A New Synthesis of Podophyllum Lignans by Weitz' Aminium Salt-Induced Free Radical Cycloaddition Reaction of a Doubly Unsaturated Ester

Yoshiaki ARA, Tetsuya TAKEYA, and Seisho TOBINAGA*

Showa College of Pharmaceutical Sciences, Machida, Tokyo 194, Japan.
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(±)-Isopodophyllotoxin (1e) and related lactones 12, 13, 14 were synthesized by a biomimetic procedure from the doubly unsaturated esters 11a and 11b by means of an oxidative free radical cycloaddition reaction utilizing a stable cation radical salt, Weitz' aminium salt, in one step. (±)-Isopicropodophyllin (1g), the *trans*-fused lactones, 12, 13, and 16, and the *cis*-fused lactone 17 were also synthesized from the esters 11c and 11d by the reaction with the same reagent.

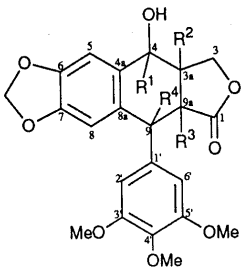
Key words synthesis; podophyllum lignan; (±)-isopodophyllotoxin; (±)-isopicropodophyllin; Weitz' aminium salt; free radical cyclo-addition reaction

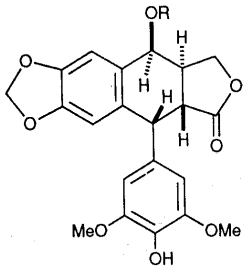
Podophyllotoxin (**1a**) belongs to the family of the naturally occurring aryltetralin lactone lignans and has been the subject of extensive studies over the years.[1] The clinical application of two glycosides, etoposide (**2**) and teniposide (**3**), in the treatment of lung and bladder cancer[2] has stimulated further studies directed toward achieving new and efficient syntheses of **1** and related analogues.[1]

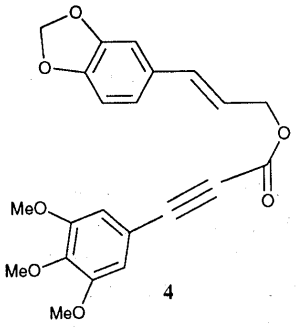
Podophyllum lignans are considered to be biosynthesized by the oxidative coupling of the corresponding cinnamyl alcohol and cinnamic acid such as (*E*)-3,4-methylenedioxycinnamyl alcohol [(*E*)-**7**] and (*E*)-3,4,5-trimethoxycinnamic acid [(*E*)-**9**]. This concept has been successfully employed in a conventional chemical synthesis of podophyllum lignans starting from the doubly unsaturated esters **4**[3] and **11a**.[4]

In the preceding paper, we reported that treatments of (*E*)-3,4-methylenedioxycinnamyl alcohol [(*E*)-**7**] and (*E*)-3,4-methylenedioxycinnamyl acetate [(*E*)-**8**] with Weitz' aminium salts, tris(4-bromophenyl)aminium hexachloroantimonate (BAHA), a stable cation radical salt, gave a well known lignan (±)-sesamin (**5**), but (*E*)-3,4,5-trimethoxycinnamic acid [(*E*)-**9**] and methyl 3,4,5-trimethoxycinnamate [(*E*)-**10**] did not afford such products.[5] Subsequently, we explored the reaction of the doubly unsaturated esters **11** with BAHA, expecting to obtain podophyllum lignans *via* free radical cycloaddition reaction.

We prepared four doubly unsaturated esters **11a**, **11b**, **11c**, and **11d** from the corresponding (*E*)- and (*Z*)-alcohols, (*E*)-**7** and (*Z*)-**7**, and acids, (*E*)-**9** and (*Z*)-**9**, for our present purpose. The (*Z*)-alcohol (*Z*)-**7** and the acid (*Z*)-**9** were synthesized from the esters (*Z*)-**6a** and (*Z*)-**6b**, which were prepared by the Horner–Emmons reaction[6] of 3,4-methylenedioxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate in the presence of







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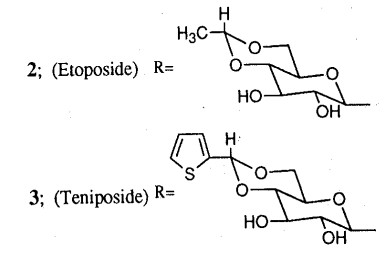
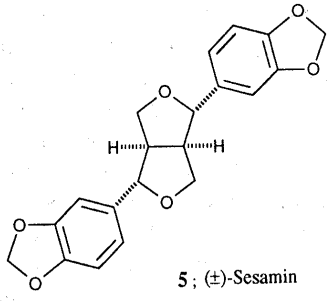




5; (±)-Sesamin

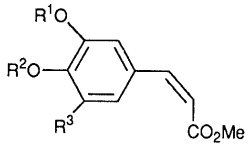
1a: R^1=β-H, R^2=α-H, R^3=β-H, R^4=β-H (Podophyllotoxin)
b: R^1=α-H, R^2=α-H, R^3=β-H, R^4=β-H (Epipodophyllotoxin)
c: R^1=β-H, R^2=α-H, R^3=α-H, R^4=β-H (Picropodophyllin)
d: R^1=α-H, R^2=α-H, R^3=α-H, R^4=β-H (Epipicropodophyllin)
e: R^1=α-H, R^2=β-H, R^3=α-H, R^4=β-H (Isopodophyllotoxin)
f: R^1=β-H, R^2=β-H, R^3=α-H, R^4=β-H (Epiisopodophyllotoxin)
g: R^1=α-H, R^2=β-H, R^3=β-H, R^4=β-H (Isopicropodophyllin)
h: R^1=β-H, R^2=β-H, R^3=β-H, R^4=β-H (Epiisopicropodophyllin)

2; (Etoposide) R=

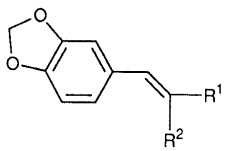
3; (Teniposide) R=

Chart 1

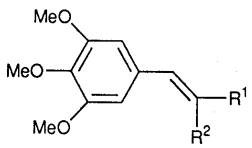
* To whom correspondence should be addressed.



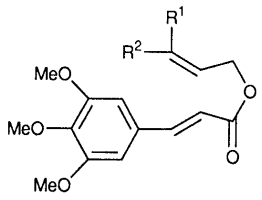
6a : $R^1+R^2=CH_2$, $R^3=H$
6b : $R^1=R^2=Me$, $R^3=OMe$

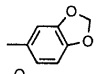
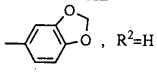


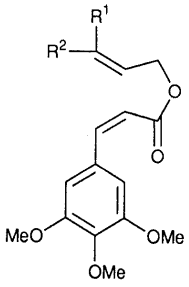
(*Z*)-**7** : $R^1=H$, $R^2=CH_2OH$
(*E*)-**7** : $R^1=CH_2OH$, $R^2=H$
(*E*)-**8** : $R^1=CH_2OAc$, $R^2=H$



(*Z*)-**9** : $R^1=H$, $R^2=CO_2H$
(*E*)-**9** : $R^1=CO_2H$, $R^2=H$
(*E*)-**10** : $R^1=CO_2Me$, $R^2=H$



11a : $R^1=H$, $R^2=$ 
11b : $R^1=$  , $R^2=H$



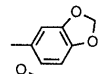
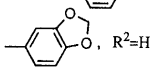
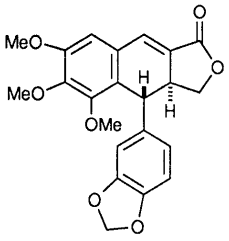
11c : $R^1=H$, $R^2=$ 
11d : $R^1=$  , $R^2=H$

Chart 2



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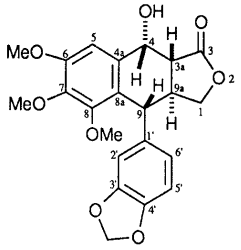

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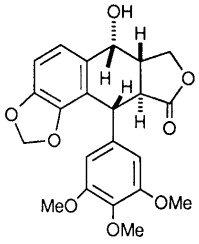

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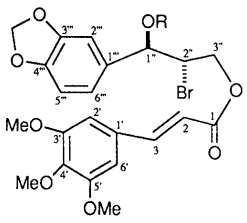
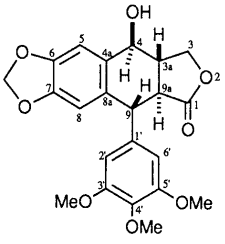
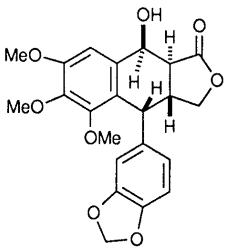


15a : R=H
15b : R=Ac



1e ;(±)-Isopodophyllotoxin



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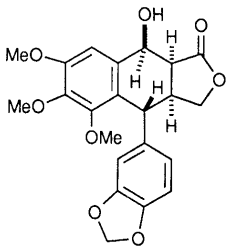

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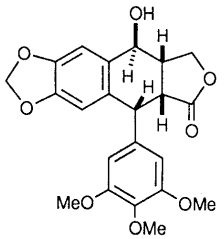


1g ;(±)-Isopicropodophyllin

Chart 3

$KN(TMS)_2$ and 18-crown-6, followed by reduction with $LiAlH_4$ and alkaline hydrolysis, respectively (Chart 2).

Reaction of the ester **11a** (*E–E* isomer) with 2 eq of BAHA in tetrahydrofuran (THF) under a nitrogen atmosphere in the presence of Na_2CO_3 gave four compounds having an arylnaphthofuran moiety, **12**, **13**, **14**, and (±)-isopodophyllotoxin (**1e**), in yields of 15.9%, 46.3%, 3.3%, and 4.4%, respectively (Chart 3 and Table 1). The structure of **1e** was identified by comparison of the physical data with those of (±)-isopodophyllotoxin.[7]

The planar structure of the lactone **13** was assigned by means of spectral analyses, including IR, ^1H- and ^{13}C-NMR spectra, ^1H–^{13}C COSY (^1H–^{13}C shift correlation spectroscopy) and COLOC (correlation spectroscopy *via* long-range coupling) experiments (Fig. 1, Tables 4 and 6). (i) It has hydroxyl and γ-lactone absorptions at 3468 and 1753 cm^{-1} in the IR spectrum. (ii) The signal of C_8-OMe, at δ 3.19, is observed at higher field than the other methoxyl signals owing to the shielding effect of the 3,4-methylenedioxyphenyl group linked at C-9 in the ^1H-NMR spectrum (in $CDCl_3$). (iii) The ^{13}C-NMR spectrum

Table 1. Radical Cycloaddition Reaction of **11a** and **11b** with BAHA

Run	Substrate	Solvent	Total	Product (yield %)				
				12	**13**	**14**	**15a**	**1e**
1	**11a**	THF	69.9	15.9	46.3	3.3	—	4.4
2		MeCN	67.4	Trace	53.2	—	14.2	—
3		MeCN–H_2O	50.6	Trace	32.3	—	18.3	—
4		CH_2Cl_2	—	—	—	—	—	—
5	**11b**	THF	70.3	14.3	48.0	4.3	—	3.7

showed signals corresponding to C-3 (δ 175.3) of the carbonyl carbon and C-4 (δ 65.4) of the hydroxy-bearing carbon. (iv) The molecular ion peak at m/z 414 (M^+) was observed in the mass spectrum (MS), and the molecular formula was determined by elemental analysis and high-resolution MS (HR-MS) to be $C_{22}H_{22}O_8$. In the COLOC experiment on **13** (Fig. 1), long-range correlations between the proton signal of C_5-H (δ 6.77) and the carbon signal of C-4 (δ 65.4), and between the proton signal of C_4-OH (δ 2.81) and the carbon signal of C-4a (δ 132.9) were observed. This suggests that the hydroxyl substituent is attached to the C-4 position. On the other hand, the correlation between the proton signal of $C_{2'}$-H (δ 6.59) and the carbon signal of C-9 (δ 46.2) indicated that the 3,4-methylenedioxyphenyl moiety is attached to the C-9 position. Consequently, the structure of **13** was assigned as a 9-arylnaphthofuran derivative.

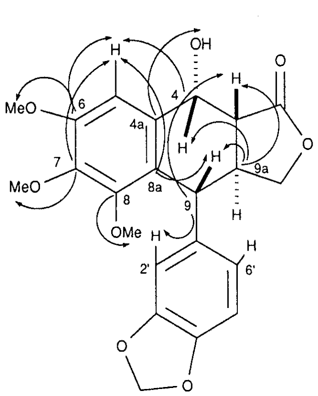


Fig. 1. Long-Range Correlations (^{13}C ^{1}H) in the COLOC Spectrum of **13**

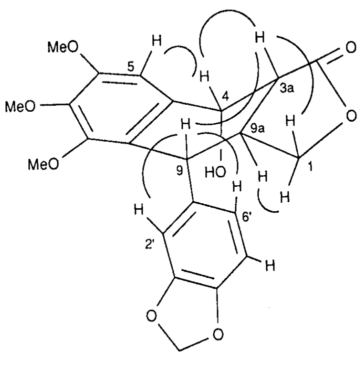


Fig. 2. Correlations in the NOESY Experiments on **13**

Table 2. Chemical Shifts (H-9, H-9a, H-3a, and H-4) and Coupling Constants ($J_{9,9a}$, $J_{9a,3a}$, and $J_{3a,4}$) of Podophyllum Lignans from ^{1}H-NMR Spectra in $CDCl_3$ at 270 MHz

Compd.	δ				J (Hz)		
	H-9	H-9a	H-3a	H-4	9,9a	9a,3a	3a,4
12	3.90	3.32—3.39	—	7.32	14.6	—	—
13	3.91	3.02—3.11	2.52	5.92	10.9	14.3	2.8
14	4.20	3.29	2.61—2.68	4.91	10.6	14.3	2.5
1e	4.08	2.56	2.51—2.60	4.92	10.7	14.4	9.8
16	4.46	3.55—3.65	3.35	4.85	1.5	10.7	6.7
17	4.31	3.38—3.44	3.27	4.98	2.8	9.3	2.8
1g	4.66	3.01	3.01—3.07	4.80	5.4	10.9	6.1

In a nuclear Overhauser enhancement and exchange spectroscopy (NOESY) experiment on **13** (Fig. 2), correlation cross peaks were observed between C_4-H and C_{3a}-H, C_5-H; between C_{3a}-H and C_1-H, C_9-H; and between C_9-H and $C_{2'}$-H, $C_{6'}$-H. Additionally, the coupling constants between C_4-H and C_{3a}-H, C_{3a}-H and C_{9a}-H, and C_{9a}-H and C_9-H of **13** were 2.8, 14.3, and 10.9 Hz, respectively. These data suggest that their relative configurations may be *cis*, *trans*, and *trans*, respectively (Table 2).

The structure of **14**, an isomer of **1e**, was supported by the *vicinal* coupling constant ($J = 8$ Hz) between C_5-H and C_6-H, and the doublet signals at δ 6.85 and δ 6.77 observed in the ^{1}H-NMR spectrum (Table 5). The structure of **12** was elucidated by the analysis and comparison of the IR spectra and the ^{1}H- and ^{13}C-NMR spectra, with the aid of ^{13}C–^1H COSY, with those of **13** (Tables 4 and 6).

The mechanism of formation of the cycloaddition products **12**, **13**, **14**, and **1e** from **11a** can be postulated to be as follows (Chart 4). The cation radical **18** derived from **11a** by one-electron oxidation with BAHA may form a *trans*-fused lactone **19**, followed by ionic cyclization of **19** to yield the radical **20**. Then, further one-electron oxidation of **20** may take place to afford the cation **21**, at the C-4″ position of which water (H_2O) contained in the reagent (BAHA) is introduced to terminate the reaction, giving the hydroxy-lactone **13**. Dehydration of **13** would afford **12**. Alternative radical cyclization of **19** may lead to (±)-isopodophyllotoxin (**1e**) and **14** after one-electron oxidation, proton elimination, and introduction of a hydroxyl group (Chart 4).

The structure of the radical-cation intermediate **18** is considered to be an important factor for preferential formation of the *trans*-fused lactone **13**. The intermediate **18**-A seems to be the most favorable based on the Newman projection formula (Chart 5). Consequently, **13** may be generated as a major product through the intermediates **19**-B, **20**-C, and **21**-D.

Subsequently, reaction of **11a** with BAHA using acetonitrile (MeCN) instead of THF under the same conditions gave arylnaphthofurans, **12** and **13** and the bromo-alcohol **15a** in yields of a trace, 53.2%, and 14.2% (run 2, Table 1). Moreover, reaction of **11a** using MeCN–H_2O (10 : 1, v/v) as a solvent provided the same products in similar yields to run 2 (run 3, Table 1). Oxidation of **11a** with BAHA in CH_2Cl_2 afforded only an inseparable complex mixture on thin layer chromatography (TLC) (run 4, Table 1). Thus, the following reactions with BAHA were performed using THF as a solvent.

Oxidation of the ester **11b** (Z–E isomer) having a (Z)-cinnamyl moiety gave the same products as those obtained by the oxidation of **11a** in similar yields (run 5, Table 1).

From the above proposal and results, it is considered that the stereochemistry of the cycloadducts will be controlled by the stereochemistry of the cinnamate moiety rather than the cinnamyl moiety of the esters **11** in oxidative cyclization. Therefore, oxidation of the esters having a (Z)-cinnamate moiety instead of the (E)-cinnamate moiety of **11a** may be expected to afford

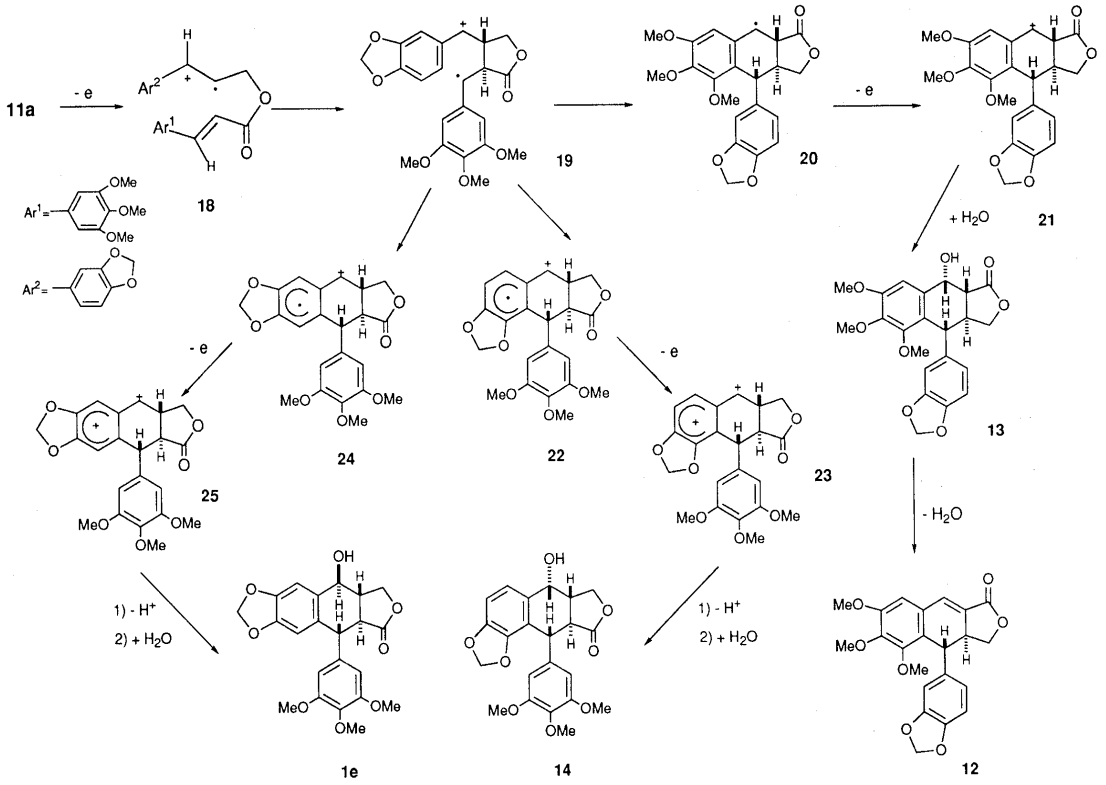


Chart 4. Proposed Mechanism of the Cycloaddition Reaction

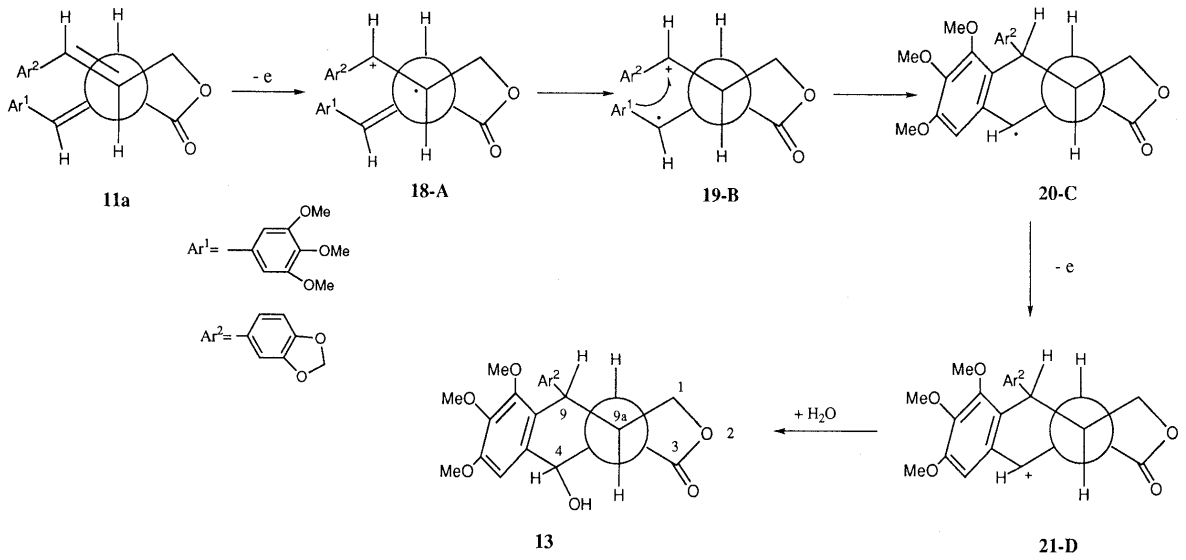


Chart 5. Mechanism of Stereoselective Cycloaddition Reaction for the Formation of **13**

products that possess different configurations from those obtained by oxidation of **11a**.

The structure of **15a** was assigned based on the following chemical transformation and spectral analyses. (i) The IR spectrum of **15a** showed the presence of a hydroxyl group absorption at 3470 cm^{-1} and an unsaturated ester group absorption at 1723 cm^{-1}. (ii) The ^{1}H-NMR spectra data of **15a** (Table 8) resembled those of haloalcohols prepared in our previous report[5] except for signals due to the 3,4,5-trimethoxycinnamate moiety, and three proton signals at higher magnetic field due to $C_{1''}$-H (δ 4.91), $C_{2''}$-H (δ 4.35—4.52), and $C_{3''}$-H (δ 4.70 and 4.35—4.52). Further, (iii) the molecular ion peak at *m/z* 494 was observed in the MS. The MS also showed a peak at *m/z* 496 ($M^+ + 2$), and the HR-MS confirmed the presence of a bromine atom in the molecule. These data suggested that **15a** may be a compound in which the hydroxyl group and bromine are attached at the C-1″ and C-2″ positions of the cinnamyl moiety, respectively. Acetylation of **15a** with Ac_2O–pyridine gave the monoacetate **15b**.

We have already reported that a *threo*-compound and its *erythro* isomer such as **15a** could be distinguished on the basis of the chemical shifts of the $C_{3''}$-H methylene proton in the ^{1}H-NMR spectrum.[5] The signal of the $C_{3''}$-H of **15a** is observed at δ 4.41 and 4.58 (see Table 8). This suggested that $C_{3''}$-H is not shielded by the

3,4-methylenedioxyphenyl group at C-1″. Therefore, **15a** was assigned as the *erythro* compound.

Thus, oxidation of **11c** (*E–Z* isomer) with BAHA in THF was investigated. Five compounds, the *trans*-fused lactones **12**, **13**, and **16**, the *cis*-fused lactone **17**, and (±)-isopicropodophyllin (**1g**), were obtained in yields of 17.7%, 19.7%, 22.3%, 18.3%, and 4.5%, respectively (run 1, Table 3). Reaction of **11d** (*Z–Z* isomer) with BAHA yielded the same products as those obtained by the oxidation of **11c** (run 2, Table 3). These results show that the oxidation of esters such as **11c** (*E–Z* isomer) and **11d** (*Z–Z* isomer) which have a (*Z*)-cinnamate moiety gives products having different stereochemistry from those prepared by oxidation of **11a** (*E–E* isomer) and **11b** (*Z–E* isomer), in agreement with the prediction.

The structure of **1g** was identified by direct comparison of physical data with those of an authentic sample of (±)-isopicropodophyllin (Tables 5 and 7).[7] The structures of **16** and **17** were also elucidated by analyses and comparison of the IR spectra and the ^{1}H- and ^{13}C-NMR spectra, with the aid of ^{1}H–^{13}C COSY, with those of **13**.

Table 3. Radical Cycloaddition Reaction of **11c** and **11d** with BAHA

Run	Substrate	Solvent	Total	Product (yield %)				
				12	**13**	**16**	**17**	**1g**
1	**11c**	THF	82.5	17.7	19.7	22.3	18.3	4.5
2	**11d**	THF	54.3	7.2	17.2	8.9	15.6	5.4

Table 4. ^{1}H-NMR Spectral Data for **12**, **13**, **16**, and **17**[a]

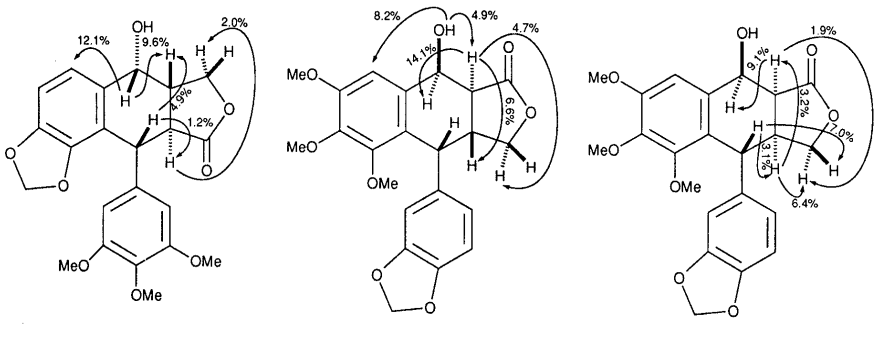
	12	**13**	**16**	**17**
H-1α	4.36, t	4.32, dd	3.96, dd	4.54, dd
(*J*=Hz)	(8.9)	(8.2)	(9.5)	(9.2)
		(7.8)	(2.6)	(7.9)
H-1β	3.98, dd	4.11, dd	4.68, t	3.99, dd
(*J*=Hz)	(8.8)	(11.1)	(9.5)	(9.2)
	(9.0)	(8.2)		(5.1)
H-3a	—	2.52, dd	3.35, dd	3.27, dd
(*J*=Hz)		(14.3)	(10.7)	(9.3)
		(2.8)	(6.7)	(2.8)
H-4	7.32, d	5.14, dd	4.85, dd	4.98, br s
(*J*=Hz)	(3.3)	(3.1)	(10.7)	
		(2.1)	(6.7)	
H-9	3.90, d	3.907, d	4.46, d	4.31, d
(*J*=Hz)	(14.6)	(10.9)	(1.52)	(2.8)
H-9a, m	3.32	3.02	3.55	3.38
	—3.39	—3.11	—3.65	—3.44
H-5 (s)	6.72	6.77	7.07	6.74
H-2′	6.76, d	6.59, br s	6.54, d	6.75, d
(*J*=Hz)	(1.5)		(1.5)	(1.8)
H-5′	6.78, d	6.74, d	6.68, d	6.71, d
(*J*=Hz)	(7.9)	(7.9)	(8.2)	(8.3)
H-6′	6.72, dd	6.61, br d	6.46, dd	6.59, dd
(*J*=Hz)	(7.9)	(7.9)	(8.2)	(8.3)
	(1.5)		(1.5)	(1.8)
Ar-OMe				
C6-OMe	3.80	3.76	3.88	3.84
C7-OMe	3.90	3.91	3.91	3.88
C8-OMe	3.24	3.19	3.76	3.59
OCH_2O	5.96	5.92	5.91	5.91
C4-OH	—	2.81, d	4.34, d	2.11
(*J*=Hz)		(2.8)	(11.0)	(5.5)

a) δ in $CDCl_3$; ^{1}H-NMR at 270 MHz.

Table 5. ^{1}H-NMR Spectral Data for **1e**, **1g**, and **14**[a]

	1e	**1g**	**14**
H-3α	4.17, dd	4.59, dd	4.30, dd
(*J*=Hz)	(8.8)	(8.8)	(8.6)
	(10.4)	(9.0)	(11.0)
H-3β	4.69, dd	3.72, dd	4.41, dd
(*J*=Hz)	(6.7)	(7.8)	(7.0)
	(8.8)	(9.0)	(8.3)
H-3a, m	2.52	3.01	2.61
	—2.60	—3.07	—2.68
H-4	4.92, dd	4.80, dd	4.91, dd
(*J*=Hz)	(9.1)	(5.5)	(2.1)
	(9.8)	(6.1)	(2.5)
H-9	4.08, d	4.66, d	4.20, d
(*J*=Hz)	(10.7)	(5.4)	(10.6)
H-9a	2.56, dd	3.27, dd	3.29, dd
(*J*=Hz)	(10.7)	(5.4)	(10.7)
	(14.4)	(10.9)	(14.3)
H-5	7.11	7.11	6.85, d
			(8.0)
H-6	—	—	6.77, d
			(8.0)
H-8	6.33	6.70	—
H-2′	6.37	6.46	6.55
H-6′	6.37	6.46	6.55
Ar-OMe			
C3′-OMe	3.82	3.76	3.80
C4′-OMe	3.84	3.83	3.84
C5′-OMe	3.82	3.76	3.80
OCH_2O	5.93	5.99	5.80, d
			(1.5)
			5.71, d
			(1.5)
C4-OH	1.84, d	2.11, d	2.01, d
(*J*=Hz)	(9.8)	(6.1)	(2.1)

a) δ in $CDCl_3$; ^{1}H-NMR at 270 MHz.



14 **16** **17**

Fig. 3

Table 6. ^{13}C-NMR Spectral Data for **12**, **13**, **16**, and **17**[a]

Carbon No.	12	13	16	17
1	72.4	71.9	74.4	73.5
3	169.7	175.3	179.3	176.7
3a	132.3	47.3	43.8	46.6
4	129.2	65.4	66.3	68.9
4a	125.4	132.9	135.0	131.3
5	109.4	109.2	103.6	108.2
6	145.2	143.0	141.3	142.8
7	152.9	153.2	153.3	153.1
8	152.9	152.4	151.4	152.0
8a	124.0	125.8	120.2	122.4
9	47.9	46.2	40.8	40.6
9a	43.8	41.3	39.2	39.4
1′	138.6	139.4	135.6	139.2
2′	108.3	107.2	107.7	108.1
3′	147.9	147.8	148.1	148.1
4′	146.1	146.0	146.3	146.3
5′	108.3	108.3	108.2	108.2
6′	119.9	119.7	119.8	120.2
C-6-OMe	60.8	60.5	60.9	60.7
C-7-OMe	56.1	56.0	56.0	56.0
C-8-OMe	60.0	59.5	61.3	60.7
O$\underline{C}$H$_2$O	101.0	101.0	101.1	101.1

a) δ in $CDCl_3$; ^{13}C-NMR at 125.65 MHz.

Table 7. ^{13}C-NMR Spectral Data for **1e**, **1g**, and **14**[a]

Carbon No.	1e[b]	1g	14
1	175.3	177.1	175.8
3	70.1	72.5	67.1
3a	44.2	44.6	40.3
4	69.7	71.0	64.7
4a	132.7	132.3	123.6
5	105.7	105.8	121.2
6	145.8	147.6	106.9
7	146.1	148.2	145.5
8	108.0	108.9	146.6
8a	134.6	133.6	133.5
9	45.9	45.2	41.0
9a	46.3	45.5	44.2
1′	139.0	137.2	138.8
2′	106.5	106.4	106.0
3′	152.5	153.1	152.1
4′	135.9	122.9	136.5
5′	152.5	153.1	152.1
6′	106.5	106.4	106.0
C-3′-OMe	55.8	56.2	55.8
C-4′-OMe	59.8	60.9	59.8
C-5′-OMe	55.8	56.2	55.8
O$\underline{C}$H$_2$O	100.8	101.3	100.5

a) δ in $CDCl_3$; ^{13}C-NMR at 125.65 MHz. b) δ in DMSO.

The stereochemistry of **16** and **17** was established from the coupling constants and a ^{1}H-NOE experiment, respectively (see Fig. 3, Tables 4 and 6).

Although we succeeded in synthesizing podophyllum lignans, (±)-isopodophyllotoxin (**1e**), (±)-isopicropodophyllin (**1g**), and related aryltetralin lactone lignans from the doubly unsaturated esters **11** by the radical cycloaddition reaction with Weitz' aminium salt BAHA in THF in one step, we failed to synthesize the major lignan podophyllotoxin (**1a**) of this family by this methodology. We are currently examining the synthesis of podophyllum lignans by means of new methodology mimicking the biosynthesis of the lignans in nature.

Table 8. ^{1}H-NMR Spectral Data for **15a** and **15b**[a]

Proton No.	15a	15b
H-2	7.60, d	7.62, d
(J=Hz)	(14.9)	(15.9)
H-3	6.33, d	6.36, d
(J=Hz)	(14.9)	(15.9)
H-2′ and 6′	6.76, s	6.78, s
H-1″	4.91, d	6.02, d
(J=Hz)	(7.4)	(5.8)
H-2″	4.35	4.50, td
(J=Hz)	—4.52, m	(5.8)
		(4.9)
H-3″	4.70, dd	4.41, dd
(J=Hz)	(11.0)	(11.0)
	(5.8)	(4.9)
	4.35	4.58, dd
	—4.52, m	(11.0)
		(5.8)
H-2‴	6.93, d	6.86, d
(J=Hz)	(2.1)	(1.5)
H-5‴	6.81, d	6.80, d
(J=Hz)	(7.9)	(7.9)
H-6‴	6.86, dd	6.87
(J=Hz)	(7.9)	—6.91, m
	(2.1)	
C-3′ and 5′-OMe	3.90, s	3.91, s
C-4′-OMe	3.89, s	3.89, s
OC$\underline{H}_2$O	5.94, d	5.96, d
(J=Hz)	(1.5)	(1.2)
	5.93, d	5.95, d
	(1.5)	(1.2)
OCOC$\underline{H}_3$		2.14, s

a) δ in $CDCl_3$; ^{1}H-NMR at 270 MHz.

Experimental

All melting points are uncorrected. IR spectra were recorded with a JASCO IR-700 spectrometer, and ^{1}H- and ^{13}C-NMR spectra with JEOL JNM-EX90, JNM-GX270 and JNM-GSX500 spectrometers, with tetramethylsilane as an internal standard ($CDCl_3$ and C_6D_6 solution). Mass spectra were recorded on a JEOL JMS-D300 spectrometer. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. Wako silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and TLC, respectively. The organic extract was dried over Na_2SO_4. High-performance liquid chromatography (HPLC) was performed on a Wakosil 5C4-200 column (25 cm × 4.6 mm i.d. for analytical scale or 25 cm × 20 mm i.d. for preparative scale) with aqueous methanol (40—60%), using a Shimadzu LC-6A apparatus for monitoring at 254 nm.

(*Z*)-Methyl 3-(3,4-Methylenedioxyphenyl)acrylate (6a) A solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (318 mg, 1 mmol) and 18-crown-6 ether (1.32 g, 5 mmol) in anhydrous THF (20 ml) was cooled to −78 °C under a nitrogen atmosphere and treated with $KN(TMS)_2$ [potassium bis(trimethylsilyl)amide; 2 ml (1 mmol); 0.5 M solution, Aldrich]. 3,4-Methylenedioxybenzaldehyde (150 mg, 1 mmol) was then added and the resulting mixture was stirred for 30 min at −78 °C. Saturated NH_4Cl was added and the product was extracted with ether (three times). The organic layer was washed with H_2O, and then dried and concentrated. The residue was subjected to silica gel column chromatography using $CHCl_3$–hexane (1 : 2, v/v) as an eluent to give 188 mg (91.3%) of **6a**, as colorless crystals, mp 52.5—53.5 °C (ether–hexane). IR (KBr) cm^{-1}: 1708, 1618, 1594, 1494. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s, CO_2Me), 5.82 (1H, d, J=12.8 Hz, Ar-CH=), 5.98 (2H, s, –OCH_2O–), 6.78 (1H, d, J=8.1 Hz, H-5), 6.81 (1H, d, J=12.8 Hz, =CHCO), 7.10 (1H, dd, J=1.8, 8.1 Hz, H-6), 7.45 (1H, d, J=1.8 Hz, H-2). MS m/z: 206 (M^+).

(*Z*)-Methyl 3-(3,4,5-Trimethoxyphenyl)acrylate (6b) Compound **6b** was synthesized as a colorless oil from 3,4,5-trimethoxybenzaldehyde

by a procedure similar to that used for **6a**, in a yield of 92%. IR (KBr) cm^{-1}: 2946, 1714, 1579, 1502. ^{1}H-NMR ($CDCl_3$) δ: 3.73 (3H, s, CO_2Me), 3.88 (9H, s, 3 × Ar-OMe), 5.90 (1H, d, J = 12.8 Hz, Ar-CH=), 6.82 (1H, d, J = 12.8 Hz, =CH–CO), 7.06 (2H, s, Ar-H). MS m/z: 252 (M^+).

(*Z*)-3,4-Methylenedioxycinnamyl Alcohol [(*Z*)-7] A solution of (*Z*)-**6a** (1.8 g, 9.0 mmol) in anhydrous ether (54 ml) was slowly added to a stirred suspension of $LiAlH_4$ (0.7 g, 18.6 mmol) in anhydrous ether (54 ml) at −15 °C over 3 h. The reaction mixture was poured into MeOH in ice (1 : 1, v/v). The precipitates were separated from the solution by filtration with Celite and the filtrate was extracted with ether. The organic layer was washed with 10% NH_4Cl and saturated brine, then dried and concentrated. The residue was subjected to silica gel column chromatography using $CHCl_3$–hexane (1 : 1, v/v) as an eluent to give 1.4 g (89.6%) of (*Z*)-**7**, as a colorless oil. IR (KBr) cm^{-1}: 3360, 2892, 1500, 1488. ^{1}H-NMR ($CDCl_3$) δ: 4.40 (2H, dd, J = 1.3, 6.4 Hz, –CH_2OH), 5.76 (1H, dt, J = 6.4, 11.7 Hz, =CH–CH_2OH), 5.95 (2H, s, –OCH_2O–), 6.40—6.85 (4H, m, aromatic-H). MS m/z: 178 (M^+).

(*Z*)-3,4,5-Trimethoxycinnamic Acid [(*Z*)-9] A solution of (*Z*)-**6b** (252 mg, 1 mmol) in 2% alcoholic KOH (20 ml) was refluxed for 1 h, then poured into ice-water, acidified with 10% HCl and extracted with ether. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel column chromatography using $CHCl_3$–hexane (1 : 7, v/v) as an eluent to give 220 mg (92.5%) of (*Z*)-**9**, as colorless crystals (ether–hexane), mp 113.5—114.5 °C. IR (KBr) cm^{-1}: 3170, 2948, 1696, 1610, 1578, 1511. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (6H, s, 2 × Ar-OMe), 3.89 (3H, s, Ar-OMe), 5.92 (1H, d, J = 12.7 Hz, Ar-CH=), 6.94 (1H, d, J = 12.7 Hz, =CHCO), 7.06 (2H, s, Ar-H). MS m/z: 238 (M^+).

General Procedure for Esterifications of Cinnamyl Alcohols, (*Z*)- or (*E*)-7 and Cinnamic Acids, (*Z*)- or (*E*)-9 Dicyclohexylcarbodiimide (DCC; 2.3 g, 11.0 mmol) was added slowly to a solution of a cinnamyl alcohol (**7**; 10 mmol), a cinnamic acid (**9**; 10 mmol), and 4-dimethylaminopyridine (8.0 mmol) in anhydrous CH_2Cl_2 at 0 °C. The resulting solution was allowed to stand at 0 °C for 5 min, then stirred at room temperature for 2 h. The precipitates were separated from the solution by filtration and the filtrate was washed with 10% HCl and saturated $NaHCO_3$, then dried and concentrated. The residue was purified by column chromatography on silica gel using $CHCl_3$–hexane (2 : 1, v/v) as an eluent.

(*E*)-3,4-Methylenedioxycinnamyl (*E*)-3-(3,4,5-Trimethoxyphenyl)acrylate (11a) Compound **11a**, colorless needles (ether–hexane), mp 122—124 °C, was synthesized from (*E*)-**7** and (*E*)-**9** in 95.2% yield *via* the above general procedure. IR (KBr) cm^{-1}: 2938, 1705, 1633, 1579. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s, Ar-OMe), 3.89 (6H, s, 2 × Ar-OMe), 4.84 (2H, dd, J = 1.22, 6.71 Hz, H-1″), 5.97 (2H, s, –OCH_2O–), 6.19 (1H, dt, J = 6.71, 15.87 Hz, H-2″), 6.39 (1H, d, J = 15.87 Hz, H-3), 6.62 (1H, d, J = 15.87 Hz, H-3″), 6.76 (2H, s, H-2′ and H-6′), 6.77(1H, d, J = 7.93 Hz, H-5‴), 6.85 (1H, dd, J = 1.53, 8.24 Hz, H-6‴), 6.96 (1H, d, J = 1.53 Hz, H-2‴), 7.64 (1H, d, J = 15.87 Hz, H-2). MS m/z: 398 (M^+).

(*Z*)-3,4-Methylenedioxycinnamyl (*E*)-3-(3,4,5-Trimethoxyphenyl)acrylate (11b) Compound **11b**, colorless needles (ether–hexane), mp 144—145 °C, was synthesized from (*Z*)-**7** and (*E*)-**9** in 98.4% yield *via* the above general procedure. IR (KBr) cm^{-1}: 2934, 1709, 1628, 1583. ^{1}H-NMR ($CDCl_3$) δ: 3.89 (9H, s, 3 × Ar-OMe), 4.96 (2H, dd, J = 1.5, 6.6 Hz, H-1″), 5.80 (1H, dt, J = 6.6, 11.7 Hz, H-2″), 5.97 (2H, s, –OCH_2O–), 6.37 (1H, d, J = 15.8 Hz, H-3), 6.55—7.00 (6H, m, aromatic-H), 7.63 (1H, d, J = 15.8 Hz, H-2). MS m/z: 398 (M^+).

(*E*)-3,4-Methylenedioxycinnamyl (*Z*)-3-(3,4,5-Trimethoxyphenyl)acrylate (11c) Compound **11c**, colorless needles (ether–hexane), mp 80.0—82.0 °C, was synthesized from (*E*)-**7** and (*Z*)-**9** in 90.3% yield *via* the above general procedure. IR (KBr) cm^{-1}: 1708, 1616, 1579. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (6H, s, 2 × Ar-OMe), 3.87 (3H, s, Ar-OMe), 4.76 (2H, dd, J = 0.9, 6.2 Hz, H-1″), 5.93 (1H, d, J = 12.8 Hz, H-3), 5.96 (2H, s, –OCH_2O–), 6.11 (1H, dt, J = 6.2, 15.8 Hz, H-2″), 6.49—7.05 (7H, m, aromatic-H). MS m/z: 398 (M^+).

(*Z*)-3,4-Methylenedioxycinnamyl (*Z*)-3-(3,4,5-Trimethoxyphenyl)acrylate (11d) Compound **11d**, colorless needles (ether–hexane), mp 135—136 °C, was synthesized from (*Z*)-**7** and (*Z*)-**9** in 92.0% yield *via* the above general procedure. IR (KBr) cm^{-1}: 2940, 1709, 1628, 1582. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (6H, s, 2 × Ar-OMe), 3.88 (3H, s, Ar-OMe), 4.87 (2H, dd, J = 1.5, 6.8 Hz, H-1″), 5.72 (1H, dd, J = 6.6, 11.7 Hz, H-2″), 5.93 (1H, d, J = 12.8 Hz, H-3), 5.96 (2H, s, –OCH_2O–), 6.43—7.04 (7H, m, aromatic-H). MS m/z: 398 (M^+).

Oxidation of 11a with BAHA in the Designated Solvents Method A in THF: Anhydrous Na_2CO_3 (3.2 g, 30 mmol), followed by BAHA[8] (1.6 g, 2 mmol), was added to a solution of **11a** (398 mg, 1 mmol) in THF (56 ml) under a nitrogen atmosphere at 0 °C. The mixture was stirred at room temperature for 30 min, when the bluish color of the BAHA had faded. At this time, the light brown reaction mixture was passed through a short column of silica gel (150 g) with AcOEt–hexane (1 : 2, v/v). The eluate was concentrated, and the residue was subjected to column chromatography on silica gel (150 g) using $CHCl_3$–hexane (1 : 1, v/v) as an eluent. The first eluate gave tris(4-bromophenyl)amine. The second eluate gave 63 mg (15.9%) of 1,3,9*β*,9a*α*-tetrahydro-6,7,8-trimethoxy-9*α*-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3-one (**12**), as colorless crystals (ethanol), mp 174—176 °C. The next eluate gave 192 mg (46.3%) of 1,3,3a*β*,4*β*,9*β*,9a*α*-hexahydro-4*α*-hydroxy-6,7,8-trimethoxy-9*α*-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3-one (**13**), as colorless crystals (CH_2Cl_2–MeOH), mp 187—189 °C. The final eluate gave a mixture of **14** and **1e**. The mixture was taken up in ether. The ether-soluble portion was concentrated and recrystallized from ether–MeOH to yield 14 mg (3.3%) of 1,3,3a*β*,4*β*,9*β*,9a*α*-hexahydro-4-hydroxy-7,8-methylenedioxy-9*α*-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1-one (**14**), as colorless prisms, mp 230—234 °C. The ether-insoluble portion was concentrated and recrystallized from acetone to yield 18 mg (4.4%) of 1,3,3a*β*,4*α*,9*β*,9a*α*-hexahydro-4*β*-hydroxy-6,7-methylenedioxy-9*α*-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1-one (**1e**), as colorless crystals, mp 266—268 °C. **12**: IR (KBr) cm^{-1}: 1762, 1666, 1590. *Anal.* Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.67; H, 5.23. HR-MS Calcd for $C_{22}H_{20}O_7$: 396.1209. Found: 396.1185. **13**: IR (KBr) cm^{-1}: 3468, 1753, 1600. *Anal.* Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.98; H, 5.42. HR-MS Calcd for $C_{22}H_{22}O_8$: 414.1315. Found: 414.1317. **14**: IR (KBr) cm^{-1}: 3492, 1759, 1591. HR-MS Calcd for $C_{22}H_{22}O_8$: 414.1315. Found: 414.1353. **1e**: IR (KBr) cm^{-1}: 3446, 1745, 1591. HR-MS Calcd for $C_{22}H_{22}O_8$: 414.1315. Found: 414.1311. ^{1}H- and ^{13}C-NMR data for **12**, **13**, **14**, and **1e** are listed in Tables 4—7.

Method B in MeCN: Oxidation of **11a** was carried out in MeCN by the same procedure (method A) as described for the oxidation of **11a** in THF. Then, hexane (28 ml) and $CHCl_3$ (14 ml) was added to the reaction mixture and the whole was passed through a short column of silica gel (150 g) with AcOEt–hexane (1 : 2, v/v). The eluate was concentrated, and the residue was further subjected to column chromatography on silica gel (150 g) using $CHCl_3$–hexane (1 : 1, v/v) as an eluent. The first eluate gave tris(4-bromophenyl)amine. The second eluate with AcOEt–hexane (1 : 1, v/v) gave a trace of **12**. The third eluate with AcOEt–hexane (1 : 3, v/v) gave 70 mg (14.2%) of *erythro*-2-bromo-3-hydroxy-3-(3,4-methylenedioxyphenyl)propyl 3-(3,4,5-trimethoxyphenyl)acrylate (**15a**), as a colorless oil. IR (KBr) cm^{-1}: 3450, 2940, 1777, 1708. MS m/z: 494, 496 (M^+). The final eluate gave 220 mg (53.2%) of **13**. ^{1}H-NMR data for **15a** are listed in Table 8.

Method C in MeCN–H_2O (10 : 1, v/v): Oxidation of **11a** in MeCN–H_2O (10 : 1, v/v) was carried out by the same procedure (method B) as described for the oxidation of **11a** in MeCN and the product was purified by column chromatography on silica gel to give **12**, **13**, and **15a**. Yields are listed in Table 1.

Oxidation of 11b with BAHA in THF Oxidation of **11b** was carried out by the procedure of method A and the product was purified by column chromatography on silica gel using AcOEt–hexane (1 : 7, v/v) as an eluate to give **12**, **13**, **14**, and **1e**. Yields are listed in Table 1.

Oxidation of 11c with BAHA in THF Oxidation of **11c** was carried out by the procedure of method A and the product was purified by column chromatography on silica gel using AcOEt–hexane (1 : 7, v/v) as an eluent to give **12**, **13**, 1,3,3a*α*,4*α*,9*β*,9a*β*-hexahydro-4*β*-hydroxy-6,7,8-trimethoxy-9*α*-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3-one (**16**), 1,3,3a*α*,4*α*,9*β*,9a*α*-hexahydro-4*β*-hydroxy-6,7,8-trimethoxy-9*α*-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3-one (**17**), and 1,3,3a*β*,4*α*,-9*β*,9a*β*-hexahydro-4*β*-hydroxy-6,7-methylenedioxy-9*α*-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1-one (**1g**). **16**: colorless crystals (CH_2Cl_2–MeOH), mp 83—84 °C. IR (KBr) cm^{-1}: 3484, 1745, 1600. HR-MS Calcd for $C_{22}H_{22}O_8$: 414.1315. Found: 414.1297. **17**: colorless oil. IR (KBr) cm^{-1}: 3472, 1767, 1600. HR-MS Calcd for $C_{22}H_{22}O_8$: 414.1315. Found: 414.1300. **1g**: amorphous powder (ethanol), mp 189—190 °C. IR (KBr) cm^{-1}: 3482, 1764, 1590. HR-MS Calcd for $C_{22}H_{22}O_8$: 414.1315. Found: 414.1323. Yields are listed in Table 3. ^{1}H- and ^{13}C-NMR data for **16**, **17**, and **1g** are listed in Tables 4—7.

Oxidation of 11d with BAHA in THF Oxidation of **11d** was carried out by the procedure of method A and the product was purified by column chromatography on silica gel using AcOEt–hexane (1 : 7, v/v) as

an eluent to give **12**, **13**, **16**, **17** and **1g**. Yields are listed in Table 3.

Acetylation of 15a Ac_2O (3 ml) was added to **15a** (45.0 mg, 0.1 mmol) in pyridine (1 ml) and the whole was stirred at room temperature for 4 h, then poured into ice-water and extracted with ether. The organic layer was washed with 10% HCl, saturated $NaHCO_3$ and brine, then dried and concentrated. The residue was subjected to silica gel column chromatography using benzene–acetone (100 : 1, v/v) as an eluent to give 12.9 mg (26.2%) of *erythro*-3-acetoxy-2-bromo-3-(3,4-methylenedioxyphenyl)propyl 3-(3,4,5-trimethoxyphenyl)acrylate **15b**, as a colorless oil. IR (KBr) cm^{-1}: 2924, 1738, 1720, 1633, 1581. MS *m/z*: 536, 538 (M^+). ^{1}H-NMR data for **15b** are listed in Table 8.

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