Synthesis and Cytotoxicity of Racemic Isodeoxypodophyllotoxin Analogues with Isoprene-Derived Side Chains

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A series of isodeoxypodophyllotoxin (**5**) analogues, **26**−**38**, with various isoprene-derived side chains at the E-ring were designed and synthesized. For comparison, compound **39**, with a benzyloxy group on the E-ring, and six D-ring opened analogues, **40**−**45**, were also prepared. All the synthetic compounds were evaluated for their cytotoxic activities in vitro against seven cultured human tumor cell lines. Compounds **27**, **43**, and **44** were more cytotoxic than etoposide on BEL-7404, A549, and HL-60 cell lines, respectively. However, none of the synthetic isodeoxypodophyllotoxins were more cytotoxic than podophyllotoxin (**1**).

Lignans are a well-known class of natural products. Among them, the best known cytotoxic lignan is podophyllotoxin (**1**) (Figure 1), which can be found in Berberidaceae plants such as *Podophyllum peltatum* Linnaeus, *P. emodi* Wall, and *P. pleianthum* Hance.[1,2] Although the therapeutic application of podophyllotoxin via oral administration has failed due to unacceptable gastrointestinal toxicity, two of its semisynthetic glucosidic acetals, etoposide (**2**) and teniposide (**3**), are currently used in clinical practice for the treatment of small-cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma.[3] The antitumor potency and clinical efficacy of compounds **2** and **3** has prompted intensive interest in the synthesis of new podophyllotoxin analogues.

The podophyllotoxin family includes podophyllotoxin (3a,9a-*trans*-9a,9-*cis*) (**1**), picropodophyllotoxin (3a,9a-*cis*-9a,9-*trans*) (**4**), and isodeoxypodophyllotoxin (3a,9a-*trans*-9a,9-*trans*) (**5**). It has been established by structure−activity relationship (SAR) studies that the 3a,9a-*trans* configuration is an important factor for high cytotoxic activity.[4] However, very little work has been done to address the significance of the 9a,9-configuration for cytotoxicity. Moreover, Zavala reported that racemic isodeoxypodophyllotoxin has inhibitory activity against microtubule assembly comparable to that of (−)-podophyllotoxin, while (−)-isodeoxypodophyllotoxin is totally inactive. These observations have prompted our interest and led to the current study.[5]

The prenylated arylnaphthalene lignan, 7-*O*-(3-methyl-2-butenyl)-isodaurinol (**6**), was isolated from *Haplophyllum myrtifolium* by Gözler and co-workers.[6] Only a few lignans have been reported to possess such an isoprene-derived side chain.[7,8] We have also reported several sinapyl alcohol derivatives with such side chains, and some of them, such as compound **7**, were cytotoxic to KB and A-549 cell lines.[9] Thus, it would be of interest to study the cytotoxic action of the isoprenyl-like podophyllotoxin derivatives.

Thus, a series of racemic isodeoxypodophyllotoxin derivatives (**26**−**38**) containing various isoprene-derived side chains on the E-ring were designed and synthesized. Compound **39**, which possesses a benzyloxy group on the E-ring at the same position, was also prepared for SAR comparison. Six D-ring opened analogues of isodeoxypodophyllotoxin lignans (**40**−**45**) were also synthesized by hydrolysis of the olide rings of compounds **23**−**39**. All the synthetic compounds were evaluated for their cytotoxic activities in vitro against seven cultured human tumor cell lines, viz., KB, BEL-7404, A549, HeLa, PC-3, CNE, and HL-60, and the results are reported herein.

Results and Discussion

Synthesis. As illustrated in Scheme 1, the synthesis of a series of racemic isodeoxypodophyllotoxin analogues was started using benzaldehydes **8** and **9**. The Stobbé condensation of compound **8** or **9** with dimethylsuccinate in the presence of sodium methoxide gave the unsaturated hemiesters **10** and **11**, which were subjected to a catalytic hydrogenation with palladium charcoal to furnish the saturated hemiesters **12** and **13**, respectively. The overall yield of the two reactive steps was 62%. Butyrolactones **14** and **15** were obtained by the reaction of **12** and **13** with potassium hydroxide, followed by reduction with sodium borohydride and calcium chloride in 75% yield.[10]

Subsequent α-hydroxyalkylation of the butyrolactones **14** and **15** with benzaldehydes **16** and **17** (Scheme 2), at low temperature in the presence of lithium diisopropylamide, afforded alcohols **18**−**21** in 76−92% yields.[11] Each of the compounds (**18**−**21**) was an approximately equimolar mixture of the *erythro* (**18a**−**21a**) and *threo* isomers (**18b**−**21b**), as indicated by the proton signals of C*H*OH around δ 4.81 (d, $J = 8.0$ Hz, C*H*OH) for the *erythro* isomer and around δ 5.29 (br s, C*H*OH) for the *threo* isomer in their ^{1}H NMR spectra. However, in the next cyclization in the presence of trifluoroacetic acid (TFA), each mixture of *erythro* and *threo* alcohols, of compounds **18**−**21**, could be used as starting materials without separation, resulting in the same cyclized products **22**−**25** in 63−72% yields. As usually described for such a cyclization

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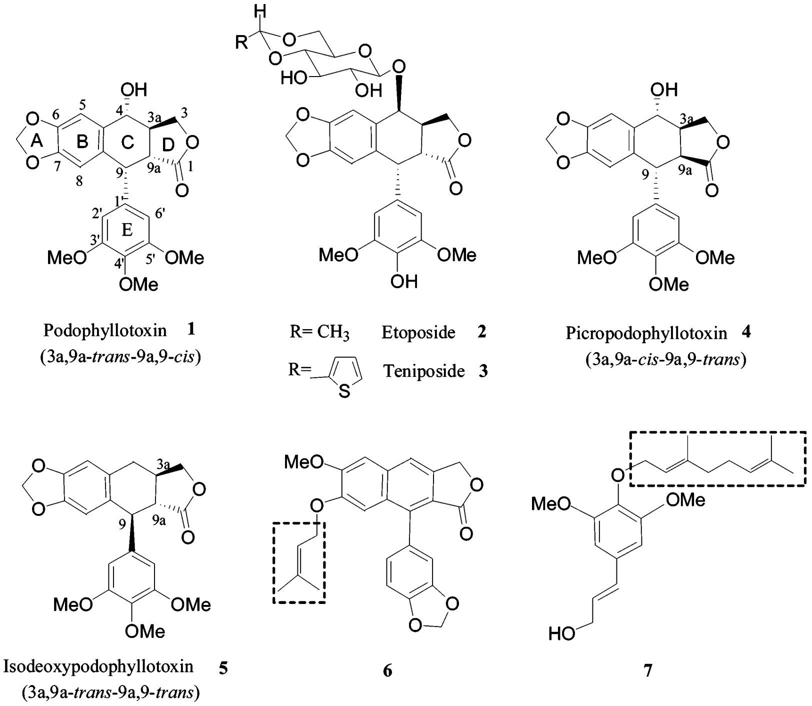


Podophyllotoxin **1**
(3a,9a-*trans*-9a,9-*cis*)

R= CH_3 Etoposide **2**
R= Teniposide **3**

Picropodophyllotoxin **4**
(3a,9a-*cis*-9a,9-*trans*)

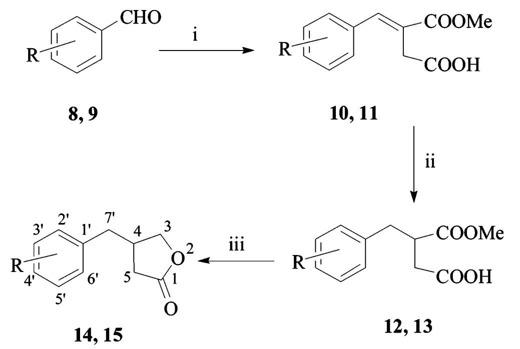
Isodeoxypodophyllotoxin **5**
(3a,9a-*trans*-9a,9-*trans*)

6

7

Figure 1.

Scheme 1[a]



8, 9 **10, 11** **12, 13** **14, 15**

8, **10**, **12**, **14** R= 3,4-$(OMe)_2$
9, **11**, **13**, **15** R= 3,4,5-$(OMe)_3$

[a] Reagents and conditions: (i) $(CH_2CO_2CH_3)_2$, $NaOCH_3$, CH_3OH, reflux 5 h, 65%; (ii) H_2, Pd/C, rt, 3 h, 95%; (iii) KOH, $CaCl_2$, $NaBH_4$, EtOH, rt, 5 h, 75%.

reaction, the products **22**−**25** were racemic isodeoxypodophyllotoxin-type compounds with 3a,9a-*trans*-9a,9-*trans* stereochemistry. This was confirmed by the signals ($J_{3a,9a} = 13.2$ Hz, $J_{9a,9} = 11.2$ Hz) of vicinal protons at the 3a, 9a, and 9 positions.[12] Furthermore, under the acidic conditions of TFA, the methoxymethyl protecting group could be removed simultaneously, as expected.

Four unsaturated aliphatic groups were chosen in order to obtain compounds with different isoprene-derived side chains. These were allyl, 3-methyl-2-butenyl, geranyl, and farnesyl, consisting of 3, 5, 10, and 15 carbons, respectively. Thirteen compounds (**26**−**38**) were prepared by reacting **22**−**25** with the bromides of the four unsaturated aliphatic groups under basic conditions, and the yields were 63−77%. Compound **39**, possessing a benzyloxy group on the E-ring, was also prepared from compound **24**. In addition, six D-ring opened derivatives (**40**−**45**) were synthesized by acid-catalyzed transesterification[13] of compounds **22**−**25**, **37**, and **38** (see Scheme 3 and Table 1).

Cytotoxic Evaluation. Synthetic compounds **26**−**45**, as well as the isodeoxypodophylltoxin intermediates **22**−**25**, were evaluated for their cytotoxicity against seven human cultured tumor cell lines, viz., KB, BEL-7404, A549, HeLa, PC-3, CNE, and HL-60. It was found that compounds **27**, **39**, **43**, and **44** showed satisfactory cytotoxicity against at least one tested cell line.

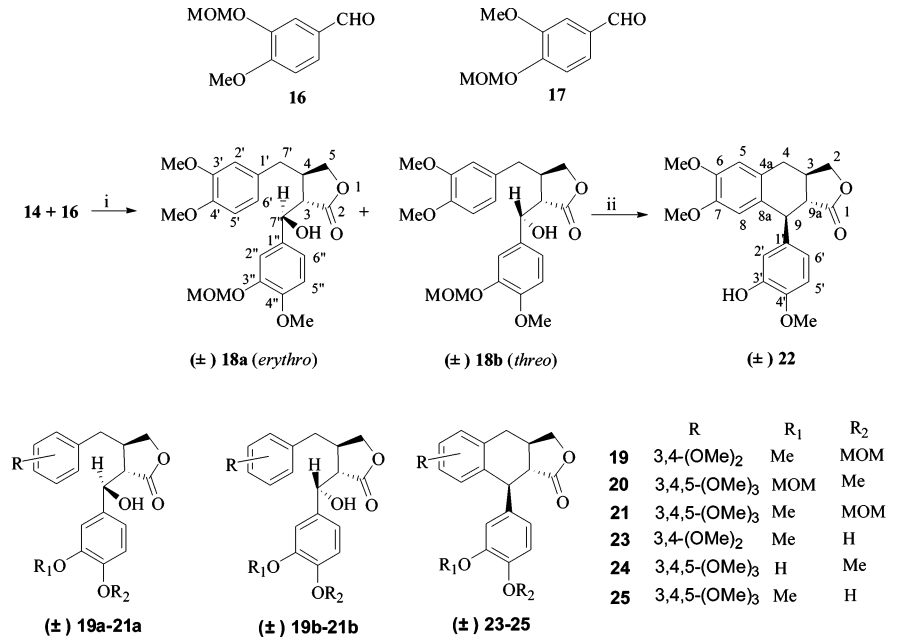
Among the series of target compounds (**26**−**38**) with a 3a,9a-*trans*-9a,9-*trans* stereochemistry and a closed D-ring, compound **27** displayed significant cytotoxicity against KB and BEL-7407 cell lines, and its IC_{50} values were 3.76 and 5.63 μM, respectively. Except compound **27**, most of the compounds with isoprene-derived side chains exhibited poor cytotoxicities against the seven tumor cell lines. Compounds **32**−**38**, with the unsaturated chains on the 4′ position of the E-ring, also exhibited almost no cytotoxicity. However, some interesting observations were made. Compound **27** was 10 times more cytotoxic against KB and BEL-7407 cell lines than compound **26**, and although compound **31** displayed weak cytotoxicity against KB and HeLa cell lines, it was more potent than compounds **28**−**30**. These facts suggest that elongation of the isoprene-derived chain could enhance the cytotoxic potency of the compounds. An additional methoxy group at C-8 of the B-ring resulted in a significant decrease of cytotoxicity of compound **31** compared to that of compound **27**, and this may be attributable to the spatial arrangement of the farnesoxyl group at C-3′ and the methoxy group at C-8. By comparing the four isodeoxypodophyllotoxin intermediates **22**−**25**, it was found that compounds **22** and **24**, bearing a hydroxy group at C-3′ of the E-ring, were more cytotoxic than compounds **23** and **25** with hydroxyl at the C-4′ position of the E-ring.

Lactone **39**, with a benzyloxy group at C-4′ on the E-ring, exhibited cytotoxicity as potent as compound **27** on KB and BEL-7407 cell lines, with IC_{50} values of 2.65 and 14.8 μM, respectively. This indicates that, to enhance cytotoxic potency, an aromatic group is more preferable than an aliphatic chain connected to the 4′-OH of the E-ring.

The *trans*-lactone D-ring is generally considered to be an important feature for the bioactivity of podophyllotoxin analogues. Among the series of compounds (**40**−**45**) with an opened D-ring, compound **44** was also found to possess significant cytotoxicity against six tumor cell lines at around 10 μM, especially against the HL-60 cell line, with an IC_{50} of 4.54 μM. In addition, compounds **40**−**45** were more selectively cytotoxic against the HL-60 cell line than compounds **22**−**39**, which possess an intact D-ring.

It should be noted that compound **44** exhibited an IC_{50} value of 4.54 μM against HL-60 cells, with a potency superior to the

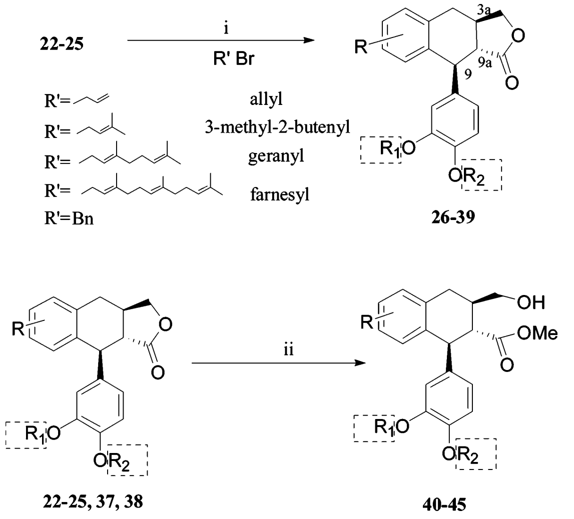
Scheme 2[a]



	R	R1	R2
19	3,4-(OMe)$_2$	Me	MOM
20	3,4,5-(OMe)$_3$	MOM	Me
21	3,4,5-(OMe)$_3$	Me	MOM
23	3,4-(OMe)$_2$	Me	H
24	3,4,5-(OMe)$_3$	H	Me
25	3,4,5-(OMe)$_3$	Me	H

[a] Reagents and conditions: (i) *n*-BuLi, (*i*-Pr)$_2$NH, THF, −80 °C, 2 h, 76−92%; (ii) TFA, CH_2Cl_2, 0 °C, 2 h, 63−72%.

Scheme 3[a]



[a] Each structure depicted represents the relative stereochemistry of a racemic compound. Reagents and conditions: (i) K_2CO_3, acetone, reflux 8 h, 63−78%; (ii) MeOH, HCl, rt, 2 h, 58−77%.

cytotoxicity of the front-line antitumor drug etoposide (IC_{50} = 10.5 μM). Moreover, compound **27** demonstrated notable cytotoxicity against the BEL-7404 cell line, with an IC_{50} value at 5.63 μM, while compound **43** showed impressive cytotoxicity against the A549 cell line, with an IC_{50} of 14.5 μM. Both compounds were more cytotoxic on the corresponding human tumor cell lines than the positive control etoposide. However, none of the synthesized compounds were more cytotoxic than podophyllotoxin, although this natural toxin is strictly confined in clinical utilization due to its unbearable side-effects on patients.

It is expected that isodeoxypodophyllotoxin lignans might offer potential for further development into therapeutic agents. Design and synthesis of additional isodeoxypodophyllotoxin derivatives containing a 3a,9a-*trans*-9a,9-*cis* configuration and studies of their structure−cytotoxicity relationships are in progress.

Experimental Section

General Experimental Procedures. Melting points were measured on a Perkin-Taike X-4 apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-400 FT-NMR instrument with TMS as the internal standard. ESIMS data were performed on a Bruker Esquire 3000+ spectrometer. HRFABMS spectra were recorded on a VG ZABHS spectrometer. Solvents and reagents were purified according to standard laboratory techniques. TLC was performed on silica gel 60 GF-254 plates (Merck). Column chromatography was performed on silica gel (200−300 mesh, Qingdao Marine) if not otherwise specified. *n*-Butyllithium, diisopropylamine, and trifluoroacetic acid were purchased from Acros Chemical Company and MTT from Sigma, St. Louis, MO. Other chemicals were mainly purchased from Tianjin Chemical Manufactory and Beijing Chemical Manufactory.

4-(3,4-Dimethoxyphenyl)-3-methoxycarbonyl-3-butenoic Acid (10). Under argon atmosphere, a solution of 3,4-dimethoxybenzaldehyde (**8**) (10 g, 0.06 mol) and dimethylsuccinate (9.5 mL, 0.072 mol) in 20 mL of MeOH was added to a stirred refluxing solution, which was prepared by dissolving sodium (2.0 g, 0.087 mol) in MeOH (10 mL). The flask was kept under reflux for 5 h and then concentrated under vacuum. The residue was partitioned between H_2O and ether, and the aqueous phase was acidified with 10% HCl at 0 °C. The resulting oil was extracted into EtOAc, washed successively with H_2O and brine, and then dried ($MgSO_4$). Evaporation and recrystallization from EtOAc/hexane gave the hemiester as an off-white powder (10.9 g, 65% yield): mp 148−150 °C (lit.[11] mp 149−150 °C).

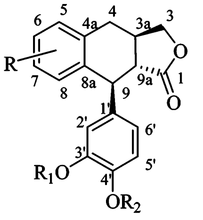
4-(3,4,5-Trimethoxyphenyl)-3-methoxycarbonyl-3-butenoic Acid (11). The preceding reaction was repeated with 3,4,5-trimethoxybenzaldehyde (**9**) (10 g, 0.051 mol) to give the crude product, which was purified by column chromatography on silica gel (hexane/EtOAc/HCOOH, 50:50:0.1) to give the title compound **11** (9.9 g, 62.6% yield) as a yellow oil.

(±)-4-(3,4-Dimethoxyphenyl)-3-methoxycarbonyl Butanoic Acid (12). A mixture of compound **10** (10.9 g, 0.039 mol) and palladium-charcoal (10%, 1.1 g) was stirred at room temperature under H_2 for 3 h. The catalyst was filtered off, and the solvent was evaporated under reduced pressure to afford the pure saturated hemiester **12** (10.1 g, 92.0% yield) as a yellowish solid: mp 107−108 °C (ether) (lit.[11] mp 108−109 °C).

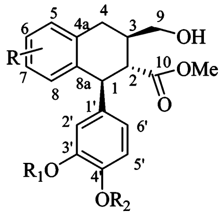
(±)-4-(3,4,5-Trimethoxyphenyl)-3-methoxycarbonylbutanoic Acid (13). By the same procedure used to obtain compound **12**, hemiester **11** (9.9 g, 0.032 mol) was converted to the saturated hemiester **13** (9.5 g, 95.2% yield) as a yellowish solid: mp 126−127 °C (ether) (lit.[14] mp 128−129 °C).

(±)-4-(3,4-Dimethoxyphenyl)-4,5-dihydro-2(3*H*)-furanone (14). To a stirred solution of 8 g (0.028 mol) of compound **12** in 150 mL of absolute EtOH was added 2 g (0.036 mol) of KOH. After dissolution,

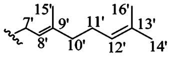
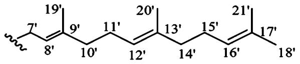
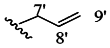
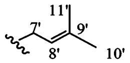
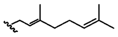
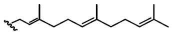
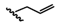
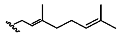
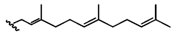
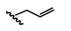
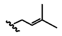
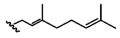
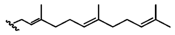
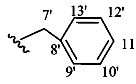
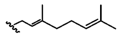
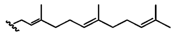
Table 1. Two Series of Isodeoxypodophyllotoxin Derivatives (±)-**26**−**45**



(±) 26-39



(±) 40-45

Compound	Substituted groups		
	R	R_1	R_2
26	3,4-(OMe)$_2$		Me
27	3,4-(OMe)$_2$		Me
28	3,4,5-(OMe)$_3$		Me
29	3,4,5-(OMe)$_3$		Me
30	3,4,5-(OMe)$_3$		Me
31	3,4,5-(OMe)$_3$		Me
32	3,4-(OMe)$_2$	Me	
33	3,4-(OMe)$_2$	Me	
34	3,4-(OMe)$_2$	Me	
35	3,4,5-(OMe)$_3$	Me	
36	3,4,5-(OMe)$_3$	Me	
37	3,4,5-(OMe)$_3$	Me	
38	3,4,5-(OMe)$_3$	Me	
39	3,4-(OMe)$_2$	Me	
40	3,4-(OMe)$_2$	H	Me
41	3,4-(OMe)$_2$	Me	H
42	3,4,5-(OMe)$_3$	H	Me
43	3,4,5-(OMe)$_3$	Me	H
44	3,4,5-(OMe)$_3$	Me	
45	3,4,5-(OMe)$_3$	Me	

6 g (0.054 mol) of powdered $CaCl_2$ was also added. A solution of 4.0 g (0.108 mol) of $NaBH_4$ in 30 mL of 1 M KOH was then introduced dropwise at 20 °C. The white suspension was stirred at room temperature for 5 h, then cooled to 0 °C and acidified with 10% HCl. Water was added until the solution became clear, and EtOH was removed in vacuo. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give compound **14** (4.9 g, 74.7% yield) as a colorless oil.

(±)-4-(3,4,5-Trimethoxyphenyl)-4,5-dihydro-2(3*H*)-furanone (15). The experimental procedure as noted above for compound **14** was repeated with compound **13** (8 g, 0.026 mol) to yield compound **15** (5.2 g, 75.7% yield) as a white solid: mp 81−83 °C (ether) (lit.[14] mp 79−82 °C).

General Procedure for Preparation of Compounds 18−21. To a solution of LDA, prepared from diisopropylamine (0.45 mL, 3.1 mmol) and *n*-butyllithium (1.6 M in hexane, 2.5 mL, 4.0 mmol) in dry THF (20 mL), was added a solution of compound **14** (1.0 g, 4.2 mmol) in 5 mL of dry THF at −80 °C. After 15 min, a solution of the benzaldehyde **16** (8.5 g, 4.3 mmol) in dry THF (8 mL) was added dropwise, and the mixture was further stirred for 2 h. The reaction was quenched by a saturated NH_4Cl solution, and the whole reaction mixture was extracted with EtOAc. The combined organic phase was dried ($MgSO_4$) and concentrated, and then the residue was chromatographed on silica gel (hexane/EtOAc, 3:1) to give a mixture (1.61 g, 88.7%) of the *erythro* isomer (**18a**) and the *threo* isomer (**18b**) as a yellow gum, whose HPLC analysis and ^1H NMR spectrum all showed an **18a** to **18b** ratio of approximately 1:1.

(±)-(3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-3-{(*S*)-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (18a) and (±)-(3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-3-{(*R*)-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (18b). ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, dd, J = 8.0, 2.0 Hz, H-6″), 6.90 (1H, d, J = 2.0 Hz, H-2″), 6.81 (1H, d, J = 8.0 Hz, H-5″), 6.65 (1H, d, J = 8.0 Hz, H-5′), 6.42 (1H, dd, J = 8.0, 2.0 Hz, H-6′), 6.36 (1H, d, J = 1.6 Hz, H-2′), 5.29 (0.5H, br s, C*H*OH for **18b**), 4.81 (0.5H, d, J = 8.0 Hz, C*H*OH for **18a**), 5.22 (2H, s, OCH_2O), 4.28 (1H, t, J = 8.4 Hz, H-5), 4.13 (1H, br s, H-5), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.50 (3H, s, OCH_2OCH_3), 2.97 (1H, br s, OH-7″), 2.87−2.82 (1H, m, H-4), 2.63−2.66 (1H, m, H-3), 2.41−2.30 (2H, m, H-7′); ESIMS *m/z* 450 $[M + NH_4]^+$.

Table 2. ^{13}C NMR Data [100 MHz, δ (ppm)] for Compounds **22**−**39** in $CDCl_3$

C no.	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**
1	175.5	175.8	176.0	175.9	175.5	175.5	175.9	175.9	175.9	176.0	175.9	175.8	175.8	175.9	175.8	175.8	175.9	175.9
3	71.0	70.4	70.7	70.5	71.0	71.1	70.7	70.7	70.7	70.7	70.4	70.4	70.4	70.5	70.5	70.5	70.6	70.4
3a	40.5	40.6	39.9	39.8	40.5	40.5	39.9	39.9	39.9	39.9	40.6	40.5	40.6	39.8	39.8	39.8	39.8	40.6
4	32.6	32.5	33.6	33.5	32.5	32.6	33.6	33.6	33.6	33.6	32.5	32.5	32.5	33.5	33.5	33.4	33.4	32.5
4a	126.8	126.9	131.2	131.1	126.8	126.8	131.2	131.2	131.2	131.2	126.9	126.9	126.8	131.1	131.1	131.1	131.1	126.9
5	108.1	108.1	107.2	107.0	108.1	108.2	107.1	107.1	107.1	107.1	108.1	108.1	108.1	107.0	107.0	107.0	107.0	108.1
6	147.6	147.8	152.3	152.2	147.5	147.5	152.3	152.3	152.4	152.3	147.8	147.8	147.8	152.2	152.2	152.2	152.2	147.8
7	146.2	146.5	141.2	141.1	146.2	146.2	141.3	141.2	141.2	141.2	146.5	146.4	146.4	141.1	141.1	141.1	141.1	146.4
8	112.9	113.0	152.3	152.5	112.9	112.9	152.6	152.6	152.7	152.7	113.0	113.0	113.0	152.5	152.6	152.5	152.6	113.0
8a	131.4	131.7	125.6	125.5	131.5	131.5	125.6	125.6	125.7	125.7	131.7	131.7	131.7	125.5	125.5	125.4	125.4	131.7
9	45.5	45.6	41.3	41.3	45.5	45.5	41.4	41.4	41.4	41.4	45.6	45.6	45.6	41.3	41.3	41.3	41.3	45.6
9a	48.8	49.1	50.9	50.8	48.9	48.9	50.9	50.9	50.9	50.9	49.1	49.1	49.1	50.8	50.8	50.8	50.8	49.1
1′	136.3	136.7	139.5	139.2	136.2	136.3	139.4	139.5	139.2	139.4	136.6	136.7	136.8	138.8	138.7	139.1	139.0	136.6
2′	113.0	112.5	110.1	110.3	112.9	113.0	110.4	110.5	110.5	110.5	112.4	112.5	112.5	110.6	110.8	111.3	111.2	112.5
3′	145.5	148.5	144.8	146.7	147.7	147.7	147.5	147.6	147.6	147.6	147.8	148.0	148.0	147.3	147.5	148.8	148.6	147.8
4′	148.7	144.9	145.2	144.6	147.4	147.4	147.3	147.3	147.5	147.5	147.5	147.4	147.5	147.0	147.4	146.1	146.0	147.5
5′	110.2	110.9	113.3	113.8	110.2	110.2	113.6	113.6	113.6	113.6	111.0	110.9	110.9	113.5	113.4	112.9	112.9	110.9
6′	121.5	121.6	120.6	120.4	121.4	121.4	120.0	120.0	119.9	120.0	121.5	121.5	121.5	120.1	120.1	120.0	120.0	121.6
OMe-6	55.8	55.9	55.8	55.8	55.8	55.8	55.8	55.8	55.8	55.8	55.8	55.8	55.9	55.7	55.7	55.8	55.8	55.9
OMe-7	55.8	55.9	59.3	59.2	55.8	55.8	59.3	59.3	59.4	59.4	55.9	55.8	55.9	59.2	59.2	59.2	59.2	55.9
OMe-8			60.4	60.4			60.4	60.4	60.4	60.4				60.2	60.2	60.2	60.2	
OMe-3′		56.3		55.8							56.4	56.3	56.3	55.7	55.6	55.7	55.6	56.4
OMe-4′	56.2		55.8		56.2	56.2	55.8	55.8	55.8	55.8								

(±)-(3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-3-{(*S*)-hydroxy[3-methoxy-4-(methoxymethoxy)phenyl]methyl}-dihydrofuran-2(3*H*)-one (19a) and (±)-(3*S*,4*R*)-4-(3,4-dimethoxybenzyl)-3-{(*R*)-hydroxy[3-methoxy-4-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (19b). Compounds **19a** and **19b** were obtained from compound **14** (0.6 g, 2.5 mmol) and compound **17** (0.49 g, 2.5 mmol) as a mixture of *erythro* and *threo* isomers by the same procedure as for the preparation of alcohol **18**. Yield 75.9% as a yellow gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, d, $J = 8.0$ Hz, H-6″), 6.80 (2H, d, $J = 8.0$ Hz, H-2″, 5″), 6.65 (1H, d, $J = 8.0$ Hz, H-5′), 6.42 (1H, s, H-2′), 6.36 (1H, d, $J = 8.0$ Hz, H-6′), 5.28 (0.5H, d, $J = 2.0$ Hz, C*H*OH for **19b**), 5.22 (2H, s, OCH_2O), 4.84 (0.5H, d, $J = 8.0$ Hz, C*H*OH for **19a**), 4.31 (1H, t, $J = 8.4$ Hz, H-5), 4.07 (1H, br s, H-5), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.48 (3H, s, OCH_2OCH_3), 3.03 (1H, br s, OH-7″), 2.85−2.80 (1H, m, H-4), 2.64 (1H, dd, $J = 12.4, 3.6$ Hz, H-3), 2.44 (1H, dd, $J = 14.4, 8.8$ Hz, H-7′), 2.30 (1H, dd, $J = 10.4, 7.2$ Hz, H-7′); ESIMS *m/z* 450 $[M + NH_4]^+$.

(±)-(3*S*,4*R*)-4-(3,4,5-Trimethoxybenzyl)-3-{(*S*)-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (20a) and (±)-(3*S*,4*R*)-4-(3,4,5-trimethoxybenzyl)-3-{(*R*)-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (20b). Compounds **20a** and **20b** were obtained from compound **15** (0.53 g, 2.0 mmol) and compound **16** (0.39 g, 2.0 mmol) as a mixture of *erythro* and *threo* isomers by the same procedure as for the preparation of alcohol **18**. Yield 92.0% as yellow gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, $J = 8.0$ Hz, H-6″), 6.89 (1H, s, H-2″), 6.80 (1H, d, $J = 8.0$ Hz, H-5"), 6.07 (2H, s, H-2′, 6′), 5.31 (0.5H, br s, C*H*OH for **20b**), 5.21 (2H, s, OCH_2O), 4.86 (0.5H, d, $J = 8.0$ Hz, C*H*OH for **20a**), 4.33 (1H, t, $J = 8.8, 8.0$ Hz, H-5), 4.10 (1H, t, $J = 7.6$ Hz, H-5), 3.85 (3H, s, OCH_3), 3.77 (9H, s, $OCH_3 \times 3$), 3.48 (3H, s, OCH_2OCH_3), 3.10 (1H, br s, OH-7″), 2.86−2.82 (1H, m, H-4), 2.68 (1H, dd, $J = 6.8, 3.2$ Hz, H-3), 2.40 (1H, dd, $J = 13.6, 8.4$ Hz, H-7′), 2.29 (1H, dd, $J = 14.0, 7.2$ Hz, H-7′); ESIMS *m/z* 480 $[M + NH_4]^+$.

(±)-(3*S*,4*R*)-4-(3,4,5-Trimethoxybenzyl)-3-{(*S*)-hydroxy[3-methoxy-4-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (21a) and (±)-(3*S*,4*R*)-4-(3,4,5-trimethoxybenzyl)-3-{(*R*)-hydroxy[3-methoxy-4-(methoxymethoxy)phenyl]methyl}dihydrofuran-2(3*H*)-one (21b). Compounds **21a** and **21b** were obtained from compound **15** (1.33 g, 5.0 mmol) and compound **17** (0.98 g, 5.0 mmol) as a mixture of *erythro* and *threo* isomers by the same procedure as for the preparation of alcohol **18**. Yield 86.6% as a yellow gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, $J = 8.4$ Hz, H-6″), 6.90 (1H, s, H-2″), 6.81 (1H, d, $J = 8.4$ Hz, H-5″), 6.08 (2H, s, H-2′, 6′), 5.31 (0.5H, br s, C*H*OH for **21b**), 5.20 (2H, s, OCH_2O), 4.86 (0.5H, d, $J = 7.2$ Hz, C*H*OH for **21a**), 4.32 (1H, t, $J = 8.0$ Hz, H-5), 4.05 (1H, br s, H-5), 3.89 (3H, s, OCH_3), 3.80 (9H, s, $OCH_3 \times 3$), 3.50 (3H, s, OCH_2OCH_3), 3.00 (1H, br s, OH-7″), 2.87−2.82 (1H, m, H-4), 2.70 (1H, dd, $J = 10.4, 4.8$ Hz, H-3), 2.39 (1H, dd, $J = 13.2, 9.2$ Hz, H-7′), 2.30 (1H, dd, $J = 13.2, 6.0$ Hz, H-7′); ESIMS *m/z* 480 $[M + NH_4]^+$.

General Procedure for the Preparation of Compounds 22−24 by Cyclization. (±)-(3a*R*,9*S*,9a*R*)-9-(3-Hydroxy-4-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (22). A mixture of compounds **18a** and **18b** (0.2 g, 0.46 mmol) was dissolved in dry CH_2Cl_2 (20 mL), and a solution of TFA (0.25 mL) in dry CH_2Cl_2 (2 mL) was added dropwise to it at 0 °C. The mixture was stirred for 2 h and extracted with CH_2Cl_2. The combined organic phase was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to afford compound **22** (0.12 g, 71.3% yield) as a gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (2H, dd, $J = 8.0, 1.2$ Hz, H-5′, 6′), 6.66 (1H, d, $J = 1.2$ Hz, H-2′), 6.60 (1H, s, H-5), 6.33 (1H, s, H-8), 5.57 (1H, s, OH), 4.52 (1H, dd, $J = 8.8, 6.4$ Hz, H-3α), 4.08 (1H, d, $J = 11.2$ Hz, H-9), 3.97 (1H, dd, $J = 10.4, 8.4$ Hz, H-3β), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.98 (1H, dd, $J = 15.2, 5.2$ Hz, H-4α), 2.93 (1H, dd, $J = 15.2, 11.6$ Hz, H-4β), 2.63−2.58 (1H, m, H-3a), 2.51 (1H, dd, $J = 13.6, 11.2$ Hz, H-9a); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2; ESIMS *m/z* 369 $[M - H]^-$; HRFABMS *m/z* 370.1404 (calcd for $C_{21}H_{22}O_6$, 370.1416).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Hydroxy-3-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (23). The experimental procedure as noted above for compound **22** was repeated with compound **19** (0.12 g, 0.27 mmol) to yield compound **23** (66 mg, 66.8% yield) as a gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (1H, d, $J = 8.4$ Hz, H-5′), 6.76 (1H, d, $J = 1.6$ Hz, H-2′), 6.71 (1H, dd, $J = 8.0, 1.6$ Hz, H-6′), 6.61 (1H, s, H-5), 6.34 (1H, s, H-8), 5.57 (1H, s, OH), 4.52 (1H, dd, $J = 8.4, 6.4$ Hz, H-3α), 4.09 (1H, d, $J = 11.2$ Hz, H-9), 3.99 (1H, dd, $J = 10.8, 8.4$ Hz, H-3β), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3),3.61 (3H, s, OCH_3), 2.99 (1H, dd, $J = 11.6, 4.2$ Hz, H-4α), 2.93 (1H, dd, $J = 14.0, 10.8$ Hz, H-4β), 2.64−2.59 (1H, m, H-3a), 2.48 (1H, dd, $J = 13.6, 11.2$ Hz, H-9a); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2; ESIMS *m/z* 369 $[M - H]^-$; HRFABMS *m/z* 370.1409 (calcd for $C_{21}H_{22}O_6$, 370.1416).

(±)-(3a*R*,9*S*,9a*R*)-9-(3-Hydroxy-4-methoxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (24). The experimental procedure as noted above for compound **22** was repeated with compound **20** (0.25 g, 0.54 mmol) to yield compound **24** (136 mg, 63.0% yield) as a gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, dd, $J = 8.0, 0.8$ Hz, H-6′), 6.78 (1H, d, $J = 8.4$ Hz, H-5′), 6.61 (1H, d, $J = 0.8$ Hz, H-2′), 6.46 (1H, s, H-5), 4.45 (1H, dd, $J = 8.4, 6.0$ Hz, H-3α), 4.27 (1H, d, $J = 9.6$ Hz, H-9), 3.90 (1H, dd, $J = 8.8, 7.2$ Hz, H-3β), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.13 (3H, s, OCH_3), 2.93−2.88 (2H, m, H-4), 2.46−2.42 (1H, m, H-3a), 2.38 (1H, dd, $J = 13.6, 10.4$ Hz, H-9a); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2; ESIMS *m/z* 399 $[M - H]^-$; HRFABMS *m/z* 400.1513 (calcd for $C_{22}H_{24}O_7$, 400.1522).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Hydroxy-3-methoxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (25). The experimental procedure as noted above for compound **22** was repeated with compound **21** (0.2 g, 0.43 mmol) to yield compound **25** (119 mg, 69.2% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.97 (1H, d, J = 1.6 Hz, H-2′), 6.76 (1H, d, J = 8.0 Hz, H-5′), 6.50 (1H, dd, J = 8.0, 1.6 Hz, H-6′), 6.46 (1H, s, H-5), 4.45 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.29 (1H, d, J = 10.0 Hz, H-9), 3.93 (1H, dd, J = 10.4, 8.4 Hz, H-3β), 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.13 (3H, s, OCH_3), 2.92−2.87 (2H, m, H-4), 2.49−2.45 (1H, m, H-3a), 2.38 (1H, dd, J = 13.2, 10.4 Hz, H-9a); ^{13}C NMR (100 MHz, CDCl$_3$), see Table 2; ESIMS m/z 399 [M − H]$^-$; HRFABMS m/z 400.1512 (calcd for $C_{22}H_{24}O_7$, 400.1522).

General Procedure for the Preparation of Compounds 26−39. (±)-(3a*R*,9*S*,9a*R*)-9-(3-Geranoxy-4-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (26). Compound **22** (0.1 g 0.27 mmol) was dissolved in dry Me$_2$CO$_3$ (10 mL) and stirred for 15 min with K$_2$CO$_3$ (0.18 g, 1.3 mmol) and KI (0.1 g, 0.60 mmol). Geranyl bromide (about 0.25 g), prepared by the reaction of geranol with PBr$_3$, was added to the flask, and the mixture was refluxed for 8 h. The reaction product was chromatographed on silica gel (hexane/EtOAc, 4:1) to give compound **26** (98 mg, 71.7% yield) as a yellow gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83 (2H, s, H-5′, 6′), 6.67 (1H, s, H-2′), 6.61 (1H, s, H-5), 6.32 (1H, s, H-8), 5.47 (1H, t, J = 6.4 Hz, H-8′), 5.07 (1H, t, J = 6.4 Hz, H-12′), 4.54−4.52 (3H, m, H-3α, 7′), 4.10 (1H, d, J = 11.2 Hz, H-9), 3.96 (1H, dd, J = 10.0, 9.6 Hz, H-3β), 3.86 (6H, s, OCH_3 × 2), 3.59 (3H, s, OCH_3), 3.02 (1H, dd, J = 14.8, 4.8 Hz, H-4α), 2.92 (1H, dd, J = 14.4, 12.0 Hz, H-4β), 2.64−2.58 (1H, m, H-3a), 2.49 (1H, dd, J = 13.2, 11.6 Hz, H-9a), 2.04−1.99 (4H, m, H-10′, 11′), 1.59, 1.63, 1.67 (CH_3 × 3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 131.7 (C, C-9′), 129.6 (C, C-13′), 124.0 (CH, C-12′), 120.1 (CH, C-8′), 69.7 (CH$_2$, C-7′), 39.6 (CH$_2$, C-10′), 26.4 (CH$_2$, C-11′), 25.7 (CH$_3$, C-14′), 17.7 (CH$_3$, C-16′), 16.4 (CH$_3$, C-15′), other data see Table 2; ESIMS m/z 524 [M + NH$_4$]$^+$; HRFABMS m/z 506.2660 (calcd for $C_{31}H_{38}O_6$, 506.2668).

(±)-(3a*R*,9*S*,9a*R*)-9-(3-Farnesoxy-4-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (27). By the same procedure used to obtain compound **26**, compound **22** (0.1 g, 0.27 mmol) was reacted with farnesyl bromide to give compound **27** (113 mg, 73.0% yield) as a yellow gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83 (2H, s, H-5′, 6′), 6.68 (1H, s, H-2′), 6.61 (1H, s, H-5), 6.32 (1H, s, H-8), 5.47 (1H, t, J = 6.4 Hz, H-8′), 5.10−5.09 (2H, m, H-12′, 16′), 4.54−4.51 (3H, m, H-3α, 7′), 4.10 (1H, d, J = 11.2 Hz, H-9), 3.96 (1H, dd, J = 11.6, 9.2 Hz, H-3β), 3.86 (6H, s, OCH_3 × 2), 3.59 (3H, s, OCH_3), 3.00 (1H, dd, J = 15.2, 4.8 Hz, H-4α), 2.92 (1H, dd, J = 15.6, 11.6 Hz, H-4β), 2.65−2.60 (1H, m, H-3a), 2.48 (1H, dd, J = 13.2, 11.6 Hz, H-9a), 2.08−1.98 (8H, m, H-10′, 11′, 14′, 15′), 1.59, 1.63, 1.67, 1.71 (CH_3 × 4); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.4 (C, C-9′), 132.2 (C, C-13′), 131.5 (C, C-17′), 124.6 (CH, C-16′), 123.7 (CH, C-12′), 120.5 (CH, C-8′), 69.4 (CH$_2$, C-7′), 39.6 (CH$_2$, C-10′, C-14′), 26.5 (CH$_2$, C-15′), 26.3 (CH$_2$, C-11′), 25.5 (CH$_3$, C-18′), 17.5 (CH$_3$, C-21′), 16.4 (CH$_3$, C-20′), 15.8 (CH$_3$, C-19′), other data see Table 2; ESIMS m/z 592 [M + NH$_4$]$^+$; HRFABMS m/z 574.3284 (calcd for $C_{36}H_{46}O_6$, 574.3294).

(±)-(3a*R*,9*S*,9a*R*)-9-(3-Allyloxy-4-methoxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (28). By the same procedure used to obtain compound **26**, compound **24** (0.1 g, 0.25 mmol) was reacted with allyl bromide to give compound **28** (86 mg, 78.1% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.85 (1H, s, H-2′), 6.76 (1H, d, J = 8.0 Hz, H-5′), 6.71 (1H, d, J = 7.6 Hz, H-6′), 6.46 (1H, s, H-5), 6.06 (1H, ddd, J = 22.4, 10.8, 5.6 Hz, H-8′), 5.33 (1H, dd, J = 17.2, 1.6 Hz, H-9′), 5.23 (1H, dd, J = 10.4, 1.2 Hz, H-9′), 4.57 (1H, d, J = 5.2 Hz, H-7′), 4.46 (1H, dd, J = 8.0, 6.4 Hz, H-3α), 4.30 (1H, d, J = 10.4 Hz, H-9), 3.95 (1H, dd, J = 10.4, 8.8 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.10 (3H, s, OCH_3), 2.94−2.86 (2H, m, H-4), 2.44−2.42 (1H, m, H-3a), 2.37 (1H, dd, J = 14.4, 10.0 Hz, H-9a); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.6 (CH, C-8′), 116.8 (CH, C-9′), 69.5 (CH$_2$, C-7′), other data see Table 2; ESIMS m/z 458 [M + NH$_4$]$^+$; HRFABMS m/z 440.1828 (calcd for $C_{25}H_{28}O_7$, 440.1835).

(±)-(3a*R*,9*S*,9a*R*)-9-[3-(3-Methylbut-2-enyloxy)-4-methoxyphenyl]-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (29). By the same procedure used to obtain compound **26**, compound **24** (0.1 g, 0.25 mmol) was reacted with 3-methyl-2-butenyl bromide to give compound **29** (91 mg, 77.7% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79−6.76 (3H, m, H-2′, 5′, 6′), 6.46 (1H, s, H-5), 5.42 (1H, t, J = 6.4 Hz, H-8′), 4.55 (1H, d, J = 6.4 Hz, H-7′), 4.47 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.30 (1H, d, J = 10.4 Hz, H-9), 3.92 (1H, dd, J = 10.4, 8.8 Hz, H-3β), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.08 (3H, s, OCH_3), 2.92−2.87 (2H, m, H-4), 2.46−2.42 (1H, m, H-3a), 2.39 (1H, dd, J = 14.0, 10.4 Hz, H-9a), 1.64, 1.71 (CH_3 × 2); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.7 (C, C-9′), 119.6 (CH, C-8′), 65.8 (CH$_2$, C-7′), 25.8 (CH$_3$, C-11′), 18.2 (CH$_3$, C-10′), other data see Table 2; ESIMS m/z 486 [M + NH$_4$]$^+$; HRFABMS m/z 468.2170 (calcd for $C_{27}H_{32}O_7$, 468.2184).

(±)-(3a*R*,9*S*,9a*R*)-9-[3-Geranoxy-4-methoxyphenyl]-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (30). By the same procedure used to obtain compound **26**, compound **24** (0.1 g, 0.25 mmol) was reacted with geranyl bromide to give compound **30** (95 mg, 70.9% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.80−6.75 (3H, m, H-2′, 5′, 6′), 6.46 (1H, s, H-5), 5.53 (1H, t, J = 6.4 Hz, H-8′), 5.07 (1H, t, J = 6.4 Hz, H-12′), 4.57 (2H, d, J = 6.4 Hz, H-7′), 4.47 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.30 (1H, d, J = 10.8 Hz, H-9), 3.93 (1H, dd, J = 10.0, 9.2 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.08 (3H, s, OCH_3), 2.94−2.88 (2H, m, H-4), 2.46−2.42 (1H, m, H-3a), 2.38 (1H, dd, J = 14.0, 10.4 Hz, H-9a), 2.08−1.98 (4H, m, H-10′, 11′), 1.59, 1.65, 1.67 (CH_3 × 3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 131.6 (C, C-9′), 129.7 (C, C-13′), 124.0 (CH, C-12′), 120.0 (CH, C-8′), 69.6 (CH$_2$, C-7′), 39.6 (CH$_2$, C-10′), 26.4 (CH$_2$, C-11′), 25.7 (CH$_3$, C-14′), 17.7 (CH$_3$, C-16′), 16.4 (CH$_3$, C-15′), other data see Table 2; ESIMS m/z 554 [M + NH$_4$]$^+$; HRFABMS m/z 536.2764 (calcd for $C_{27}H_{32}O_7$, 536.2774).

(±)-(3a*R*,9*S*,9a*R*)-9-[3-Farnesoxy-4-methoxyphenyl]-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (31). By the same procedure used to obtain compound **26**, compound **24** (0.1 g, 0.25 mmol) was reacted with farnesyl bromide to give compound **31** (112 mg, 74.2% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.82−6.66 (3H, m, H-2′, 5′, 6′), 6.46 (1H, s, H-5), 5.47 (1H, t, J = 6.4 Hz, H-8′), 5.10 (2H, t, J = 6.4 Hz, H-12′, 16′), 4.57 (2H, d, J = 6.4 Hz, H-7′), 4.46 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.30 (1H, d, J = 10.0 Hz, H-9), 3.92 (1H, dd, J = 10.0, 9.2 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.09 (3H, s, OCH_3), 2.95−2.91 (2H, m, H-4), 2.47−2.41 (1H, m, H-3a), 2.38 (1H, dd, J = 14.0, 10.4 Hz, H-9a), 2.10−1.98 (8H, m, H-10′, 11′, 14′, 15′), 1.64, 1.66, 1.67, 1.71 (CH_3 × 4); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.5 (C, C-9′), 132.1 (C, C-13′), 131.5 (C, C-17′), 124.7 (CH, C-16′), 123.9 (CH, C-12′), 120.2 (CH, C-8′), 69.9 (CH$_2$, C-7′), 39.5 (CH$_2$, C-10′, C-14′), 26.6 (CH$_2$, C-15′), 26.3 (CH$_2$, C-11′), 25.5 (CH$_3$, C-18′), 17.5 (CH$_3$, C-21′), 16.4 (CH$_3$, C-20′), 15.9 (CH$_3$, C-19′), other data see Table 2; ESIMS m/z 622 [M + NH$_4$]$^+$; HRFABMS m/z 604.3392 (calcd for $C_{37}H_{48}O_7$, 604.3400).

(±)-(3a*R*,9*S*,9a*R*)-9-[4-Allyloxy-3-methoxyphenyl]-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (32). By the same procedure used to obtain compound **26**, compound **23** (0.1 g, 0.27 mmol) was reacted with allyl bromide to give compound **32** (79 mg, 71.4% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83 (1H, d, J = 8.0 Hz, H-5′), 6.75 (1H, d, J = 8.0 Hz, H-6′), 6.72 (1H, s, H-2′), 6.61 (1H, s, H-5), 6.32 (1H, s, H-8), 6.10 (1H, ddd, J = 23.2, 11.2, 5.6 Hz, H-8′), 5.40 (1H, d, J = 15.6 Hz, H-9′), 5.28 (1H, d, J = 10.4 Hz, H-9′), 4.60 (2H, d, J = 5.6 Hz, H-7′), 4.53 (1H, dd, J = 8.0, 6.8 Hz, H-3α), 4.11 (1H, d, J = 11.2 Hz, H-9), 3.99 (1H, dd, J = 10.0, 8.8 Hz, H-3β), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.00 (1H, dd, J = 14.8, 4.4 Hz, H-4α), 2.97 (1H, dd, J = 15.2, 13.2 Hz, H-4β), 2.65−2.57 (1H, m, H-3a), 2.51 (1H, dd, J = 13.2, 11.2 Hz, H-9a); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.5 (CH, C-8′), 116.8 (CH, C-9′), 69.4 (CH$_2$, C-7′), other data see Table 2; ESIMS m/z 428 [M + NH$_4$]$^+$; HRFABMS m/z 410.1718 (calcd for $C_{24}H_{26}O_6$, 410.1729).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Geranoxy-3-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (33). By the same procedure used to obtain compound **26**, compound **23** (0.1 g, 0.27 mmol) was reacted with geranyl bromide to give compound **33** (91 mg, 66.6% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83 (1H, d, J = 7.6 Hz, H-5′), 6.76 (1H, dd, J = 7.2, 0.8 Hz, H-6′), 6.70 (1H, d, J = 0.8 Hz, H-2′), 6.61 (1H, s, H-5), 6.33 (1H, s, H-8), 5.53 (1H, t, J = 6.4 Hz, H-8′), 5.09 (1H, t, J = 6.4 Hz, H-12′), 4.60 (2H, d, J = 6.8 Hz, H-7′), 4.55 (1H, dd, J = 7.6, 7.2 Hz, H-3α), 4.12 (1H, d, J = 10.8 Hz, H-9), 3.99 (1H, dd, J = 10.0, 9.2 Hz, H-3β), 3.87 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.02−2.95 (2H, m, H-4), 2.66−2.58 (1H, m, H-3a), 2.51 (1H, dd, J = 13.2, 11.6 Hz, H-9a), 2.08−2.06 (4H, m, H-10′, 11′), 1.60, 1.67, 1.72 (CH_3 × 3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 131.7 (C, C-9′), 129.9 (C, C-13′), 124.1 (CH, C-12′), 120.0 (CH, C-8′), 69.7 (CH$_2$, C-7′), 39.6 (CH$_2$, C-10′), 26.4

(CH$_2$, C-11′), 25.7 (CH$_3$, C-14′), 17.8 (CH$_3$, C-16′), 16.4 (CH$_3$, C-15′), other data see Table 2; ESIMS m/z 524 [M + NH$_4$]$^+$; HRFABMS m/z 506.2674 (calcd for C$_{31}$H$_{38}$O$_6$, 506.2668).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Farnesoxy-3-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (34). By the same procedure used to obtain compound **26**, compound **23** (0.1 g, 0.27 mmol) was reacted with farensyl bromide to give compound **34** (98 mg, 63.2% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83 (1H, d, J = 8.4 Hz, H-5′), 6.76 (1H, d, J = 8.0 Hz, H-6′), 6.70 (1H, s, H-2′), 6.61 (1H, s, H-5), 6.33 (1H, s, H-8), 5.54 (1H, t, J = 6.4 Hz, H-8′), 5.10 (2H, t, J = 6.4 Hz, H-12′, 16′), 4.60 (2H, d, J = 6.4 Hz, H-7′), 4.53 (1H, dd, J = 8.0, 7.6 Hz, H-3α), 4.12 (1H, d, J = 10.8 Hz, H-9), 4.00 (1H, dd, J = 10.0, 9.6 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.96−2.90 (2H, m, H-4), 2.68−2.60 (1H, m, H-3a), 2.48 (1H, dd, J = 13.2, 11.6 Hz, H-9a), 2.08−2.03 (8H, m, H-10′, 11′, 14′, 15′), 1.60, 1.67, 1.72, 1.74 (CH_3 × 4); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.6 (C, C-9′), 132.0 (C, C-13′), 131.5 (C, C-17′), 124.7 (CH, C-16′), 123.7 (CH, C-12′), 120.2 (CH, C-8′), 69.9 (CH$_2$, C-7′), 39.8 (CH$_2$, C-10′), 39.6 (CH$_2$, C-14′), 26.7 (CH$_2$, C-15′), 26.5 (CH$_2$, C-11′), 25.5 (CH$_3$, C-18′), 17.5 (CH$_3$, C-21′), 16.4 (CH$_3$, C-20′), 15.9 (CH$_3$, C-19′), other data see Table 2; ESIMS m/z 592 [M + NH$_4$]$^+$; HRFABMS m/z 574.3280 (calcd for C$_{36}$H$_{46}$O$_6$, 574.3294).

(±)-(3a*R*,9*S*,9a*R*)-9-[4-Allyloxy-3-methoxyphenyl]-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (35). By the same procedure used to obtain compound **26**, compound **25** (0.1 g, 0.25 mmol) was reacted with allyl bromide to give compound **35** (84 mg, 76.5% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.84 (1H, s, H-2′), 6.76 (1H, d, J = 8.0 Hz, H-5′), 6.71 (1H, d, J = 8.0 Hz, H-6′), 6.46 (1H, s, H-5), 6.04 (1H, ddd, J = 22.8, 10.4, 5.6 Hz, H-8′), 5.33 (1H, dd, J = 17.2, 1.6 Hz, H-9′), 5.23 (1H, dd, J = 10.4, 1.2 Hz, H-9′), 4.55 (1H, dd, J = 13.2, 6.0 Hz, H-7′), 4.46 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.29 (1H, d, J = 10.0 Hz, H-9), 3.92 (1H, dd, J = 10.0, 8.8 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.09 (3H, s, OCH_3), 2.96−2.90 (2H, m, H-4), 2.47−2.42 (1H, m, H-3a), 2.37 (1H, dd, J = 13.6, 11.6 Hz, H-9a); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.5 (CH, C-8′), 116.7 (CH, C-9′), 69.5 (CH$_2$, C-7′), other data see Table 2; ESIMS m/z 458 [M + NH$_4$]$^+$; HRFABMS m/z 440.1827 (calcd for C$_{25}$H$_{28}$O$_7$, 440.1835).

(±)-(3a*R*,9*S*,9a*R*)-9-[4-(3-Methylbut-2-enyloxy)-3-methoxyphenyl]-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (36). By the same procedure used to obtain compound **26**, compound **25** (0.1 g, 0.25 mmol) was reacted with 3-methyl-2-butenyl bromide to give compound **36** (83 mg, 70.9% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.77−6.74 (3H, m, H-2′, 5′, 6′), 6.47 (1H, s, H-5), 5.43 (1H, t, J = 6.4 Hz, H-8′), 4.56 (1H, d, J = 6.0 Hz, H-7′), 4.47 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.29 (1H, d, J = 10.0 Hz, H-9), 3.92 (1H, dd, J = 10.4, 9.2 Hz, H-3β), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.08 (3H, s, OCH_3), 2.94−2.88 (2H, m, H-4), 2.49−2.44 (1H, m, H-3a), 2.37 (1H, dd, J = 14.0, 10.4 Hz, H-9a), 1.63, 1.70 (CH_3 × 2); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.0 (C, C-9′), 120.0 (CH, C-8′), 65.5 (CH$_2$, C-7′), 25.8 (CH$_3$, C-11′), 17.9 (CH$_3$, C-10′), other data see Table 2; ESIMS m/z 486 [M + NH$_4$]$^+$; HRFABMS m/z 468.2172 (calcd for C$_{27}$H$_{32}$O$_7$, 468.2184).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Geranoxy-3-methoxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (37). By the same procedure used to obtain compound **26**, compound **25** (0.1 g, 0.25 mmol) was reacted with geranyl bromide to give compound **37** (91 mg, 68.0% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88 (1H, br s, H-2′), 6.76 (1H, d, J = 8.4 Hz, H-5′), 6.62 (1H, d, J = 8.4 Hz, H-6′), 6.46 (1H, s, H-5), 5.48 (1H, J = 6.4 Hz, H-8′), 5.07 (1H, t, J = 6.0 Hz, H-12′), 4.57 (2H, d, J = 6.4 Hz, H-7′), 4.49 (1H, dd, J = 8.4, 6.4 Hz, H-3α), 4.31 (1H, d, J = 9.6 Hz, H-9), 3.95 (1H, dd, J = 10.0, 8.8 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.08 (3H, s, OCH_3), 2.93−2.87 (2H, m, H-4), 2.46−2.40 (1H, m, H-3a), 2.40 (1H, dd, J = 14.0, 10.0 Hz, H-9a), 2.08−1.99 (4H, m, H-10′, 11′), 1.58, 1.66, 1.69 (CH_3 × 3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 131.4 (C, C-9′), 129.9 (C, C-13′), 123.7 (CH, C-12′), 120.1 (CH, C-8′), 69.5 (CH$_2$, C-7′), 39.6 (CH$_2$, C-10′), 26.4 (CH$_2$, C-11′), 25.7 (CH$_3$, C-14′), 17.6 (CH$_3$, C-16′), 16.4 (CH$_3$, C-15′), other data see Table 2; ESIMS m/z 554 [M + NH$_4$]$^+$; HRFABMS m/z 536.2758 (calcd for C$_{27}$H$_{32}$O$_7$, 536.2774).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Farnesoxy-3-methoxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (38). By the same procedure used to obtain compound **26**, compound **25** (0.1 g, 0.25 mmol) was reacted with farnesyl bromide to give compound **38** (97 mg, 64.2% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88 (1H, br s, H-2′), 6.76 (1H, d, J = 8.4 Hz, H-5′), 6.63 (1H, d, J = 8.4 Hz, H-6′), 6.46 (1H, s, H-5), 5.49 (1H, t, J = 6.4 Hz, H-8′), 5.09 (2H, m, H-12′, H-16′), 4.56 (2H, d, J = 6.4 Hz, H-7′), 4.49 (1H, dd, J = 8.8, 8.4 Hz, H-3α), 4.30 (1H, d, J = 10.0 Hz, H-9), 3.96 (1H, dd, J = 11.2, 9.2 Hz, H-3β), 3.86 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.08 (3H, s, OCH_3), 2.95−2.89 (2H, m, H-4), 2.46−2.42 (1H, m, H-3a), 2.41 (1H, dd, J = 10.0, 9.6 Hz, H-9a), 2.04−1.98 (8H, m, H-10′, 11′, 14′, 15′), 1.59, 1.67, 1.69, 1.76 (CH_3 × 4); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.6 (C, C-9′), 132.1 (C, C-13′), 131.5 (C, C-17′), 124.6 (CH, C-16′), 123.8 (CH, C-12′), 120.4 (CH, C-8′), 69.9 (CH$_2$, C-7′), 39.8 (CH$_2$, C-10′), 39.7 (CH$_2$, C-14′), 26.5 (CH$_2$, C-15′), 26.2 (CH$_2$, C-11′), 25.5 (CH$_3$, C-18′), 17.6 (CH$_3$, C-21′), 16.5 (CH$_3$, C-20′), 16.0 (CH$_3$, C-19′), other data see Table 2; ESIMS m/z 622 [M + NH$_4$]$^+$; HRFABMS m/z 604.3388 (calcd for C$_{37}$H$_{48}$O$_7$, 604.3400).

(±)-(3a*R*,9*S*,9a*R*)-9-(4-Benzyloxy-3-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (39). By the same procedure used to obtain compound **26**, compound **23** (0.1 g, 0.27 mmol) was reacted with benzyl bromide to give compound **39** (97 mg, 78.4% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45−7.29 (5H, m, OCH$_2$Ph-H), 6.84 (1H, d, J = 8.4 Hz, H-5′), 6.72−6.70 (2H, m, H-2′, 6′), 6.60 (1H, s, H-5), 6.30 (1H, s, H-8), 5.14 (2H, s, OCH_2Ph), 4.53 (1H, dd, J = 8.0, 7.2 Hz, H-3α), 4.11 (1H, d, J = 12.0 Hz, H-9), 3.99 (1H, dd, J = 10.4, 9.6 Hz, H-3β), 3.87 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 2.98−2.92 (2H, m, H-4), 2.65−2.60 (1H, m, H-3a), 2.50 (1H, dd, J = 13.2, 11.2 Hz, H-9a); ^{13}C NMR (100 MHz, CDCl$_3$) δ 128.5 (CH, C-9′, C-13′), 128.3 (CH, C-10′, C-12′), 128.1 (CH, C-11′), 125.4 (C, C-8′), 75.0 (CH$_2$, C-7′), other data see Table 2; ESIMS m/z 478 [M + NH$_4$]$^+$; HRFABMS m/z 460.1878 (calcd for C$_{37}$H$_{48}$O$_7$, 460.1886).

General Procedure for the Preparation of Compounds 40−45. (±)-(1*S*,2*R*,3*R*)-Methyl 1-(3-hydroxy-4-methoxyphenyl)-3-(hydroxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (40). To a solution of compound **22** (74 mg, 0.2 mmol) in 5 mL of MeOH was added 1 M H$_2$SO$_4$ (1 mL) at room temperature. After stirring for 2 h, the solvent was removed under reduced pressure, and the residue was redissolved in EtOAc (10 mL). The organic phase was washed with H$_2$O and brine, dried (MgSO$_4$), and concentrated in vacuo to afford a crude product, which was purified by column chromatography on silica gel with hexane/EtOAc, 1:1, as eluent to give the pure product **40** (62 mg, 77.1% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.84 (1H, d, J = 8.0 Hz, H-5′), 6.65 (1H, d, J = 8.0 Hz, H-6′), 4.24 (1H, d, J = 10.8 Hz, H-1), 3.86 (3H, s, OCH_3), 6.61 (1H, s, H-2′), 6.56 (1H, s, H-5), 6.22 (1H, s, H-8), 5.57 (1H, s, OH-3′), 3.80 (3H, s, OCH_3), 3.66 (2H, d, J = 4.0 Hz, H-9), 3.59 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.92−2.88 (2H, m, H-4), 2.74 (1H, dd, J = 12.4, 11.2 Hz, H-2), 2.34−2.26 (1H, m, H-3); ^{13}C NMR (100 MHz, CDCl$_3$), see Table 3; ESIMS m/z 401 [M − H]$^-$; HRFABMS m/z 402.1668 (calcd for C$_{22}$H$_{26}$O$_7$, 402.1679).

(±)-(1S,2R,3R)-Methyl 1-(4-Hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (41). The experimental procedure as noted above for compound **40** was repeated with compound **23** (74 mg, 0.2 mmol) to yield compound **41** (58 mg, 72.6% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.84 (1H, d, J = 8.0 Hz, H-5′), 6.65 (1H, dd, J = 8.0, 2.0 Hz, H-6′), 6.61 (1H, s, H-5), 6.55 (1H, d, J = 2.0 Hz, H-2′), 6.22 (1H, s, H-8), 5.58 (1H, br s, OH-4′), 4.24 (1H, d, J = 11.2 Hz, H-1), 3.86 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.66 (2H, d, J = 4.4 Hz, H-9), 3.59 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.90−2.88 (2H, m, H-4), 2.73 (1H, dd, J = 11.6, 10.8 Hz, H-2), 2.34−2.28 (1H, m, H-3); ^{13}C NMR (100 MHz, CDCl$_3$), see Table 3; ESIMS m/z 401 [M − H]$^-$; HRFABMS m/z 402.1664 (calcd for C$_{22}$H$_{26}$O$_7$, 402.1679).

(±)-(1*S*,2*R*,3*R*)-Methyl 1-(3-Hydroxy-4-methoxyphenyl)-3-(hydroxymethyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (42). The experimental procedure as noted above for compound **40** was repeated with compound **24** (80 mg, 0.2 mmol) to yield compound **42** (60 mg, 69.3% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.71 (1H, d, J = 8.4 Hz, H-5′), 6.59 (1H, s, H-2′), 6.56 (1H, dd, J = 8.4, 1.2 Hz, H-6′), 6.46 (1H, s, H-5), 5.53 (1H, s, OH-3′), 4.46 (1H, d, J = 9.2 Hz, H-1), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.61 (2H, d, J = 3.6 Hz, H-9), 3.28 (3H, s, OCH_3), 2.80−2.75 (2H, m, H-4), 2.66 (1H, dd, J = 11.2, 9.6 Hz, H-2), 2.14−2.05 (1H, m, H-3); ^{13}C NMR (100

Table 3. ^{13}C NMR Data [100 MHz, δ (ppm)] for Compounds **40**−**45** in CDCl$_3$

C no.	**40**	**41**	**42**	**43**	**44**	**45**
1	48.8	48.8	44.0	44.0	44.0	44.0
2	53.0	53.0	54.2	54.1	54.2	54.2
3	40.0	40.0	40.0	40.0	40.0	40.0
4	31.9	32.0	33.0	33.0	33.0	33.0
4a	127.4	127.4	124.0	124.1	124.1	124.0
5	110.7	110.9	106.6	106.5	106.5	106.5
6	147.5	147.5	151.9	151.9	151.9	151.9
7	147.3	147.2	140.8	141.0	140.9	141.0
8	112.1	112.0	152.0	152.0	152.1	152.0
8a	130.2	130.2	132.1	132.1	132.1	152.1
9	65.4	65.4	65.4	65.4	65.4	65.4
10	175.1	175.1	175.6	175.5	175.5	175.6
1′	135.4	135.5	140.3	140.2	140.1	140.2
2′	114.0	114.1	113.4	113.6	113.5	113.5
3′	144.6	146.6	144.7	146.0	147.3	147.1
4′	145.5	144.4	145.3	144.5	146.5	146.6
5′	110.3	111.0	110.3	110.4	110.8	110.7
6′	122.5	122.2	124.0	124.1	124.3	124.3
OMe-6	55.8	55.8	55.8	55.7	55.8	55.8
OMe-7	55.9	55.9	59.4	59.4	59.4	59.4
OMe-8			60.5	60.5	60.5	60.5
OMe-10	53.0	53.0	51.8	51.8	51.8	51.8
OMe-3′	55.8	55.8				
OMe-4′			55.8	55.7	55.8	55.8

MHz, CDCl$_3$), see Table 3; ESIMS *m/z* 431 [M − H]$^-$; HRFABMS *m/z* 432.1772 (calcd for C$_{23}$H$_{28}$O$_8$, 432.1784).

(±)-(1*S*,2*R*,3*R*)-Methyl 1-(4-Hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (43). The experimental procedure noted above for compound **40** was repeated with compound **25** (80 mg, 0.2 mmol) to yield compound **43** (65 mg, 75.7% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.76 (1H, d, J = 8.0 Hz, H-5′), 6.55 (1H, d, J = 2.0 Hz, H-2′), 6.51 (1H, dd, J = 8.0, 2.0 Hz, H-6′), 6.46 (1H, s, H-5), 5.53 (1H, s, OH-4′), 4.45 (1H, d, J = 9.2 Hz, H-1), 3.84 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.60 (2H, d, J = 4.8 Hz, H-9), 3.15 (3H, s, OCH_3), 2.78 (2H, dd, J = 14.0, 10.0 Hz, H-4), 2.65 (1H, dd, J = 11.2, 9.6 Hz, H-2), 2.14−2.06 (1H, m, H-3); ^{13}C NMR (100 MHz, CDCl$_3$), see Table 3; ESIMS *m/z* 431 [M − H]$^-$; HRFABMS *m/z* 432.1788 (calcd for C$_{23}$H$_{28}$O$_8$, 432.1784).

(±)-(1*S*,2*R*,3*R*)-Methyl 1-(4-Geranoxy-3-methoxyphenyl)-3-(hydroxymethyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (44). The experimental procedure as noted above for compound **40** was repeated with compound **37** (54 mg, 0.1 mmol) to yield compound **44** (35 mg, 62.2% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.73 (1H, d, J = 8.4 Hz, H-5′), 6.59 (1H, s, H-2′), 6.52 (1H, d, J = 8.4 Hz, H-6′), 6.46 (1H, s, H-5), 5.49 (1H, J = 6.4 Hz, H-8′), 5.07 (1H, t, J = 6.8 Hz, H-12′), 4.55 (2H, d, J = 6.4 Hz, H-7′), 4.47 (1H, d, J = 9.6 Hz, H-1), 3.85 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.61 (2H, d, J = 7.2 Hz, H-9), 3.12 (3H, s, OCH_3), 2.83 (1H, dd, J = 16.0, 11.6 Hz, H-4β), 2.76 (1H, dd, J = 16.0, 4.0 Hz, H-4α), 2.67 (1H, dd, J = 16.0, 7.2 Hz, H-2), 2.14−2.06 (5H, m, H-3, 10′, 11′), 1.59, 1.66, 1.68 (CH_3 × 3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 131.6 (C, C-9′), 129.7 (C, C-13′), 124.0 (CH, C-12′), 120.1 (CH, C-8′), 69.6 (CH$_2$, C-7′), 39.6 (CH$_2$, C-10′), 26.4 (CH$_2$, C-11′), 25.7 (CH$_3$, C-14′), 17.6 (CH$_3$, C-16′), 16.4 (CH$_3$, C-15′), other data see Table 3; ESIMS *m/z* 586 [M + NH$_4$]$^+$; HRFABMS *m/z* 568.3026 (calcd for C$_{33}$H$_{44}$O$_8$, 568.3036).

(±)-(1*S*,2*R*,3*R*)-Methyl 1-(4-Farnesoxy-3-methoxyphenyl)-3-(hydroxymethyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (45). The experimental procedure as noted above for compound **40** was repeated with compound **38** (60 mg, 0.1 mmol) to yield compound **45** (37 mg, 58.2% yield) as a gum: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.73 (1H, d, J = 8.0 Hz, H-5′), 6.59 (1H, d, J = 2.0 Hz, H-2′), 6.51 (1H, dd, J = 8.0, 2.0 Hz, H-6′), 6.46 (1H, s, H-5), 5.49 (1H, t, J = 6.4 Hz, H-8′), 5.10−5.08 (2H, m, H-12′, H-16′), 4.54 (2H, d, J = 6.8 Hz, H-7′), 4.47 (1H, d, J = 9.6 Hz, H-9), 3.85 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.61 (2H, d, J = 4.2 Hz, H-9), 3.12 (3H, s, OCH_3), 2.83 (1H, dd, J = 15.6, 11.2 Hz, H-4β), 2.77 (1H, dd, J = 16.0, 4.4 Hz, H-4α), 2.66 (1H, dd, J = 14.0, 12.8 Hz, H-2), 2.19−2.14 (9H, m, H-3, 10′, 11′, 14′, 15′), 1.60, 1.66, 1.68, 1.70 (CH_3 × 4); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.5 (C, C-9′), 132.1 (C, C-13′), 131.5 (C, C-17′), 124.5 (CH, C-16′), 123.7 (CH, C-12′), 120.2 (CH, C-8′), 69.9 (CH$_2$, C-7′), 39.5 (CH$_2$, C-10′, C-14′), 26.6 (CH$_2$, C-15′), 26.3 (CH$_2$, C-11′), 25.5 (CH$_3$, C-18′), 17.5 (CH$_3$, C-21′), 16.4 (CH$_3$, C-20′), 15.9 (CH$_3$, C-19′), other data see Table 3; ESIMS *m/z* 654 [M + NH$_4$]$^+$; HRFABMS *m/z* 604.3654 (calcd for C$_{38}$H$_{52}$O$_8$, 636.3662).

Cytotoxicity Assays. Cytotoxicities of the test compounds against cultured human KB, BEL-7404, A549, HeLa, PC-3, CNE, and HL-60 cell lines were determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay.[15] This was performed by assessment of the remaining number of viable cells after exposure of a given number of cells in culture to a particular concentration of the test compounds. Cell viability was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyl-2*H*-tetrazolium bromide (MTT).[15] Briefly, a fresh solution was prepared in phosphate-buffered saline immediately before use. The different cell lines were diluted in fresh complete medium and seeded in 96-well plates, applying 10^4 cells/well. After 24 h of incubation, the cells were treated with the synthetic compounds at various concentrations during 72 h. Then, MTT solution (10 μL) was added to each well. The plates were placed in a CO$_2$ incubator (Shellab) for 4 h and then lysed and incubated with DMSO. The plates were analyzed in a multiwell plate reader (Bio-Tek ELX800) at 570 nm. The 50% inhibitory concentration (IC$_{50}$) was calculated as the compound concentration required to reduce the MTT signal by 50% compared with untreated control cultures, which was determined graphically from the dose−response curves.

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