters with modifications at C-3 showed excellent hypocholesterolemic and high-density lipoprotein (HDL) cholesterol-elevating activities. Structure–activity analysis indicated that the 2-pyridylmethyl ester 5l has the optimum activity.

Key words lignan; hypocholesterolemic activity; high-density lipoprotein

We have recently reported on a series of aryl naphthalene lignans as potent hypocholesterolemic agents.[1)] From this series, compound **1** (TA-7552, Chart 1) was found effectively to lower total serum cholesterol while raising high-density lipoprotein (HDL) cholesterol in rats with diet-induced hypercholesterolemia. The results of mechanistic study indicated that compound **1** inhibits intestinal absorption of both cholesterol and bile acids.[2)] The effective dose of compound **1** is 100 times less than that of cholestyramine. Structure–activity relationship studies on this series of compounds indicated the need for a 1-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-4-hydroxynaphthalene skeleton (I) for high potency. Since the ester groups of **1** were restricted to methyl esters, we sought to explore the impact of modification of the ester side chain on the hypocholesterolemic activity. Because heteroaromatic systems offer a high degree of variability with regard to lipophilic, electronic, and steric nature, a series of compounds in which the A ring of **1** was modified to a heterocycle was prepared to optimize the activity. The present study describes some of the structure–activity relationships.

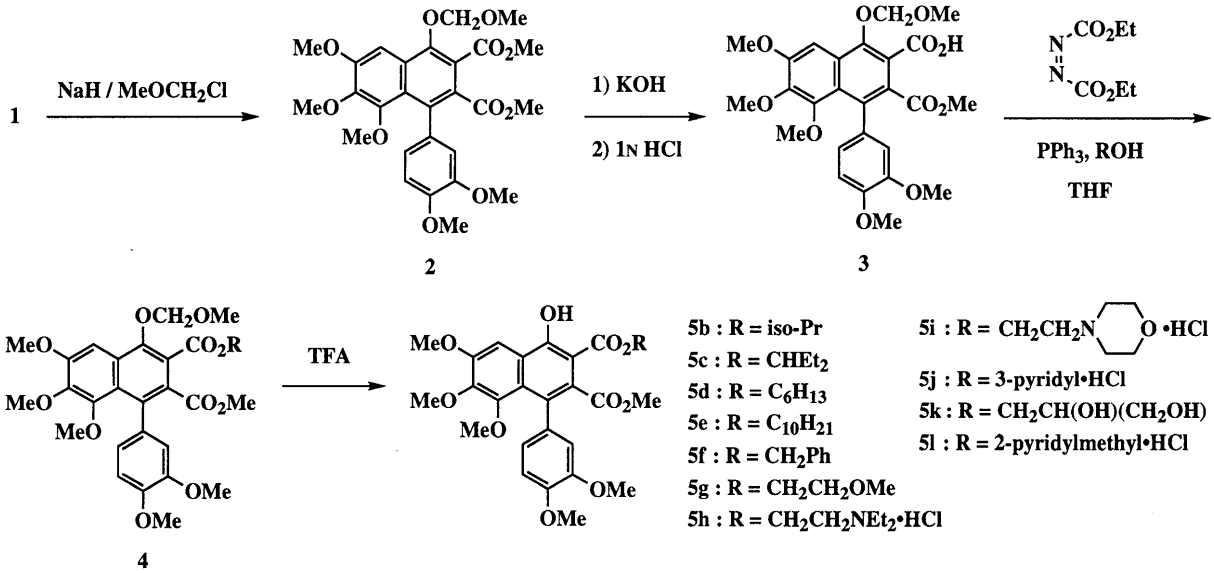


1 **I**

Chart 1

Chemistry

The compounds prepared for this study are shown in Table 1. The diesters bearing various alkoxycarbonyl groups at C-3 (**5b**—**l**) were prepared by the procedure outlined in Chart 2. Methoxymethylation of **1** followed by hydrolysis of the less hindered C-3 methoxycarbonyl group with 1 eq of aqueous KOH gave the half acid-ester **3**. Similar regioselective transformation of 2,3-bis(methoxycarbonyl)naphthalenes has been reported.[3)] Esterification of **3** with alcohols under the Mitsunobu conditions, followed by deblocking with trifluoroacetic acid (TFA) yielded the desired C-3 esters **5b**—**l**. Alternatively, the C-3 ethyl ester **5a** was obtained *via* regioselective transesteri-



2 **3** **4**

Chart 2

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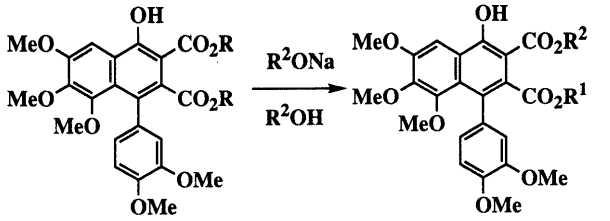
fication of **1** (Chart 3). The C-2 ethyl ester **9a** was prepared from the diethyl ester **9b** (*vide infra*) by the same method. The position of the transesterification was deduced from the following ^{1}H-NMR data. The C-2 ethoxycarbonyl signals of **9a** were shifted significantly upfield compared to the corresponding resonances for the C-3 isomer **5a**, due to shielding by the C-1 aryl group.

The synthesis of the diesters having the same side chain, **9b** and **10**—**13**, is illustrated in Chart 4. Treatment of the acetal **6** with butyllithium followed by 3,4-dimethoxybenzaldehyde gave the alcohol **7**, which, on treatment with dialkyl acetylenedicarboxylates **8a**—**e** in the presence of acetic acid, gave the diesters **9b** and **10**—**13**.[4] The



1 : R = Me
9b : R = Et

5a : R^1 = Me, R^2 = Et
9a : R^1 = Et, R^2 = Me

Chart 3

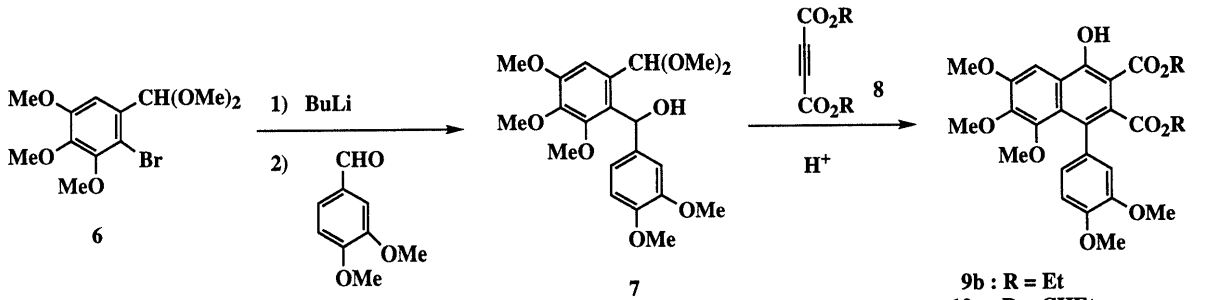
amides **17a**, **b** were obtained *via* condensation of the protected carboxylic acid **15** with amines followed by catalytic hydrogenation (Chart 5).

The synthetic strategy employed to prepare the heteroaromatic analogs **20** and **23** was based on the Diels–Alder reaction of heteroaromatic isobenzofurans generated from the acetoxy-aldehydes **19** and **22** with dimethyl acetylenedicarboxylate (Chart 6).[5] Selective reduction of the heteroaromatic diesters **20a** and **23** to the corresponding lactones **21** and **24** was accomplished with diborane.[4a] Deprotection of **24** was accomplished by electrochemical reduction to afford **25**.[6]

Biological Results

The compounds described in this paper have been examined for hypolipidemic activity in diet-induced hypercholesterolemic rats following the general protocols outlined in the previous paper in this series.[1] Plasma total cholesterol and HDL cholesterol were measured and percent change *vs.* the control was determined. The results are summarized in Table 1.

In general, derivatives possessing a modified ester side chain lowered total serum cholesterol while raising HDL cholesterol as effectively as, or better than, the parent compound **1**. Replacement of both the C-2 and C-3 ester

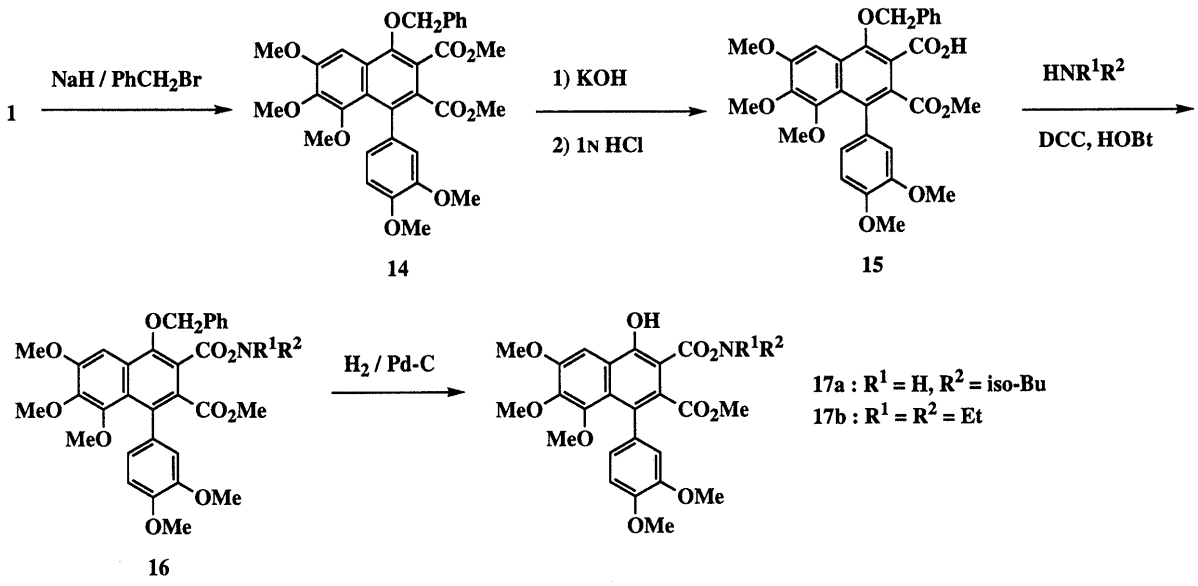


6

7

9b : R = Et
10 : R = $CHEt_2$
11 : R = C_6H_{13}
12 : R = cyclohexylmethyl
13 : R = CH_2Ph

Chart 4



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15

16

17a : R^1 = H, R^2 = iso-Bu
17b : R^1 = R^2 = Et

Chart 5

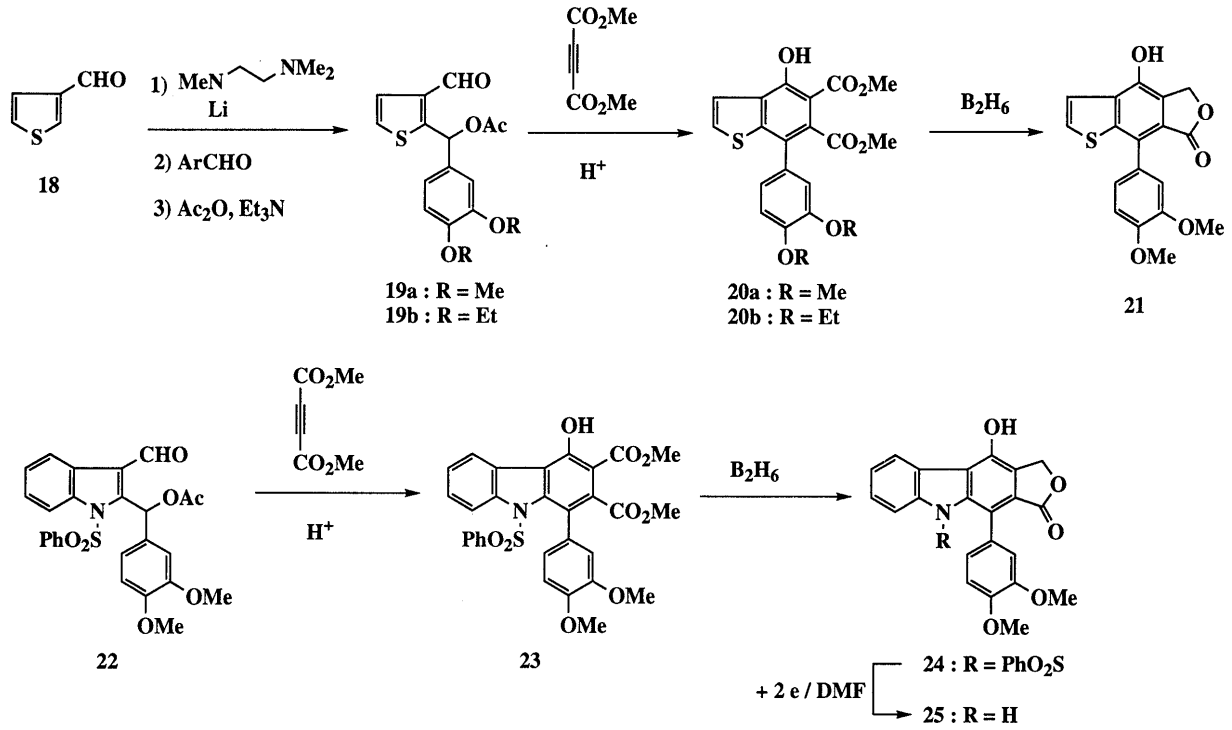


Chart 6

methyl groups of **1** with ethyl (**9b**) or benzyl groups (**13**) resulted in retention of the activity. The introduction of higher ester groups (**10**, **11**) led to a marked reduction in activity. The dicyclohexylmethyl ester **12**, however, retained activity. Replacement of the C-2 ester methyl group with an ethyl group (**9a**) increased the activity significantly. This enhanced activity was more pronounced with **5a**, which differs from **1** only by the introduction of the ethyl group in the C-3 ester. Thus, addition of even a single carbon atom to one of the ester groups led to a dramatic improvement in activity. On the basis of these results, it was concluded that modification of the C-3 ester side chain has a maximal effect on hypolipidemic activity. Accordingly, various diesters with modification at the C-3 ester group were designed. Introduction of longer alkyl chain esters at C-3 (**5b**—**e**) led to a reduction of activity compared to the ethyl ester **5a** and the activity of the esters decreases with increasing chain length. In general, introduction of substituted ester groups at C-3 (**5f**—**j**) resulted in a decrease in activity relative to **5a**. Incorporation of a (1,2-dihydroxy)ethyl group (**5k**) into the side chain, however, yielded comparable activity to that of **5a** and the optimal HDL cholesterol-raising activity was found in 2-pyridylmethyl ester **5l**. Replacement of the C-3 ester group by amide groups (**17a** and **17b**) retained the activity compared to that of compound **1**. At this point, it is not clear whether the dramatic change in activity shown by C-3-modified esters is a consequence of a change in cellular penetration or some other factor.

In general, the heteroaromatic analogs are less active than the parent compound **1**. Among these analogs, only the benzo[*b*]thiophene derivative **20a** exhibited comparable activity to **1**. Modification of the 3,4-dimethoxy groups of the C-ring (**20b**) resulted in reduction of the activity. Conversion of the ester groups in **20a** to a lactone **21** also resulted in substantial loss of activity. In contrast, transformation of the diester of **23** into the lactone derivative **24** led to an increase in activity. The phenylsulfonyl group in compound **24** is required for HDL cholesterol-raising activity because replacement of this group by a hydrogen atom led to an inactive compound, **25**.

In conclusion, hypolipidemic activity of diesters of arylnaphthalene lignans was markedly affected by the precise nature of the ester groups in the B ring. The 2-pyridylmethyl derivative **5l** was found to be more active than the parent compound **1** both in hypocholesterolemic and HDL cholesterol-elevating properties. Additional efficacy evaluations of **5l** are in progress.

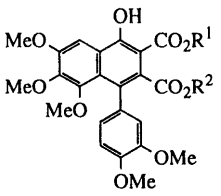
Experimental

General Methods The general synthetic and analytical methods used, and the protocols followed during biological studies, have been summarized in the previous paper.[1)]

2,3-Bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-methoxymethoxy-6,7,8-trimethoxynaphthalene (2) A solution of 2,3-bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene[1)] (**1**, 72.9 g, 0.15 mol) in *N*,*N*-dimethylformamide (DMF, 500 ml) was added dropwise to a suspension of NaH (61.4%, 7.0 g, 0.18 mol) in dry DMF (50 ml) at 5 °C with stirring. The mixture was stirred at room temperature for 1 h, and then chloromethyl methyl ether (18.0 g, 0.23 mol) was added at 5 °C. This mixture was stirred at room temperature for 2 h and poured into a mixture of AcOEt (1 l) and water (1 l) . The aqueous layer was extracted with AcOEt and the combined organic extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from hexane to give **2** (78 g, 98%) as colorless prisms. mp 91—93 °C. IR (Nujol): 1710, 1600 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.29 (s, 3H), 3.49 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 3.90 (s, 9H), 4.02 (s, 3H), 5.22 (s, 2H), 6.82 (s, 3H), 7.57 (s, 1H). MS *m*/*z*: 530 (M^+). *Anal.* Calcd for $C_{27}H_{30}O_{11}$: C, 61.13; H, 5.70. Found : C, 61.19; H, 5.91.

1-(3,4-Dimethoxyphenyl)-2-methoxycarbonyl-4-methoxymethoxy-6,7,8-trimethoxy-3-naphthoic Acid (3) A solution of KOH (83.5 g, 0.149 mol) in water (150 ml) and MeOH (600 ml) was added to a solution of **2** (78 g, 0.147 mol) in 1,4-dioxane (1 l). The mixture was stirred at

Table 1. Hypolipidemic Activity in Cholesterol-Fed Rats[a]



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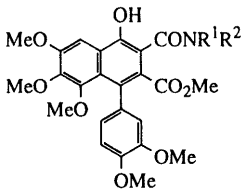

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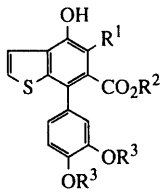
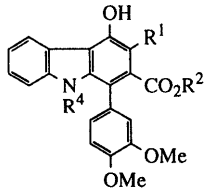


20a: R^3 = Me
20b: R^3 = Et
21 : R^3 = Me



23: R^4 = PhO_2S
24: R^4 = PhO_2S
25: R^4 = H

Compd.	R^1		R^2	Serum cholesterol[b]	HDL-cholesterol[b]
1	Me		Me	−52	+98
5a	Et		Me	−71	+178
5b	iso-Pr		Me	−66	+157
5c	$CHEt_2$		Me	−67	+163
5d	C_6H_{13}		Me	−55	+129
5e	$C_{10}H_{21}$		Me	−39	+74
5f	CH_2Ph		Me	−51	+142
5g	CH_2CH_2OMe		Me	−66	+111
5h	$CH_2CH_2NEt_2 \cdot HCl$		Me	−52	+71
5i	CH_2CH_2N⟨⟩$O \cdot HCl$		Me	−49	+111
5j	3-Pyridyl·HCl		Me	−57	+103
5k	$CH_2CH(OH)(CH_2OH)$		Me	−61	+170
5l	2-Pyridylmethyl·HCl		Me	−64	+192
9a	Me		Et	−68	+144
9b	Et		Et	−58	+95
10	$CHEt_2$		$CHEt_2$	−7	+50
11	C_6H_{13}		C_6H_{13}	−9	+24
12	Cyclohexylmethyl		Cyclohexylmethyl	−44	+122
13	CH_2Ph		CH_2Ph	−47	+109
17a	H		iso-Bu	−60	+99
17b	Et		Et	−64	+88
20a	CO_2Me		Me	−51	+88
20b	CO_2Me		Me	−25	+31
21		$-CH_2-$		−35	+39
23	CO_2Me		Me	+6	−4
24		$-CH_2-$		−20	+74
25		$-CH_2-$		−10	+14

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 values in the table were determined on the 8th day. *b*) % change *vs.* control. +: increase of cholesterol; −: decrease of cholesterol.

room temperature overnight and concentrated under reduced pressure. The residue was taken up in water (4 l), and to this solution, 1 N HCl (164 ml) was added dropwise with ice cooling. The mixture was extracted with $CHCl_3$ (2 l). The organic phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from Et_2O and recrystallized from AcOEt–hexane to give **3** (70 g, 92%) as colorless prisms. mp 114 °C (dec.). IR (Nujol): 3340, 1710, 1600 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.29 (s, 3H), 3.49 (s, 3H), 3.69 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.02 (s, 3H), 5.28 (s, 2H), 6.85 (s, 3H), 7.56 (s, 1H), 10.78 (s, 1H). MS *m/z*: 516 (M^+). *Anal.* Calcd for $C_{26}H_{28}O_{11}$: C, 60.46; H, 5.46. Found: C, 60.19; H, 5.78.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-3-isopropyloxycarbonyl-2-methoxycarbonyl-6,7,8-trimethoxynaphthalene (5b) A solution of dibenzyl azodicarboxylate (2.2 g, 7.5 mmol) in THF (5 ml) was added to a solution of **3** (3.87 g, 7.5 mmol), isopropyl alcohol (0.63 ml, 8.2 mmol), and triphenyl phospine (2.0 g, 7.5 mmol) in THF (20 ml) at 5 °C, and the mixture was stirred at room temperature for 1 h, then concentrated under reduced pressure. The residual diester **4** was used without purification in the next step. The residue was dissolved in an ice-cooled mixture of trifluoroacetic acid (TFA, 8.3 ml) and water (1.7 ml). The reaction mixture was stirred at room temperature for 15 min, then concentrated under reduced pressure, and the residue was taken up in Et_2O. This solution was washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from AcOEt–iso-Pr_2O to give **5b** (1.8 g, 47%) as colorless prisms. mp 155—157 °C. IR (Nujol): 1740, 1650, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.32 (d, J=6 Hz, 6H), 3.21 (s, 3H), 3.38 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 5.09—5.36 (m, 1H), 6.71 (s, 3H), 7.52 (s, 1H), 12.42 (s, 1H). MS *m/z*: 514 (M^+), 454. *Anal.* Calcd for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 63.34; H, 5.90

Compounds **5c—l** were prepared by the same procedure as described above.

1-(3,4-Dimethoxyphenyl)-3-(1-ethylpropyloxycarbonyl)-4-hydroxy-2-methoxycarbonyl-6,7,8-trimethoxynaphthalene (5c) 32% yield. mp 130—132 °C (AcOEt–hexane). IR (Nujol): 1740, 1650, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.92 (t, J=7 Hz, 6H), 1.50—1.90 (m, 4H), 3.21 (s, 3H), 3.35 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.90—5.20 (m, 1H), 6.71 (s, 3H), 7.55 (s, 1H), 12.60 (s, 1H). MS *m/z* : 542 (M^+), 454. *Anal.* Calcd for $C_{29}H_{34}O_{10}$: C, 64.20; H, 6.32. Found : C, 64.51; H, 6.19.

1-(3,4-Dimethoxyphenyl)-3-hexyloxycarbonyl-4-hydroxy-2-methoxycarbonyl-6,7,8-trimethoxynaphthalene (5d) 58% yield. mp 119—120 °C (iso-Pr_2O). IR (Nujol): 1735, 1650, 1605, 1585, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.60—1.90 (m, 11H), 3.20 (s, 3H), 3.36 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.95 (s, 3H), 4.25 (t, J=6 Hz, 2H), 6.70 (s, 3H), 7.52 (s, 1H), 12.34 (s, 1H). MS *m/z*: 556 (M^+), 454. *Anal.* Calcd for $C_{30}H_{36}O_{10}$: C, 64.74; H, 6.52. Found: C, 64.63; H, 6.56.

3-Decyloxycarbonyl-1-(3,4-dimethoxyphenyl)-4-hydroxy-2-methoxy-

carbonyl-6,7,8-trimethoxynaphthalene (5e) 36% yield. mp 93 °C (MeOH–AcOEt). IR (Nujol): 1740, 1650, 1590, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.70—2.00 (m, 19H), 3.20 (s, 3H), 3.35 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.25 (t, J=6 Hz, 2H), 6.70 (s, 3H), 7.50 (s, 1H), 12.35 (s, 1H). MS m/z: 612 (M^+), 454. *Anal.* Calcd for $C_{34}H_{44}O_{10}$: C, 66.65; H, 7.24. Found: C, 66.43; H, 7.51.

3-Benzyloxycarbonyl-1-(3,4-dimethoxyphenyl)-4-hydroxy-2-methoxycarbonyl-6,7,8-trimethoxynaphthalene (5f) 83% yield. mp 174—175 °C (AcOEt–THF). IR (Nujol): 1740, 1660, 1610, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.87 (s, 3H), 3.20 (s, 3H), 3.74 (s, 3H), 3.82 (s, 6H), 3.96 (s, 3H), 5.23 (s, 2H), 6.67 (s, 3H), 7.23 (s, 5H), 7.53 (s, 1H), 12.39 (s, 1H). MS m/z: 562 (M^+), 471, 454. *Anal.* Calcd for $C_{31}H_{30}O_{10}$: C, 66.19; H, 5.38. Found: C, 65.94; H, 5.16.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-2-methoxycarbonyl-3-methoxyethoxycarbonyl-6,7,8-trimethoxynaphthalene (5g) 20% yield. mp 156—157 °C (AcOEt–hexane). IR (Nujol): 1740, 1660, 1605, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.21 (s, 3H), 3.32 (s, 3H), 3.42 (s, 3H), 3.60 (t, J=5 Hz, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 4.40 (t, J=5 Hz, 2H), 6.71 (s, 3H), 7.53 (s, 1H), 12.15 (s, 1H). MS m/z: 530 (M^+), 454. *Anal.* Calcd for $C_{27}H_{30}O_{11}$: C, 61.13; H, 5.70. Found : C, 61.17; H, 5.59.

3-(2-Diethylaminoethyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-2-methoxycarbonyl-6,7,8-trimethoxynaphthalene Hydrochloride (5h) The obtained free base was converted to the corresponding hydrochloride in a usual manner, 58% yield. mp 199 °C (dec.) (AcOEt). IR (Nujol): 2300, 1720, 1680, 1590, 1515 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.37 (t, J=6 Hz, 6H), 3.00—3.50 (m, 6H), 3.18 (s, 3H), 3.42 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 4.88 (t, J=6 Hz, 2H), 6.67 (s, 3H), 7.51 (s, 1H), 11.88 (s, 1H), 12.50 (br, 1H). MS m/z: 571 (M^+), 428. *Anal.* Calcd for $C_{30}H_{37}NO_{11}\cdot HCl$: C, 59.25; H, 6.30; Cl, 5.83; N, 2.30. Found: C, 59.31; H, 6.19; Cl, 5.78; N, 2.42.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-2-methoxycarbonyl-3-(2-morpholinoethoxycarbonyl)-6,7,8-trimethoxynaphthalene Hydrochloride (5i) The obtained free base was converted to the corresponding hydrochloride in a usual manner, 27% yield. mp 199 °C (dec.) (1,4-dioxane–AcOEt). IR (Nujol): 2130, 1730, 1660, 1590, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.00—4.00 (m, 6H), 3.18 (s, 3H), 3.40 (s, 3H), 3.70—4.00 (m, 4H), 3.75 (s, 3H), 3.80 (s, 6H), 3.95 (s, 3H), 4.30 (br, 1H), 4.60—4.80 (m, 2H), 6.65 (s, 3H), 7.50 (s, 1H), 12.50 (br, 1H). MS m/z: 569 (M^+). *Anal.* Calcd for $C_{30}H_{35}NO_{11}\cdot HCl$: C, 57.92; H, 5.83; Cl, 5.70; N, 2.25. Found : C, 58.13; H, 5.69; Cl, 5.66; N, 2.34.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-2-methoxycarbonyl-3-(3-pyridyloxycarbonyl)-6,7,8-trimethoxynaphthalene Hydrochloride (5j) The obtained free base was converted to the corresponding hydrochloride in a usual manner, 51% yield. mp 140—141 °C (1,4-dioxane–AcOEt). IR (Nujol): 2120, 2040, 1950, 1740, 1690, 1600, 1590 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.21 (s, 3H), 3.34 (s, 3H), 3.78 (s, 3H), 3.85 (s, 6H), 3.96 (s, 3H), 6.72 (s, 3H), 7.53 (s, 1H), 7.80—8.30 (m, 3H), 8.60—8.90 (m, 2H), 12.41 (br, 1H). MS m/z: 549 (M^+), 454, 422. *Anal.* Calcd for $C_{29}H_{27}NO_{10}\cdot HCl$: C, 59.44; H, 4.82; Cl, 6.05; N, 2.39. Found : C, 59.42; H, 4.67; Cl, 5.95; N, 2.58.

2-[(2*RS*)-(2,3-Dihydroxypropoxycarbonyl)]-4-(3,4-dimethoxyphenyl)-1-hydroxy-3-methoxycarbonyl-5,6,7-trimethoxynaphthalene (5k) 12% yield. mp 166—167 °C (AcOEt–Et_2O). IR (Nujol): 3520, 3460, 1690, 1665, 1590, 1515 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.29 (t, J=6 Hz, 1H), 3.07 (d, J=5 Hz, 1H), 3.19 (s, 3H), 3.38 (s, 3H), 3.50—4.00 (m, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 4.25—4.45 (m, 2H), 6.68 (s, 3H), 7.51 (s, 1H), 12.09 (s, 1H). MS m/z: 546 (M^+), 454, 428. *Anal.* Calcd for $C_{27}H_{30}O_{12}$: C, 59.34; H, 5.53. Found: C, 59.57; H, 5.64.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-2-methoxycarbonyl-3-[(2-pyridyl)-methoxycarbonyl]-6,7,8-trimethoxynaphthalene Hydrochloride (5l) The free base was converted to the corresponding hydrochloride in a usual manner, 60% yield. mp 121—122 °C (1,4-dioxane–AcOEt). IR (Nujol): 1715, 1665, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.22 (s, 3H), 3.27 (s, 3H), 3.63 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 5.96 (s, 2H), 6.71 (s, 3H), 7.53 (s, 1H), 7.70—8.80 (m, 5H), 12.40 (br, 1H). MS m/z: 563 (M^+), 454. *Anal.* Calcd for $C_{30}H_{29}NO_{10}\cdot HCl$: C, 60.05; H, 5.04; Cl, 5.91; N, 2.33. Found: C, 60.19; H, 4.91; Cl, 6.18; N, 2.08.

Preparation of the Dialkyl Acetylenedicarboxylates (8b—e) Bis(1-ethylpropyl) acetylenedicarboxylate (**8b**), dihexyl acetylenedicarboxylate (**8c**), dicyclohexyl acetylenedicarboxylate (**8d**), and dibenzyl acetylenedicarboxylate (**8e**) were prepared from acetylenedicarboxylic acid according to the reported method.[7]

1-(3,4-Dimethoxyphenyl)-2-ethoxycarbonyl-4-hydroxy-3-methoxycarbonyl-6,7,8-trimethoxynaphthalene (9a) A solution of **9b** (10.3 g, 20 mmol) in MeOH (500 ml) was added to a solution of NaOMe (6.5 g, 0.12 mol) in MeOH (500 ml), and the mixture was heated under reflux for 3 h. Then acetic acid (7.2 ml) was added and the mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (200 ml). This solution was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from AcOEt–hexane to give **9a** (5.6 g, 56%) as colorless prisms. mp 156 °C. IR (Nujol): 1730, 1655, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.15 (t, J=6 Hz, 3H), 3.26 (s, 3H), 3.80—4.08 (m, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 3.91 (s, 6H), 4.03 (s, 3H), 6.83 (s, 3H), 7.66 (s, 1H), 12.35 (s, 1H). MS m/z: 500 (M^+), 468, 440. *Anal.* Calcd for $C_{26}H_{28}O_{10}$: C, 62.39; H, 5.64. Found : C, 62.41; H, 5.58.

1-(3,4-Dimethoxyphenyl)-3-ethoxycarbonyl-4-hydroxy-2-methoxycarbonyl-6,7,8-trimethoxynaphthalene (5a) This compound was prepared by the reaction of **1** with NaOEt in EtOH as described above, 72% yield. Colorless prisms, mp 151—152 °C (AcOEt–hexane). IR (Nujol): 1730, 1655, 1600, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.35 (t, J=6 Hz, 3H), 3.26 (s, 3H), 3.45 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.03 (s, 3H), 4.40 (q, J=6 Hz, 2H), 6.83 (s, 3H), 7.66 (s, 1H), 12.39 (s, 1H). MS m/z: 500 (M^+), 468, 440. *Anal.* Calcd for $C_{26}H_{28}O_{10}$: C, 62.39; H, 5.64. Found: C, 62.31; H, 5.78.

2,3-Bis(ethoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (9b) A solution of 2-(3,4-dimethoxy-α-hydroxybenzyl)-3,4,5-trimethoxybenzaldehyde dimethylacetal[1] (**7**, 6.0 g, 14.7 mmol) and diethyl acetylenedicarboxylate (**8a**, 2.5 g, 14.7 mmol) in acetic acid (6 ml) was heated under reflux for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from MeOH to give **9b** (4.8 g, 64%) as colorless needles. mp 138—140 °C. IR (Nujol): 1720, 1650, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.01 (t, J=6 Hz, 3H), 1.35 (t, J=6 Hz, 3H), 3.23 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.74—3.96 (m, 2H), 3.97 (s, 3H), 4.34 (q, J=6 Hz, 2H), 6.74 (s, 3H), 7.55 (s, 1H), 12.36 (s, 1H). MS m/z: 514 (M^+), 468, 440. *Anal.* Calcd for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 63.21; H, 5.99.

Compounds **10**—**13** were prepared by the same procedure as described above.

2,3-Bis(1-ethylpropyloxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (10) 65% yield. Oil. IR (Nujol): 2130, 1730, 1660, 1590, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.50—2.00 (m, 20H), 3.14 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 6.20—6.60 (m, 1H), 6.90—7.20 (m, 1H), 6.70 (s, 3H), 7.52 (s, 1H), 12.40 (s, 1H). MS m/z: 598 (M^+), 528, 440. *Anal.* Calcd for $C_{33}H_{42}O_{10}$: C, 66.21; H, 7.07. Found: C, 66.40; H, 7.02.

2,3-Bis(hexyloxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (11) 56% yield. mp 67 °C (AcOEt–hexane). IR (Nujol): 1720, 1660, 1590, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.70—1.90 (m, 22H), 3.20 (s, 3H), 3.75 (t, J=6 Hz, 2H), 3.76 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.27 (t, J=6 Hz, 2H), 6.70 (s, 3H), 7.53 (s, 1H), 13.27 (s, 1H). MS m/z: 626 (M^+), 440. *Anal.* Calcd for $C_{35}H_{46}O_{10}$: C, 67.07; H, 7.40. Found: C, 67.22; H, 7.19.

2,3-Bis(cyclohexylmethoxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (12) 60% yield. mp 116 °C (AcOEt–hexane). IR (Nujol): 1720, 1640, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.60—2.00 (m, 22H), 3.22 (s, 3H), 3.55 (d, J=6 Hz, 2H), 3.75 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 3.95 (s, 3H), 4.10 (d, J=6 Hz, 2H), 6.70 (s, 3H), 7.51 (s, 1H), 12.42 (s, 1H). MS m/z: 650 (M^+), 440. *Anal.* Calcd for $C_{37}H_{46}O_{10}$: C, 68.29; H, 7.12. Found: C, 68.35; H, 7.10.

2,3-Bis(benzyloxycarbonyl)-1-(3,4-dimethoxyphenyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (13) 61% yield. mp 130—132 °C (AcOEt–hexane). IR (Nujol): 1725, 1655, 1590, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.15 (s, 3H), 3.57 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 4.18 (s, 2H), 5.19 (s, 2H), 6.60—7.30 (m, 13H), 7.51 (s, 1H), 12.33 (s, 1H). MS m/z: 638 (M^+), 547, 540, 439. *Anal.* Calcd for $C_{37}H_{34}O_{10}$: C, 69.58; H, 5.37. Found: C, 69.82; H, 5.21.

4-Benzyloxy-2,3-bis(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)-6,7,8-trimethoxynaphthalene (14) A solution of the phenol **1** (24.3 g, 50 mmol) in DMF (300 ml) was added dropwise to a suspension of NaH (63.8%, 2.25 g, 60 mmol) in dry DMF (300 ml) at 5 °C with stirring. The mixture was treated with benzyl bromide (8.9 g, 52 mmol) as described for **2**. The crude product was crystallized from hexane to give **14** (29.1 g, 99%) as colorless prisms. mp 142 °C. IR (Nujol): 1730, 1710, 1600,

1510 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.20 (s, 3H), 3.40 (s, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 3.79 (s, 6H), 3.83 (s, 3H), 5.10 (s, 2H), 6.60—7.60 (m, 9H). MS *m/z*: 576 (M^+), 403. *Anal.* Calcd for $C_{32}H_{32}O_{10}$: C, 66.66; H, 5.59. Found: C, 66.89; H, 5.42.

4-Benzyloxy-1-(3,4-dimethoxyphenyl)-2-methoxycarbonyl-4-methoxymethoxy-6,7,8-trimethoxy-3-naphthoic Acid (15) A solution of KOH (16.8 g, 0.3 mol) in water (100 ml) was added to a solution of **14** (17.6 g, 30 mmol) in THF (200 ml) and MeOH (200 ml). The mixture was stirred at room temperature overnight and processed as described for **3**. The residue obtained by the evaporation was crystallized from Et_2O to give **15** (14.0 g, 83%) as colorless prisms. mp 172 °C (dec.). IR (Nujol): 1740, 1730, 1685, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.20 (s, 3H), 3.42 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 5.10 (s, 2H), 6.60—6.85 (m, 4H), 7.12—7.50 (m, 5H), 9.16 (s, 1H). MS *m/z*: 562 (M^+). *Anal.* Calcd for $C_{31}H_{30}O_{10}$: C, 66.19; H, 5.38. Found: C, 66.35; H, 5.19.

4-Hydroxy-3-*N*-isobutylcarbamoyl-2-methoxycarbonyl-1-(3,4-dimethoxyphenyl)-6,7,8-trimethoxynaphthalene (17a) A solution of **15** (1.41 g, 2.5 mmol), isobutylamine (183 mg, 2.5 mmol), and 1-hydroxybenzotriazole (HOBt, 340 mg, 2.5 mmol) in THF (40 ml) was prepared, then 1,3-dicyclohexylcarbodiimide (DCC, 570 mg, 2.8 mmol) was added and the mixture was stirred at room temperature overnight. It was then concentrated under reduced pressure and the residual amide **16a** was used without purification in the next step. A solution of the residue in THF (20 ml) and MeOH (20 ml) was hydrogenated over 10% Pd–C (600 mg) at the pressure of 15 psi and 25 °C for 1 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from acetone–Et_2O–hexane to give **17a** (1.0 g, 78%) as colorless prisms. mp 135—137 °C (dec.). IR (Nujol): 3400, 1740, 1620, 1580 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.93 (d, J=6 Hz, 6H), 1.50—2.00 (m, 1H), 3.10—3.24 (m, 2H), 3.20 (s, 3H), 3.35 (s, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.92 (s, 3H), 6.67 (s, 3H), 6.60—7.00 (br, 1H), 7.47 (s, 1H), 13.06 (s, 1H). MS *m/z*: 527 (M^+), 495. *Anal.* Calcd for $C_{28}H_{33}NO_9$: C, 63.75; H, 6.30; N, 2.65. Found: C, 63.83; H, 6.39; N, 2.58 .

3-*N*,*N*-Diethylcarbamoyl-4-hydroxy-2-methoxycarbonyl-1-(3,4-dimethoxyphenyl)-6,7,8-trimethoxynaphthalene (17b) Compound **17b** was prepared by the same procedure as described above, 59% yield. mp 162—163 °C (acetone–Et_2O–hexane). IR (Nujol): 1745, 1720, 1600 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.00—1.40 (m, 6H), 3.03 (s, 3H), 3.20—3.70 (m, 4H), 3.39 (s, 3H), 3.75 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 6.30—6.80 (m, 3H), 7.35 (s, 1H), 9.82 (s, 1H). MS *m/z*: 527 (M^+), 454. *Anal.* Calcd for $C_{28}H_{33}NO_9$: C, 63.75; H, 6.30; N, 2.65. Found : C, 63.66; H, 6.33; N, 2.71.

3-(α-Acetoxy-3,4-diethoxybenzyl)thiophene-2-carbaldehyde (19b) The title compound was prepared by the reaction of 3-thiophenecarbaldehyde (**18**) with 3,4-diethoxybenzaldehyde according to the reported method,[5] 76% yield. Oil. IR (Nujol): 1740, 1670 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.38 (t, J=7 Hz, 6H), 2.10 (s, 3H), 4.02 (q, J=7 Hz, 4H), 6.68—7.00 (m, 3H), 7.16 (d, J=5 Hz, 1H), 7.34 (d, J=5 Hz, 1H), 7.50 (s, 1H), 9.94 (s, 1H). MS *m/z*: 348 (M^+), 290, 288.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[*b*]thiophene (20a) A mixture of 3-(α-acetoxy-3,4-dimethoxybenzyl)-thiophene-2-carbaldehyde[5] (**19a**, 5.1 g, 16 mmol), dimethyl acetylenedicarboxylate (13 g, 80 mmol), and TFA (90 mg, 0.8 mmol) in benzene (9 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1). Crystallization from petroleum ether–acetone followed by recrystallization from AcOEt–hexane gave **20a** (5.7 g, 88%) as colorless prisms. The spectral data of this compound were identical with reported values.[5]

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-diethoxyphenyl)benzo[*b*]-thiophene (20b) Compound **20b** was prepared from **19b** by the same procedure as described above, 52% yield. mp 129—130 °C (AcOEt–hexane). IR (Nujol): 1750, 1670 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.41 (t, J=7 Hz, 3H), 1.45 (t, J=7 Hz, 3H), 3.55 (s, 3H), 3.87 (s, 3H), 4.04 (q, J=7 Hz, 2H), 4.09 (q, J=7 Hz, 2H), 6.85 (s, 3H), 7.31 (d, J=5 Hz, 1H), 7.58 (d, J=5 Hz, 1H), 11.66 (s, 1H). MS *m/z*: 430 (M^+), 398, 281. *Anal.* Calcd for $C_{22}H_{22}O_7S$: C, 61.38; H, 5.15; S, 7.45. Found: C, 61.66; H, 5.22; S, 7.15.

4-(3,4-Dimethoxyphenyl)-8-hydroxy-1*H*,3*H*-thieno[2,3-*f*]isobenzofuran-3-one (21) 12 M Borane dimethyl sulfide (5.5 ml, 60 mmol) was added to a stirred solution of the diester **20a** (5.0 g, 15 mmol) in THF (50 ml) and the mixture was heated under reflux for 2.5 h. The resulting solution was concentrated under reduced pressure. The residue was crystallized from MeOH and recrystallized from AcOEt–THF to give **21** (3.95 g, 77%) as pale green prisms. mp 223—224 °C (dec.). IR (Nujol): 3200, 1710, 1600, 1580, 1525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (s, 3H), 3.93 (s, 3H), 5.32 (s, 2H), 6.92—7.20 (m, 3H), 7.53 (d, J=5 Hz, 1H), 7.71 (d, J=5 Hz, 1H), 9.96 (br, 1H). MS *m/z*: 342 (M^+), 327. *Anal.* Calcd for $C_{18}H_{14}NO_5S$: C, 63.15; H, 4.12; S, 9.36. Found: C, 63.42; H, 4.09; S, 9.18.

1-(Phenylsulfonyl)-2-(α-acetoxy-3,4-dimethoxybenzyl)indole-3-carbaldehyde (22) The acetoxy-aldehyde **22** was prepared in 66% yield from 1-(phenylsulfonyl)indole-3-carbaldehyde and 3,4-dimethoxybenzaldehyde by the reported method.[5] mp 185—187 °C (AcOEt–hexane). IR (Nujol): 1755, 1660, 1530 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 6.62 (s, 2H), 7.34—7.61 (m, 6H), 7.84—7.89 (m, 2H), 8.11—8.20 (m, 2H), 8.40—8.44 (m, 1H), 10.68 (s, 1H). MS *m/z*: 493 (M^+). *Anal.* Calcd for $C_{26}H_{23}NO_7S$: C, 63.28; H, 4.70; N, 2.84; S, 6.50. Found: C, 63.35; H, 4.52; N, 2.90; S, 6.15.

1-(3,4-Dimethoxyphenyl)-2,3-bis(methoxycarbonyl)-4-hydroxy-9-phenylsulfonylcarbazole (23) Compound **23** was prepared from the acetoxy-aldehyde **22** by the same procedure as described for the preparation of **20a**, 52% yield. mp 222—225 °C (dec.) (DMF–MeOH). IR (Nujol): 1750, 1670 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.52 (s, 3H), 3.86 (s, 3H), 3.91 (s, 6H), 6.40—8.38 (m, 12H), 11.85 (s, 1H). MS *m/z*: 575 (M^+), 435. *Anal.* Calcd for $C_{30}H_{25}NO_9S$: C, 62.60; H, 4.38; N, 2.43; S, 5.57. Found: C, 62.66; H, 4.22; N, 2.57; S, 5.85.

4-(3,4-Dimethoxyphenyl)-10-hydroxy-5-phenylsulfonyl-1*H*,3*H*-furo[3,4-*b*]carbazole-3-one (24) This compound was prepared from the diester **23** by the same procedure as used for the preparation of **21**, 65% yield. mp 192—193 °C (DMF–MeOH). IR (Nujol): 1710 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 3.86 (s, 3H), 5.27 (s, 2H), 6.60—8.33 (m, 12H), 9.90—10.16 (m, 1H). MS *m/z*: 515 (M^+), 375. *Anal.* Calcd for $C_{28}H_{21}NO_7S$: C, 65.23; H, 4.11; N, 2.72; S, 6.22. Found: C, 65.39; H, 4.23; N, 2.65; S, 6.10.

4-(3,4-Dimethoxyphenyl)-10-hydroxy-1*H*,3*H*-furo[3,4-*b*]carbazole-3-one (25) Mercury was used as a cathode, and graphite was employed as an anode. A saturated calomel electrode (SCE) was employed as a reference electrode. The lactone **24** (500 mg, 1.0 mmol) and tetraethylammonium tosylate (2.0 g) were dissolved in DMF (50 ml). This solution was put in an electrolysis cell and electrolyzed at a constant current of 200 mA at 10 °C.[6] The amount of current passed was 7.2 faraday/mol. Then acetic acid (0.5 ml) was added and the solution was concentrated under reduced pressure. The residue was taken up in saturated aqueous $NaHCO_3$ and the resulting solid was collected by filtration. The crude product was recrystallized from DMF–MeOH to give **25** (260 mg, 70%) as pale brown needles, mp 290—291 °C (dec.). IR (Nujol): 3340, 1710, 1600 cm^{-1}. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 3.96 (s, 3H), 4.01 (s, 3H), 5.30 (s, 2H), 6.90—7.51 (m, 7H), 8.18—8.33 (m, 1H), 10.10—10.80 (m, 1H). MS *m/z*: 375 (M^+). *Anal.* Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.56; N, 3.73. Found: C, 70.23; H, 4.81; N, 3.89.

Biological Method Male Sprague–Dawley rats (4 weeks of age) 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 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 at 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. The hypolipidemic and HDL-elevating activities of the test compounds are summarized in Table 1 as percent changes in the cholesterols compared to the mean cholesterol levels of the control group after the experimental period. The average mean levels (±S.D.) of serum cholesterol and HDL cholesterol of the control group in 13 experiments were 189±27 mg and 18.6±3.6 mg/100 ml, respectively.

References and Notes

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