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On the Absolute Structure of Optically Active Neolignans Containing a Dihydrobenzo[*b*]furan Skeleton†

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Abstract: Several optically pure neolignans containing a dihydrobenzo[*b*]furan skeleton were synthesized. Based on an X-ray crystallographic study and circular dichroism results, the absolute configurations of some naturally occurring neolignans, namely balanophonin (**1**), PGI_2 inducer (**2**), dehydrodiconiferyl alcohol-4-β-D-glucoside (**3**), dehydroconiferyl alcohol (**4**) and 3',4-di-*O*-methylcedrusin (**5**) have been unambiguously established.

Introduction

Neolignans have attracted a great deal of interests due to their widespread occurrence in Nature and their broad spectrum of biological and pharmacological activities.[2-11] Several naturally occurring optically active neolignans containing a dihydrobenzo[*b*]furan skeleton, namely balanophonin (**1**),[12] PGI_2 inducer (**2**),[13] dehydrodiconiferyl alcohol-4-β-D-glucoside (**3**),[14,15] dehydroconiferyl alcohol (**4**)[16] and 3',4-di-*O*-methylcedrusin (**5**)[17-19] have already been isolated and structurally elucidated. Their structures were determined by ^1H NMR and ^{13}C NMR spectroscopy as well as by mass spectrometry.[12-19] The determination of the absolute configurations for balanophonin (**1**) and 3',4-di-*O*-methylcedrusin (**5**) was based on the comparison of their CD and ORD curves with those of the known and structurally similar natural products.[12,18] Ito[12] and Pieters[18] assigned tentative (2*S*,3*R*) configurations to balanophonin (**1**) and 3',4-di-*O*-methylcedrusin (**5**) by comparison with (2*S*,3*S*)-melanoxin[20] and (2*S*,3*S*)-licarins A and B, respectively.[21] The absolute configuration of PGI_2 inducer (**2**), dehydrodiconiferyl alcohol-4-β-D-glucoside (**3**) and dehydroconiferyl alcohol (**4**), however, have never been ascertained (Scheme 1).

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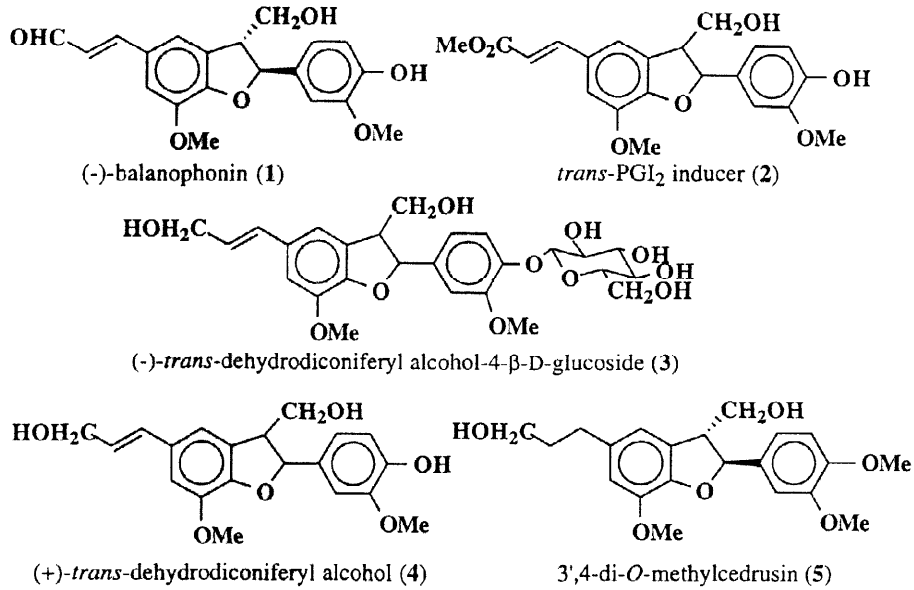


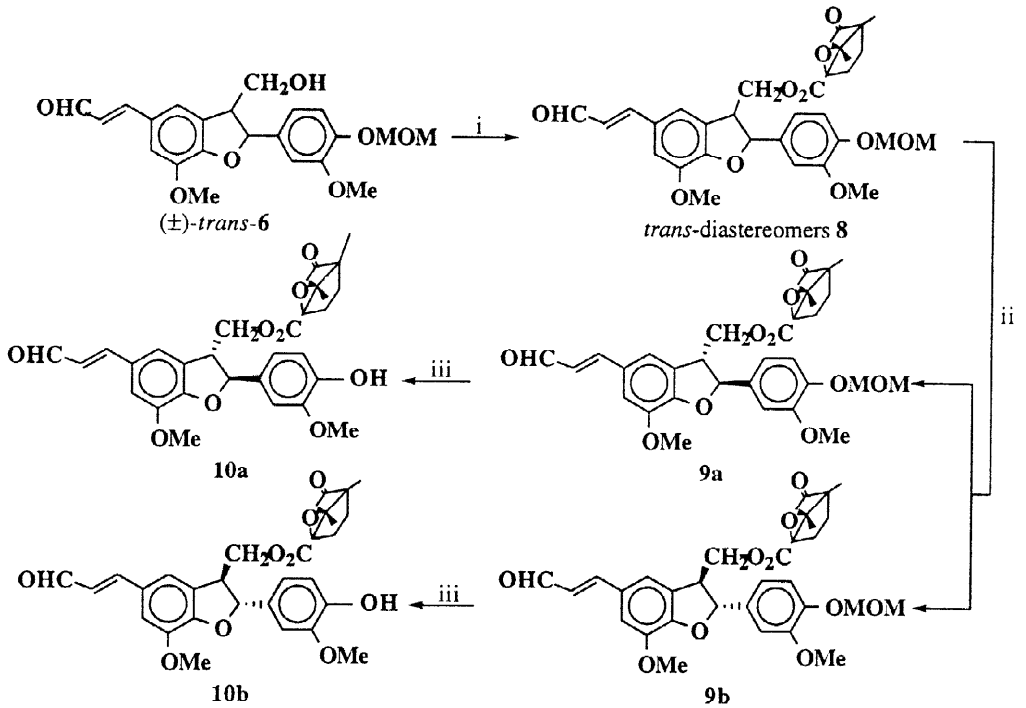
Scheme 1 Some Naturally Occurring Neolignans

Herein we would like to report the synthesis of the five aforementioned naturally occurring neolignans and their antipodes in optically pure forms. Through an X-ray crystallographic analysis of a dihydrobenzo[*b*]furan diastereomer and the CD study of some dihydrobenzo[*b*]furans, the C-2 and C-3 absolute configurations of these five molecules have been substantiated. Interestingly, the absolute configurations of balanophonin (**1**) and 3',4-di-*O*-methylcedrusin (**5**) are found to be antipodal to those reported previously.[12,18]

Results and Discussion

Racemic compound **6** was synthesized by employing the procedure deviseed by Wagner through an oxidative coupling promoted by silver oxide.[22] The optically pure (-)-(1*S*,4*R*)-camphanoyl chloride (**7**)[23] was then introduced to **6** to offer a pair of diastereomers **8**, which were separated by column chromatography on silica gel (Scheme 2). Since the less polar component **9a** and the more polar component **9b** of the diastereomeric mixture **8** were both in oil forms, their methoxymethyl protecting group were removed by reacting with dilute hydrochloric acid in methanol to furnish phenols **10a** and **10b**, respectively (Scheme 2).

Fortunately, dihydrobenzo[*b*]furan **10b** crystallized readily from hexanes/acetone to give single crystals while its diastereomer **10a** did not crystallize from the same hexanes/acetone solvent mixture, as well as from several other organic solvents. An X-ray diffraction analysis of a single crystal of **10b** successfully secured the configuration of (*E*)-3-[(2*R*,3*S*)-2,3-dihydro-3-camphanoyloxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxy-phenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (**10b**) (Figure 1).§ In an indirect manner, the absolute structure (*E*)-3-[(2*S*,3*R*)-2,3-dihydro-3-camphanoyloxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxy-phenyl)-1-benzo[*b*]furan-5-yl]-2-propenal was given to **10a**.



Scheme 2 Reagents: i, (-)-(1*S*,4*R*)-camphanoyl chloride (7), $^{i}Pr_2NEt$, CH_2Cl_2; ii, C_6H_6-THF, column chromatography on silica gel; iii, dil. HCl, MeOH

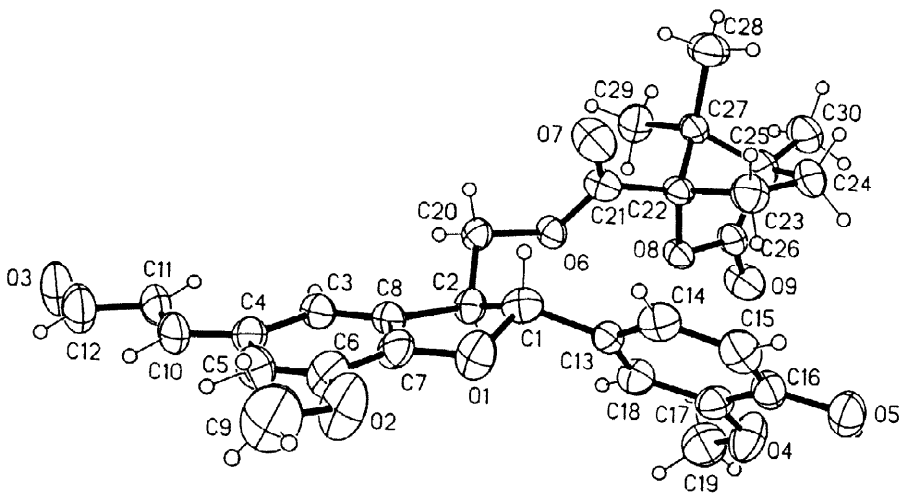
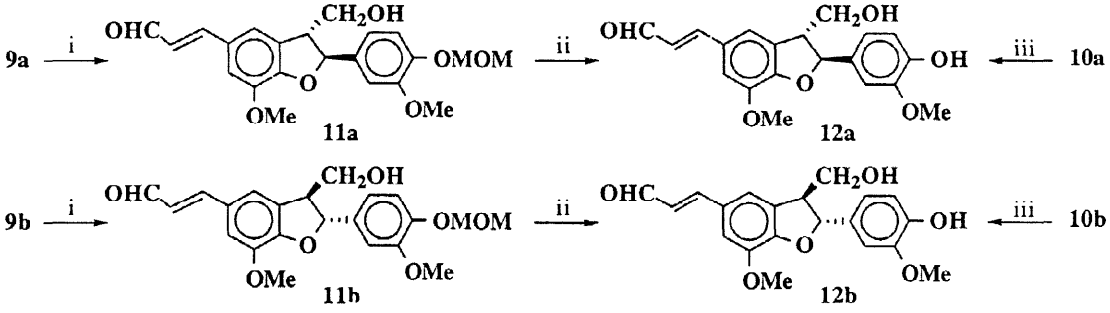


Figure 1. X-ray Crystal Structure of **10b**

Due to the fact that an inversion of configuration was not possible during the conversion from **9a** and **9b** to **10a** and **10b**, respectively, the absolute configurations of **9a** and **9b** could therefore be identical to those of **10a** and **10b**. From optically pure diastereomers **9a** and **9b**, the five natural products **1-5** and their antipodes were realized via classical and straightforward procedures as shown in Schemes 3-7.

Synthesis of balanophonin.

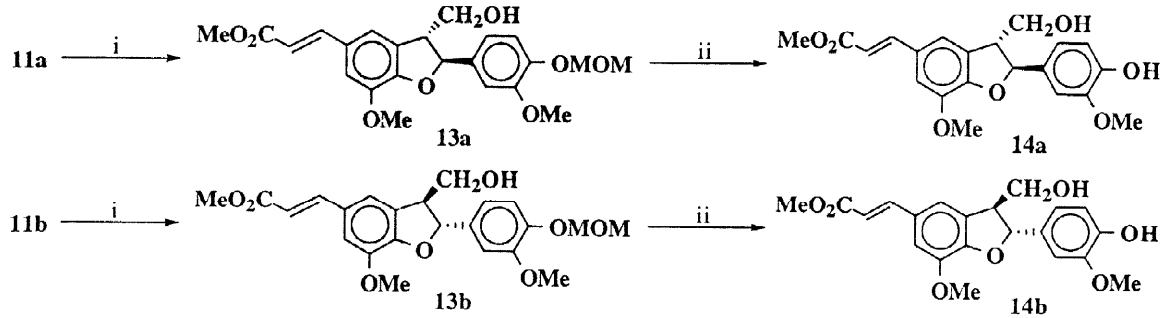
As shown in Scheme 3, (+)-(2*S*,3*R*)-**12a** and (-)-(2*R*,3*S*)-**12b** were prepared via **11a** and **11b** utilizing **9a** and **9b** as starting materials. The phenols **10a** and **10b** also furnished **12a** and **12b** respectively in a single step. The synthetic (+)-(2*S*,3*R*)-**12a** and (-)-(2*R*,3*S*)-**12b** exhibited many similar properties (^{1}H NMR, ^{13}C NMR, MS) as the natural balanophonin (**1**) reported by Ito.[12] The gross structures of these three products are identical except for their stereochemistry. However, the specific rotation and the CD spectrum of the synthetic (+)-(2*S*,3*R*)-**12a** were opposite to, while (-)-(2*R*,3*S*)-**12b** were similiar to those of the natural balanophonin (**1**).[12] Ito[12] compared the CD and ORD curves of balanophonin (**1**) with those of (2*S*,3*S*)-melanoxin[20] and postulated that the CD and ORD curves of (2*S*,3*S*)-melanoxin were similar to those of balanophonin (**1**), thereby he attributed the (2*S*,3*R*)-configuration to balanophonin (**1**). It is worth noting that the assignment of (2*S*,3*R*)-configuration to **1** by comparing with (2*S*,3*S*)-melanoxin was not convincing.[24,25] On the basis of the chemical correlation between the X-ray crystallographic analysis, specific rotation and CD data (Table 1), we are confident that the absolute configuration of natural balanophonin is identical to (-)-(2*R*,3*S*)-**12b**. Ito's assignment of (2*S*,3*R*) configuration to balanophonin (**1**) should therefore be amended.



Scheme 3 Reagents: i, K_2CO_3, MeOH; ii, dil. HCl, MeOH; iii, K_2CO_3, MeOH

Synthesis of PGI_2 inducer.

As illustrated in Scheme 4, compounds (+)-(2*S*,3*R*)-**14a** and (-)-(2*R*,3*S*)-**14b** were synthesized starting from **11a** and **11b**, respectively. A comparison of the synthetic (+)-(2*S*,3*R*)-**14a** and (-)-(2*R*,3*S*)-**14b** with natural PGI_2 inducer (**2**)[13] revealed that **14a** and **14b** exhibited the same optical (Table 1), physical and spectrometric data as those of the natural PGI_2 inducer. Fukuyama[13] reported the structure of PGI_2 inducer, which was elucidated as a congener of balanophonin (**1**)[12] except for the absolute configuration correlation. Due to the fact that insufficient information on the absolute configuration of natural PGI_2 inducer (**2**) was recorded, we could only propose that the PGI_2 inducer (**2**) should possess the same absolute configuration as either (+)-(2*S*,3*R*)-**14a** or (-)-(2*R*,3*S*)-**14b**.



Scheme 4 Reagents: i, KCN, MnO_2, MeOH; ii, dil. HCl, MeOH

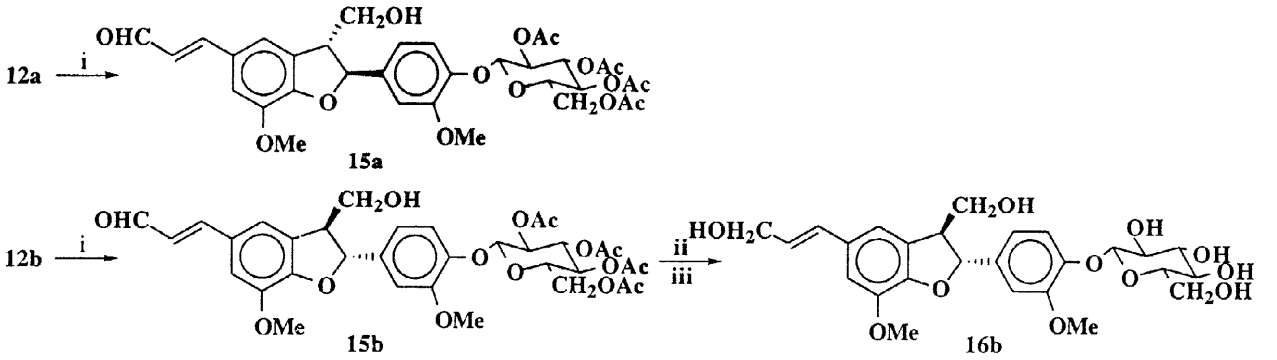
Table 1. CD Extrema of Some Dihydrobenzo[*b*]furans.[a]

nm	(+)-**12a** (EtOH)	(-)-**12b** (EtOH)	(+)-**14a** (CH_2Cl_2)	(-)-**14b** (CH_2Cl_2)	(-)-**16b** (MeOH)	(-)-**17b** (EtOH)	(-)-**20b** (CH_2Cl_2)
200						+49958	
205					+47837		
208					0		
211	0	0				0	
213	+5956	-6616			-25167	-6667	
216	0	0					
222						0	0
224					0		
228							+4554
234	-20615	+18976	-12394	+9695	+22485	+12672	0
244					0		
246	0	0	0	0		0	-2229
255	+5447	-5092	+5473	-4780			0
263							+581
271	0	0					
276			0	0			
279	-1732	+2240				-11372	0
284	0	0			-28985		
296							-1739
303							0
318					0		
327			+13296	-9884		0	
335	+10442	-9862					
363			0	0			
376			+1199	+806			

a. Concentration (x 10^{-4} mol/L): (+)-**12a**, 1.85; (-)-**12b**, 1.91; (+)-**14a**, 2.59; (-)-**14b**, 2.46; (-)-**16b**, 4.81; (-)-**17b**, 4.20; (-)-**20b**, 6.68.

Synthesis of dehydrodiconiferyl alcohol-4-β-D-glucoside.

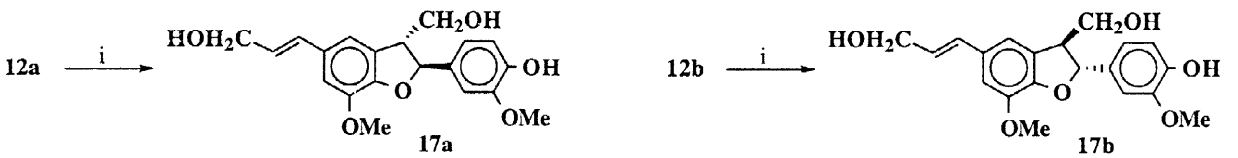
The synthetic (-)-(2*R*,3*S*)-**16b** was obtained from (-)-**12b** in a usual manner (Scheme 5). Since (-)-(2*R*,3*S*)-**16b** showed almost identical ^{1}H NMR, ^{13}C NMR, MS and optical rotation data (Table 1) as those reported for natural dehydrodiconiferyl alcohol-4-β-D-glucoside (**3**),[14,15] the absolute configuration of natural dehydrodiconiferyl alcohol-4-β-D-glucoside was determined as (-)-(2*R*,3*S*)-**16b**.



Scheme 5 Reagents: i, α-D-glucopyranoyl bromide tetraacetate, K_2CO_3, acetone; ii, $NaBH_4$, MeOH; iii, K_2CO_3, MeOH

Synthesis of dehydrodiconiferyl alcohol.

Again, compounds (+)-(2*S*,3*R*)-**17a** and (-)-(2*R*,3*S*)-**17b** were prepared from **12a** and **12b**, respectively (Scheme 6). It was discovered that the synthetic (+)-(2*S*,3*R*)-**17a** displayed the same optical (Table 1), physical and spectrometric characteristics as the natural dehydrodiconiferyl alcohol (**4**), while the synthetic (-)-(2*S*,3*R*)-**17b** showed the same physical and spectrometric data, but an opposite specific rotation as natural (+)-dehydrodiconiferyl alcohol (**4**). For this reason, the absolute configuration of (+)-(2*S*,3*R*)-**17a** was assigned to the natural dehydrodiconiferyl alcohol (**4**).

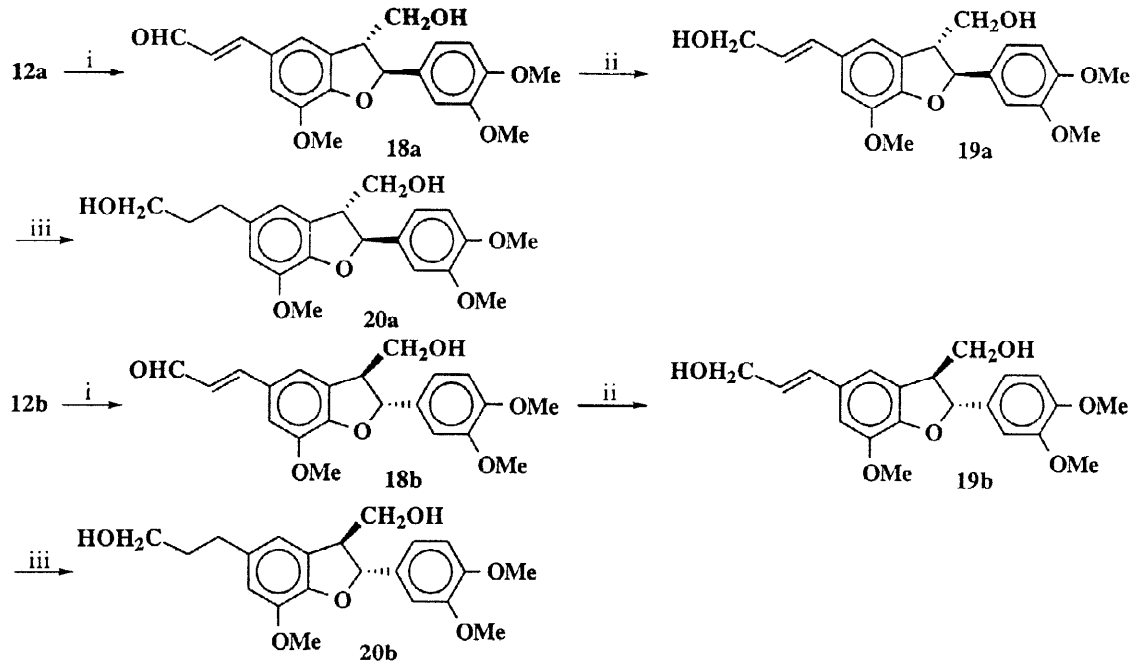


Scheme 6 Reagents: i, DIBAL, 0°C, Et_2O-THF

Synthesis of 3',4--di-O-methylcedrusin.

As shown in Scheme 7, compounds (+)-(2*S*,3*R*)-**20a** and (-)-(2*R*,3*S*)-**20b** were synthesized employing **12a** and **12b** respectively as precursors. In determining the absolute configuration of natural 3',4-di-*O*-methylcedrusin (**5**), there have been two literature assignments. Pieters[18] provided a tentative (2*S*,3*R*)-configuration to the natural 3',4-di-*O*-methylcedrusin (**5**) through a comparison of its CD spectrum with that of (2*S*,3*S*)-licarins A and B.[21] Due to the aforementioned reason for the absolute configuration assignment for natural balanophonin (**1**),[24,25] we considered that the (2*S*,3*R*)-configuration, as compared with (2*S*,3*S*)-licarins A and B, also demanded a rectification. On the other hand, Lemière[19] reported that a tentative (2*R*,3*S*)-configuration could be assigned to the natural 3',4-di-*O*-methylcedrusin (**5**). In his study, Lemière found that the CD spectrum of methyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-7-methoxy-3-methoxycarbonyl-2-(3'-methoxy-4'-methoxymethoxyphenyl)-1-benzo[*b*]furan-5-yl]propenoate compared well with that of (2*R*,3*R*)-ephedradine A,[26] which was determined by an anomalous dispersion X-ray crystallography of ephedradine A. Thus, the structure of the compound was accordingly assigned as (2*R*,3*R*).[19] It appeared to us that this comparison with (2*R*,3*R*)-ephedradine A was more reasonable. Thus, reduction of **18b** gave **19b**, whose subsequent catalytic hydrogenation afforded (2*R*,3*S*)-**20b**. It is noteworthy that the CD spectrum of **20b** was identical to that of natural 3',4-di-*O*-methylcedrusin (**5**). Lemière's assignment[19] of the absolute configuration to the natural 3',4-

di-*O*-methylcedrusin is in full agreement with our result. In this way, we confirmed that the absolute configuration of the natural 3',4-di-*O*-methylcedrusin is the same as (-)-(2*R*,3*S*)-**20b**.



Scheme 7 Reagents: i, MeI, K_2CO_3, Acetone; ii, DIBAL, 0°C, Et_2O-THF; iii, H_2, PtO_2, EtOH

Table 2 Comparison of Specific Rotation Between Synthetic and Natural Molecules

Compound	Synthetic	Natural
12a	$[\alpha]_D^{23}$ = +108° (*c* = 0.41, $CHCl_3$)	-
Balanophonin (**12b**)	$[\alpha]_D^{22}$ = -114° (*c* = 0.34, $CHCl_3$)	$[\alpha]_D$ = -115.1° (*c* = 1.3, $CHCl_3$)[12]
PGI_2 inducer (**14a**)	$[\alpha]_D^{20}$ = +82° (*c* = 0.25, $CHCl_3$)	No Record[13]
PGI_2 inducer (**14b**)	$[\alpha]_D^{20}$ = -81° (*c* = 0.10, $CHCl_3$)	No Record[13]
Dehydrodiconiferyl alcohol-4-β-D-glucoside (**16b**)	$[\alpha]_D^{20}$ = -76° (*c* = 0.25, MeOH)	$[\alpha]_D^{20}$ = -71.2° (*c* = 0.56, MeOH)[15]
Dehydrodiconiferyl alcohol (**17a**)	$[\alpha]_D^{23}$ = +11.5° (*c* = 0.13, $CHCl_3$)	$[\alpha]_{578}^{20}$ = +10.9° (*c* = 2, Me_2CO)[16]
17b	$[\alpha]_D^{23}$ = -11° (*c* = 0.8, $CHCl_3$)	-
20a	$[\alpha]_D^{20}$ = +9.5° (*c* = 0.20, $CHCl_3$)	No Record[18,19]
3',4-Di-*O*-methylcedrusin (**20b**)	$[\alpha]_D^{23}$ = -8.5° (*c* = 0.25, $CHCl_3$)	No Record[18,19]

Conclusion

As can be seen in the aforementioned experiments, the five aforementioned naturally occurring neolignans, namely balanophonin, dehydrodiconiferyl alcohol-4-β-D-glucoside, 3',4-di-*O*-methylcedrusin and dehydrodiconiferyl alcohol should possess the absolute structures as shown by formulae **12b**, **16b**, **20b** and **17a**, respectively. The absolute structure of the PGI_2 inducer, however, cannot be assigned due to insufficient literature data.

Experimental

Optical rotations were measured on a ATAGO POLAX-L polarimeter, a JASCO DIP-370 polarimeter or a 341 PERKIN-ELMER polarimeter. Circular dichroism spectra were recorded on a JASCO-715 spectropolarimeter. The column chromatography of diastereomers **9a** and **9b** was performed on E. Merck silica gel 230-400 mesh (Art. 9385).

(*E*)-3-[(2*S,3*R**)-2,3-Dihydro-3-camphanoyloxymethyl-7-methoxy-2-(3'-methoxy-4'-methoxymethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (8), (*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-3-camphanoyloxymethyl-7-methoxy-2-(3'-methoxy-4'-methoxymethoxyphenyl)-1-benzo[*b*]-furan-5-yl]-2-propenal (9a) and (*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-3-camphanoyloxy-methyl-7-methoxy-2-(3'-methoxy-4'-methoxymethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (9b).**

To a stirred solution of **6**[22] (1 g, 2.5 mmol) in dichloromethane (40 mL), (-)-(1*S*,4*R*)- camphanoyl chloride (**7**)[23] (542 mg, 2.5 mmol) and *N*,*N*-diisopropylethylamine (0.7 mL, 3.75 mmol) were added at room temperature. After stirred for 3 h, water (5 mL) was added. The product was extracted with dichloromethane (3 x 100 mL), dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was first purified by column chromatography on silica gel (30 g, hexanes/ethyl acetate 2:1) to give a mixture of diastereomers **8** as a yellowish oil (1.2 g, 83%). The diastereomeric mixture **8** (10 mg) was separated by carefully flash chromatography on silica gel (200 g, benzene/tetrahydrofuran 48:1) to afford the less polar **9a** (5 mg) and the more polar **9b** (5 mg), both as yellowish oil.

Compound **8**: ^{1}H NMR δ 0.83 (m, 3H), 0.98 (m, 3H), 1.09 (s, 3H), 1.67-1.73 (m, 1H), 1.87-1.98 (m, 2H), 2.29-2.36 (m, 1H), 3.49 (s, 3H), 3.88 (s, 3H), 3.92-3.94 (m, 1H), 3.94 (s, 3H), 4.49-4.55 (m, 1H), 4.57-4.63 (m, 1H), 5.22 (s, 2H), 5.62 (d, *J* = 6.8 Hz, 1H), 6.56-6.67 (m, 1H), 6.90-7.18 (m, 5H), 7.43 (d, *J* = 15.8 Hz, 1H), 9.66 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 9.48, 14.02, 16.39, 28.72, 30.56, 30.62, 50.01, 54.00, 54.61, 56.00, 65.67, 88.64, 90.76, 95.43, 109.76, 112.55, 116.71, 118.47, 126.64, 127.66, 128.44, 133.75, 144.81, 146.79, 150.21, 151.13, 152.29, 167.20, 177.59, 193.13; MS *m/e* 580 (M^+). Anal. Calcd. for $C_{32}H_{36}O_{10}$: C, 66.19; H, 6.24. Found: C, 65.83; H, 6.27.

Compound **9a**: $[\alpha]_D^{23.5}$ + 85° (*c* 1.06 , $CHCl_3$); ^{1}H NMR δ 0.82 (s, 3H), 0.93 (s, 3H), 1.09 (s, 3H), 1.66-1.73 (m, 1H), 1.86-1.96 (m, 2H), 2.27-2.35 (m, 1H), 3.49 (s, 3H), 3.88 (s, 3H), 3.86-3.91 (m, 1H), 3.94 (s, 3H), 4.47-4.53 (m, 1H), 4.59-4.66 (m, 1H), 5.22 (s, 2H), 5.62 (d, *J* = 6.8 Hz, 1H), 6.58-6.67 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.90-7.17 (m, 5H), 7.43 (d, *J* = 15.8 Hz, 1H), 9.67 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 9.60, 16.53, 28.80, 30.66, 50.17, 54.15, 54.74, 56.10, 56.21, 65.73, 88.74, 90.87, 95.49, 109.82, 112.64, 116.68, 118.54, 126.75, 127.70, 128.49, 133.77, 144.90, 146.86, 150.24, 151.24, 152.44, 167.34, 177.72, 193.31; MS *m/e* 580 (M^+). Anal. Calcd. for $C_{32}H_{36}O_{10}$: C, 66.19; H, 6.24. Found: C, 65.95; H, 6.17.

Compound **9b**: $[\alpha]_D^{20}$ -46° (*c* 0.98, $CHCl_3$); ^{1}H NMR δ 0.82 (s, 3H), 0.93 (s, 3H), 1.1 (s, 3H), 1.66-1.73 (m, 1H), 1.86-2.07 (m, 2H), 2.29-2.39 (m, 1H), 3.51 (s, 3H), 3.88 (s, 3H), 3.92-3.94 (m, 1H), 3.94 (s, 3H), 4.49-4.55 (m, 1H), 4.59-4.66 (m, 1H), 5.22 (s, 2H), 5.63 (d, *J* = 6.8 Hz, 1H), 6.61 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 7.09-7.18 (m, 5H), 7.43 (d, *J* = 15.8 Hz, 1H), 9.65 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 9.43, 16.33, 28.69, 30.57, 49.94, 53.89, 54.54, 55.96, 56.06, 65.7, 88.55, 90.71, 95.36, 109.66, 112.44,

116.61, 118.42, 126.57, 127.63, 128.4, 133.68, 144.75, 146.72, 150.14, 151.16, 152.3, 167.11, 177.49, 193.13; MS *m/e* 580 (M^+). Anal. Calcd. for $C_{32}H_{36}O_{10}$: C, 66.19; H, 6.24. Found: C, 65.97; H, 6.28.

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-3-camphanoyloxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (10a)

To the less polar **9a** (20 mg, 34.5 mmoL) in methanol (10 mL) was added dilute hydrochloric acid. The mixture was stirred for 2 h. Then the mixture was extracted with ethyl acetate (3 x 20 mL). The organic solution was dried over anhyd. magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 3:2) to give **10a** (15.8 mg, 85.5%) as a yellowish oil; $[\alpha]_D^{20}$ + 64.5° (*c* 1.1, $CHCl_3$); ^1H NMR δ 0.84 (s, 3H), 0.95 (s, 3H), 1.09 (s, 3H), 1.63-1.70 (m, 1H), 1.84-1.95 (m, 2H), 2.27-2.37 (m, 1H), 3.00 (m, 4H), 3.94 (s, 3H), 4.47-4.53 (m, 1H), 4.58-4.66 (m, 1H), 5.59 (d, *J* = 7.1 Hz, 1H), 5.72 (s, 1H), 6.62 (dd, *J* = 15.8 Hz, 7.6 Hz, 1H), 6.90 (s, 3H), 7.06 (s, 1H), 7.16 (s, 1H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.67 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 9.63, 16.50, 28.75, 30.61, 50.11, 54.20, 54.76, 56.07, 65.66, 89.07, 90.88, 108.67, 112.23, 114.45, 118.50, 119.28, 126.65, 127.64, 128.35, 131.26, 144.84, 146.09, 146.79, 151.18, 152.65, 167.36, 177.84, 193.52; MS *m/e* 536 (M^+). Accurate mass calcd for $C_{30}H_{32}O_9$ 536.2037, Found 536.2035.

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-3-camphanoyloxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (10b)

The more polar **9b** (20 mg, 34.5 mmol) was converted to **10b** using the same procedure as described for the preparation of **10a**. Chromatography on silica gel (2 g, hexanes/ethyl acetate 3:2) provided **10b** (16 mg, 86.5%) as a yellowish oil. Pure **10b** crystallized from hexanes/acetone to give single crystals, mp 157-158°C; $[\alpha]_D^{20}$ -77° (*c* 1.58, $CHCl_3$); ^1H NMR δ 0.82 (s, 3H), 0.94 (s, 3H), 1.09 (s, 3H), 1.65-1.74 (m, 1H), 1.85-2.01 (m, 2H), 2.28-2.35 (m, 1H), 3.89 (m, 4H), 3.94 (s, 3H), 4.47-4.62 (m, 2H), 5.59 (d, *J* = 6.9 Hz, 1H), 5.75 (s, 1H), 6.60 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.89 (s, 3H), 7.07 (s, 1H), 7.16 (s, 1H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.66 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 9.62, 16.49, 28.81, 30.72, 50.03, 54.14, 54.72, 56.07, 65.86, 89.05, 90.86, 108.56, 112.06, 114.46, 118.58, 119.31, 126.65, 127.69, 128.39, 131.26, 144.85, 146.13, 146.83, 151.14, 152.62, 167.33, 177.77, 193.52; MS *m/e* 536 (M^+). Accurate mass calcd for $C_{30}H_{32}O_9$: 536.2037, Found 536.2042.

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(3'-methoxy-4'-methoxymethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (11a)

To a stirred solution of **9a** (58 mg, 0.1 mmol) in methanol (15 mL) and tetrahydrofuran (2 mL), potassium carbonate (21 mg, 0.15 mmol) was added. After 30 min, the mixture was diluted with water, and extracted with diethyl ether (3 x 80 mL). The organic layer was dried over anhyd. magnesium sulfate. The mixture was filtered and evaporated. The desired product **11a** was obtained by column chromatography on silica gel (3 g) with hexanes/ethyl acetate (3:2) as yellowish oil (35 mg, 88%); $[\alpha]_D^{23}$ + 87° (*c* 0.52, $CHCl_3$); ^1H NMR δ 3.41 (s, 3H), 3.48-3.63 (m, 1H), 3.84 (s, 3H), 3.91 (s, 3H), 3.91-4.0 (m, 2H), 5.20 (s, 2H), 5.67 (d, *J* = 6.8 Hz, 1H), 6.58 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.90-7.13 (m, 5H), 7.40 (d, *J* = 15.8 Hz, 1H), 9.59 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 53.06, 56.01, 56.10, 56.17, 63.97, 88.59, 95.59, 110.04, 112.69, 116.80, 118.25, 118.57, 126.40, 128.17, 129.28, 134.87, 144.80, 146.67, 150.19, 151.57, 152.92, 193.37; MS *m/e* 400 (M^+). Accurate mass calcd for $C_{22}H_{24}O_7$: 400.1522, Found: 400.1498.

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-2-(4'-hydroxy-3'-methoxyphenyl)-3-hydroxymethyl-7-methoxy-1-benzo[*b*]furan-5-yl]-2-propenal (12a)

Method 1 : To a solution of **11a** (30 mg, 0.08 mmol) in methanol (15 mL), 10% hydrochloric acid (1.5 mL) was added. The mixture was stirred for 3 h, and then diluted with water (10 mL). The mixture was extracted with diethyl ether (3 x 50 mL). The organic layer was dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 1:1) to give **12a** as a yellowish oil (24 mg, 90%).

Method 2 : To compound **10a** (28 mg, 0.05 mmol) was added potassium carbonate (15 mg, 0.11 mmol) in methanol (10 mL). The mixture was stirred for 30 min. and then water (10 mL) was added. The mixture was extracted with diethyl ether (3 x 50 mL). The organic layer was dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 1:1) to afford **12a** as a yellowish oil (16.4 mg, 88%).

Compound **12a**: $[\alpha]_D^{23}$ + 108° (*c* 0.41, $CHCl_3$); ^1H NMR δ 3.64-3.72 (m, 1H), 3.87 (s, 3H), 3.97 (s, 3H), 3.93-4.03 (m, 2H), 5.65 (d, *J* = 7.1 Hz, 1H), 5.77 (br s, 1H), 6.60 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.89 (s, 3H), 7.04 (s, 1H), 7.14 (s, 1H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.63 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 53.07, 56.06, 56.21, 64.03, 88.95, 108.87, 112.64, 114.55, 118.19, 119.41, 126.53, 128.22, 129.29, 132.34, 144.89, 146.05, 146.84, 151.63, 152.87, 193.39; MS *m/e* 356 (M^+). Accurate mass calcd for $C_{20}H_{20}O_6$: 356.1260, Found: 356.1257.

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(3'-methoxy-4'-methoxy-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (11b)

Compound **9b** (50 mg, 0.09 mmol) was converted to **11b** using the same procedure as described for the preparation of **11a**. The desired **11b** was obtained by column chromatography on silica gel (3 g, hexanes/ethyl acetate 3:2) as a yellowish oil (31 mg, 90%); $[\alpha]_D^{23}$ - 88° (*c* 0.7, $CHCl_3$); ^1H NMR δ 3.49 (s, 3H), 3.64-3.71 (m, 1H), 3.86 (s, 3H), 3.93 (s, 3H), 3.95-4.0 (m, 2H), 5.21 (s, 2H), 5.68 (d, *J* = 6.8 Hz, 1H), 6.60 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.90-7.13 (m, 5H), 7.41 (d, *J* = 15.8 Hz, 1H), 9.63 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 53.09, 56.04, 56.18, 64.03, 88.64, 95.59, 109.99, 112.63, 116.73, 118.19, 118.62, 126.52, 128.24, 129.19, 134.81, 144.87, 146.73, 150.18, 151.60, 152.85, 193.38; MS *m/e* 400 (M^+). Accurate mass calcd for $C_{22}H_{24}O_7$: 400.1522, Found: 400.1523.

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-2-(4'-hydroxy-3'-methoxyphenyl)-3-hydroxymethyl-7-methoxy-1-benzo[*b*]furan-5-yl]-2-propenal (12b)[12]

Method 1 : Compound **11b** (35 mg, 0.1 mmol) was converted to **12b** using the same procedure as described for the preparation of **12a** (Method 1). The resulting residue was purified by column chromatography on silica gel (3 g, hexanes/ethyl acetate 1:1) to give **12b** as a yellowish oil (28 mg, 90%);

Method 2 : Compound **10b** (25 mg, 0.05 mmol) was converted to **12b** using the same procedure as described for the preparation of **12a** (Method 2). The resulting residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 1:1) to give **12b** as a yellowish oil (14.6 mg, 88%).

Compound **12b**: $[\alpha]_D^{23}$ - 114° (*c* 0.34, $CHCl_3$) [lit.[12] $[\alpha]_D$ -115.1° (*c* 1.3, $CHCl_3$)]; ^1H NMR δ 3.64-3.72 (m, 1H), 3.87 (s, 3H), 3.97 (s, 3H), 3.93-4.03 (m, 2H), 5.65 (d, *J* = 7.1 Hz, 1H), 5.74 (br s, 1H), 6.60 (dd, *J* = 15.8 Hz, 7.8 Hz, 1H), 6.89 (s, 3H), 7.04 (s, 1H), 7.17 (s, 1H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.63 (d, *J* =

7.8 Hz, 1H); ^{13}C NMR δ 53.11, 56.08, 56.27, 64.10, 88.98, 108.89, 112.76, 114.57, 118.18, 119.45, 126.63, 128.28, 129.31, 132.37, 144.94, 146.11, 146.86, 151.66, 152.70, 193.25; MS *m/e* 356 (M^+). Accurate mass calcd. for $C_{20}H_{20}O_6$: 356.1260, Found: 356.1262.

Methyl (*E*)-3-[(2*S*,3*R*)-2,3-dihydro-3-hydroxymethyl-7-methoxy-2-(3'-methoxy-4'-methoxy-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-propenoate (13a)

To a solution of **11a** (22.8 mg, 0.05 mmol) in methanol (15 mL), potassium cyanide (5 equiv, 17.2 mg, 0.26 mmol) and manganese dioxide[27,28] (20 equiv, 92.2 mg, 1.1 mmol) were added. The mixture was stirred at room temperature for 5 h. The mixture was filtered and evaporated. The residue was purified by column chromatography on silica gel (3 g, hexanes/ethyl acetate 2:1) to give **13a** as a yellowish oil (18 mg, 71%); $[\alpha]_D^{20}$ + 28.9° (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 3.49 (s, 3H), 3.64-3.72 (m, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 3.89-4.02 (m, 2H), 5.21 (s, 2H), 5.66 (d, *J* = 6.8 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 6.90-7.13 (m, 5H), 7.64 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR δ 51.61, 53.14, 55.95, 56.15, 63.88, 88.41, 95.36, 109.61, 111.79, 115.16, 116.20, 117.25, 118.61, 128.49, 134.74, 144.59, 144.87, 146.48, 149.86, 150.56, 167.70; MS *m/e* 430 (M^+). Accurate mass calcd. for $C_{23}H_{26}O_8$: 430.1620, Found: 430.1636.

Methyl (*E*)-3-[(2*S*,3*R*)-2,3-dihydro-3-hydroxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxy-phenyl)-1-benzo[*b*]furan-5-yl]-propenoate (14a)[13]

To a solution of **13a** (16 mg, 0.04 mmol) in methanol (10 mL), 10% hydrochloric acid (1.5 mL) was added. The mixture was stirred for 2 h. Then the mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 50 mL). The ethereal layer was dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 2:1) to give **14a** as white solids (12.6 mg, 88%); mp 188-190°C [lit.[13] mp 190-192°C]; $[\alpha]_D^{20}$ + 82° (*c* 0.25, $CHCl_3$); ^{1}H NMR δ 3.46-3.67 (m, 1H), 3.80 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 3.92-4.14 (m, 2H), 5.63 (d, *J* = 7 Hz, 1H), 5.64 (s, 1H), 6.31 (d, *J* = 16 Hz, 1H), 6.90 (s, 3H), 7.01 (s, 1H), 7.07 (s, 1H), 7.65 (d, *J* = 16 Hz, 1H); ^{13}C NMR δ 51.63, 53.13, 55.96, 63.85, 88.70, 108.68, 111.74, 114.35, 115.12, 117.26, 119.40, 128.61, 128.61, 132.39, 144.58, 144.92, 145.79, 146.66, 150.55, 167.74; MS *m/e* 386 (M^+). Accurate mass calcd for $C_{21}H_{22}O_7$: 386.1357, Found: 386.1357.

Methyl (*E*)-3-[(2*R*,3*S*)-2,3-dihydro-3-hydroxymethyl-7-methoxy-2-(3'-methoxy-4'-methoxy-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-propenoate (13b)

Compound **11b** (22 mg, 0.06 mmol) was converted to **13b** using the same procedure as described for the preparation of **13a**. The resulting residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 2:1) to give **13b** as a yellowish oil (17 mg, 72%); $[\alpha]_D^{20}$ -29.3° (*c* 1.69, $CHCl_3$); ^{1}H NMR δ 3.50 (s, 3H), 3.65-3.68 (m, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 3.92-3.98 (m, 2H), 5.21 (s, 2H), 5.66 (d, *J* = 7 Hz, 1H), 6.31 (d, *J* = 16 Hz, 1H), 6.90-7.13 (m, 5H), 7.64 (d, *J* = 16 Hz, 1H); ^{13}C NMR δ 51.62, 53.14, 55.95, 56.15, 88.41, 95.38, 109.61, 111.79, 115.17, 116.20, 117.24, 118.61, 128.48, 134.72, 144.60, 144.86, 146.48, 149.86, 150.55, 167.69; MS *m/e* 430 (M^+). Accurate mass calcd. for $C_{23}H_{26}O_8$: 430.1620, Found: 430.1620.

Methyl (*E*)-3-[(2*R*,3*S*)-2,3-dihydro-3-hydroxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxy-phenyl)-1-benzo[*b*]furan-5-yl]-propenoate (14b)[13]

Compound **13b** (15 mg, 0.03 mmol) was converted to **14b** using the same procedure as described for the preparation of **14a**. The resulting residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 2:1) to give **14b** as white solids (11.6 mg, 86%); mp 188-190°C [lit.[13] mp 190-192°C]; $[\alpha]_D^{20}$ -81° (*c* 0.10, $CHCl_3$); ^1H NMR δ 3.64-3.68 (m, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 3.91-3.97 (m, 2H), 5.63 (d, *J* = 7.2, 1H), 5.70 (s, 1H), 6.31 (d, *J* = 16 Hz, 1H), 6.89 (s, 3H), 7.0 (s, 1H), 7.07 (s, 1H), 7.64 (d, *J* = 16 Hz, 1H); ^{13}C NMR (acetone -d_6) δ 51.33, 54.18, 56.09, 56.21, 64.14, 89.01, 110.34, 113.06, 115.40, 115.53, 118.64, 119.51, 128.76, 130.27, 133.69, 145.33, 145.68, 147.28, 148.24, 151.49, 167.69; MS *m/e* 386 (M^+). Accurate mass calcd for $C_{21}H_{22}O_7$: 386.1357, Found: 386.1358.

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-2-(3'-methoxy-4'-tetraacetyl-β-D-glucose-phenyl)-3-hydroxymethyl-7-methoxy-1-benzo[*b*]furan-5-yl]-2-propenal (15a)

To a solution of compound **12a** (20 mg, 0.06 mmol) in acetone (10 mL) was added α-D-glucopyranosyl bromide tetraacetate (24 mg, 0.06 mmol) in the presence of potassium carbonate (10 equiv, 78 mg, 0.6 mmol). The mixture was stirred at room temperature for 20 h. Water (20 mL) was then added. The mixture was extracted with diethyl ether (3 x 50 mL). The ethereal layer was dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 1:1) to give **15a** as a yellowish oil (21.6 mg, 56 %); $[\alpha]_D^{20}$ + 30.5° (*c* 0.90, $CHCl_3$); ^1H NMR δ 1.66 (br s, 1H), 2.04 (s, 6H), 2.08 (s, 6H), 3.46-3.52 (m, 1H), 3.63-3.77 (m, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 3.94-3.99 (m, 2H), 4.12-4.17 (m, 1H), 4.23-4.31 (dd, *J* = 4.8 Hz, 12.3 Hz, 1H), 4.93 (d, *J* = 7.5 Hz, 1H), 5.12-5.29 (m, 3H), 5.69 (d, *J* = 6.6 Hz, 1H), 6.61 (dd, *J* = 15.8 Hz, 7.8 Hz, 1H), 6.89-7.12 9m, 5H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.65 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 20.65, 53.13, 56.15, 61.86, 64.04, 68.33, 71.15, 71.97, 72.53, 88.42, 100.76, 110.62, 112.22, 118.27, 118.27, 120.24, 126.57, 128.32, 128.77, 137.10, 144.83, 146.09, 150.83, 152.89, 169.40, 170.30, 170.63, 193.53. Accurate mass calc for $C_{34}H_{38}O_{15}$: 686.2199, Found 709.2097 (ESI, $C_{34}H_{38}O_{15}Na$).

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-2-(3'-methoxy-4'-tetraacetyl-β-D-glucose-phenyl)-3-hydroxy-methyl-7-methoxy-1-benzo[*b*]furan-5-yl]-2-propenal (15b)

Compound **12b** (22 mg, 0.06 mmol) was converted to **15b** using the same procedure as described for the preparation of **15a**. The resulting residue was purified by column chromatography on silica gel (3 g, hexanes/ethyl acetate 1:1) to give **15b** as a yellowish oil (23.3 mg, 55 %); $[\alpha]_D^{20}$ -71° (*c* 0.90, $CHCl_3$); ^1H NMR δ 2.04 (s, 6H), 2.07 (s, 6H), 3.65-3.67 (m, 1H), 3.67-3.71(m, 1H), 3.79 (s, 3H), 3.94 (s, 3H), 3.87-3.94 (m, 2H), 4.12-4.16 (m, 1H), 4.24-4.28 (m, 1H), 4.93 (d, *J* = 7.7 Hz, 1H), 5.12-5.19 (m, 1H), 5.26-5.29 (m, 2H), 5.69 (d, *J* = 6.5 Hz, 1H), 6.61 (dd, *J* = 15.8 Hz, 7.8 Hz, 1H), 6.90-7.12 (m, 5H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.64 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 20.64, 53.13, 56.10, 61.87, 63.99, 68.33, 71.14, 71.96, 72.52, 88.42, 100.74, 110.33, 112.22, 118.11, 118.50, 120.20, 126.55, 128.31, 137.11, 144.82, 146.09, 150.94, 151.38, 152.93, 169.40, 170.29, 170.62, 193.55. Accurate mass calc for $C_{34}H_{38}O_{15}$: 686.2199, Found: 709.2097 (ESI, $C_{34}H_{38}O_{15}Na$).

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-2-(3'-methoxy-4'-β-D-glucosylphenyl)-3-hydroxymethyl-7-methoxy-1-benzo[*b*]furan-5-yl]-2-propen-1-ol (16b)[15]

Compound **15b** (20 mg, 0.03 mmol) in methanol (10 mL) was reduced with sodium borohydride (1 equiv, 1.1 mg, 0.03 mmol) at room temperature for 30 min. Then potassium carbonate (5 equiv, 21 mg, 0.14 mmol) was added. The mixture continued to stir for 30 min. Water (10 mL) was added and the resulting mixture was extracted with diethyl ether (3 x 50 mL). The ethereal layer was dried over anhyd. magnesium sulfate. The solvent was filtered and evaporated. The pure product of **16b** was obtained by reversed phase C_{18} thin layer plate as white powders (12 mg, 79%); $[\alpha]_D^{20}$ -76° (*c* 0.25, MeOH) [lit.[15] $[\alpha]_D^{20}$ -71.2° (*c* 0.56, MeOH)]; ^{1}H NMR (270 MHz) (DMSO-d_6) δ 3.25-3.37 (m, 2H), 3.55-3.64 (m, 2H), 3.64-3.69 (m, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 4.06 (d, *J* = 4.9 Hz, 2H), 4.87 (d, *J* = 7.3 Hz, 1H), 5.51 (d, *J* = 6.8 Hz, 1H), 6.22 (dt, *J* = 16 Hz, 5.3 Hz, 1H), 6.45 (d, *J* = 16 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.92-6.94 (m, 3H), 7.05 (d, *J* = 8.4 Hz, 1H) [lit[15] ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.44 (m, 2H), 3.65 (m, 2H), 3.75 (m, 1H), 3.75 (s, 3H), 3.82 (s, 3H), 4.06 (d, *J* = 4.9 Hz, 2H), 4.88 (d, *J* = 7.3 Hz, 1H), 5.51 (d, *J* = 6.5 Hz, 1H), 6.22 (dt, *J* = 16 Hz, 5.3 Hz, 1H), 6.47 (d, *J* = 16 Hz, 1H), 6.84 (dd, *J* = 8.5 Hz, 2 Hz, 1H), 6.93 (d, *J* = 2 Hz, 2H), 6.96 (d, *J* = 2 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H)]; ^{13}C NMR (270 MHz, DMSO-d_6) δ 53.25, 55.69, 55.69, 60.59, 61.66, 62.95, 63.06, 69.63, 73.19, 76.86, 77.06, 86.89, 100.00, 110.29, 114.93, 115.22, 118.02, 128.11, 128.91, 129.26, 130.66, 135.20, 143.72, 146.22, 147.03, 148.93; MS *m/e* 520 (M^+).

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propen-1-ol (17a)[16]

To compound **12a** (10 mg, 0.03 mmol) in a mixture of anhyd. diethyl ether (5 mL) and tetrahydrofuran (5 mL) was added a solution of diisobutylaluminum hydride (1.5 mL, 1 M, 1.5 mmol) in hexane at 0°C with stirring under nitrogen atmosphere. After 1 h, a few drops of ethyl acetate was added to the stirred solution to decompose the excess diisobutylaluminum hydride. After dilution with water (5 mL) and neutralized with dilute hydrochloric acid, the product was extracted with diethyl ether (3 x 30 mL), then dried over anhyd. magnesium sulfate, filtered and evaporated. Column chromatography of the resulting residue on silica gel (1 g, hexanes/ethyl acetate 2:3) furnished **17a** as colorless solids (8 mg, 80%); mp 141-142°C; $[\alpha]_D^{23}$ +11.6° (*c* 0.13, $CHCl_3$) [lit.[16] mp 141-142°C; $[\alpha]_{578}^{20}$ +10.9°, $[\alpha]_{546}^{20}$ +13.3° (*c* 2, acetone)]; ^{1}H NMR δ 3.58-3.66 (m, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 3.90-4.00 (m, 2H), 4.29-4.31 (m, 2H), 5.58 (d, *J* = 7.2 Hz, 1H), 5.68 (br s, 1H), 6.18-6.29 (dt, *J* = 15.8 Hz, 5.8 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.82-6.91 (m, 5H); ^{13}C NMR δ 53.49, 55.97, 55.97, 63.79, 88.21, 108.73, 110.48, 114.31, 114.76, 119.38, 126.40, 128.08, 130.81, 131.29, 132.84, 144.40, 145.69, 146.66, 148.31; MS *m/e* 358 (M^+).

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(4'-hydroxy-3'-methoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propen-1-ol (17b)[16]

Compound **12b** (10 mg, 0.03 mmol) was converted to **17b** using the same procedure as described for the preparation of **17a**. Column chromatography of the resulting residue on silica gel (1 g, hexanes/ethyl acetate 2:3) provided **17b** as colorless solids (8 mg, 80%); mp 141-142°C [lit.[16] mp 141-142°C]; $[\alpha]_D^{23}$ -11° (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 3.58-3.66 (m, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 3.90-4.00 (m, 2H), 4.29-4.31 (m, 2H), 5.58 (d, *J* = 7.2 Hz, 1H), 5.68 (s, 1H), 6.18-6.29 (dt, *J* = 15.8 Hz, 5.8 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H),

6.82-6.91 (m, 5H); ^{13}C NMR δ 53.49, 55.97, 55.97, 63.79, 88.21, 108.73, 110.48, 114.31, 114.76, 119.38, 126.40, 128.08, 130.81, 131.29, 132.84, 144.40, 145.69, 146.66, 148.31; MS *m/e* 358 (M^+).

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (18a)

To a stirred solution of **12a** (52 mg, 0.15 mmol) and potassium carbonate (25 mg, 0.15 mmol) in dry acetone (10 mL) was added methyl iodide (0.01 mL, 0.16 mmol). After 1 h, water (2 mL) was added. The product was extracted with diethyl ether (3 x 50 mL). The organic layer was dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was separated by flash column chromatography on silica gel (3 g, hexanes/ ethyl acetate 1:1) to afford **18a** as a yellowish oil (48 mg, 89%); $[\alpha]_D^{23}$ + 49° (*c* 1.85, $CHCl_3$); ^{1}H NMR δ 3.63-3.70 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.89-4.00 (m, 2H), 3.95 (s, 3H), 5.66 (d, *J* = 7 Hz, 1H), 6.57 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.81-6.84 (m, 1H), 6.88-6.92 (m, 2H), 6.70 (s, 1H), 7.13 (s, 1H), 7.39 (d, *J* = 15.8 Hz, 1H), 9.57 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 52.98, 55.92, 56.12, 63.86, 88.7, 109.5, 111.41, 112.62, 118.24, 118.60, 126.25, 128.05, 129.37, 133.03, 144.72, 149.31, 151.55, 153.04, 193.42; MS *m/e* 370 (M^+). Accurate mass calcd for $C_{21}H_{22}O_6$: 370.1417, Found: 370.1417.

(*E*)-3-[(2*S*,3*R*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propen-1-ol (19a)

To compound **18a** (25 mg, 0.07 mmol) in a mixture of anhyd. diethyl ether (5 mL) and tetrahydrofuran (5 mL) was added lithium aluminum hydride (5 mg, 0.13 mmol) at 0°C with stirring under nitrogen atmosphere. After 1 h, a few drops of ethyl acetate was added to the stirred solution to decompose the excess lithium aluminium hydride. After dilution with water (5 mL) and neutralized with dilute hydrochloric acid, the product was extracted with diethyl ether (3 x 30 mL), then dried over anhyd. magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 2:3) to give **19a** as a colorless oil (21 mg, 84%); $[\alpha]_D^{23}$ +13.6° (*c* 0.66, $CHCl_3$); ^{1}H NMR δ 3.56-3.63 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 3.92-3.96 (m, 2H), 4.25-4.27 (m, 2H), 5.57 (d, *J* = 7 Hz, 1H), 6.14-6.26 (dt, *J* = 15.8 Hz, 5.8 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.70-7.07 (m, 5H); ^{13}C NMR δ 53.45, 55.89, 55.97, 63.62, 63.93, 88.02, 109.37, 110.57, 111.10, 114.84, 118.59, 126.40, 128.21, 130.82, 131.14, 133.52, 144.33, 148.25, 149.01, 149.14; MS *m/e* 372 (M^+). Accurate mass calcd for $C_{21}H_{24}O_6$: 372.1573, Found: 372.1583.

[(2*S*,3*R*)-3-Hydroxymethyl-7-methoxy-2,3-dihydro-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-propan-1-ol (20a)[17-19]

A solution of compound **19a** (15 mg, 0.04 mmol) in ethanol (20 mL) was hydrogenated over a catalytic amount of platinum dioxide for 1 h with stirring. Then the mixture was filtered and evaporated. The product **20a** was obtained by column chromatography on silica gel (2 g, hexanes/ethyl acetate 2:3) (11.2 mg, 74%); $[\alpha]_D^{23}$ +9.5° (*c* 0.2, $CHCl_3$) [lit[17-19] $[\alpha]_D$ no record]; ^{1}H NMR δ 1.83-1.94 (m, 2H), 2.68 (t, *J* = 7.7 Hz, 7.7 Hz, 2H), 3.58-3.63 (m, 1H), 3.69 (t, *J* = 6.3 Hz, 6.3 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.88-3.98 (m, 2H), 5.57 (d, *J* = 7.4 Hz, 1H), 6.68-6.98 (m, 5H); ^{13}C NMR δ 32.00, 34.61, 53.81, 55.97, 55.97, 62.29, 64.04, 87.74, 109.56, 111.22, 112.73, 116.02, 118.67, 127.78, 133.85, 135.41, 144.24, 146.66, 149.07, 149.26; MS *m/e* 374 (M^+).

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propenal (18b)

Compound **12b** (45 mg, 0.13 mmol) was converted to **18b** using the same procedure as described for the preparation of **18a**. The resulting residue was purified by flash column chromatography on silica gel (3 g, hexanes/ethyl acetate 1:1) to afford **18b** as a yellowish oil (40 mg, 86%); $[\alpha]_D^{24}$ - 44° (*c* 1.07, $CHCl_3$); ^1H NMR δ 3.65-3.73 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89-4.00 (m, 2H), 3.95 (s, 3H), 5.67 (d, *J* = 7 Hz, 1H), 6.61 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 6.83-6.86 (d, *J* =8.1 Hz, 1H), 6.92-6.94 (m, 2H), 6.98 (s, 1H), 7.0 (s, 1H), 7.42 (d, *J* = 15.8 Hz, 1H), 9.64 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 53.06, 56.02, 56.21, 64.04, 88.84, 109.58, 111.40, 112.60, 118.18, 118.72, 126.55, 128.24, 129.23, 132.99, 144.89, 149.43, 151.63, 152.85, 193.38; MS *m/e* 370 (M^+). Accurate mass calcd for $C_{21}H_{22}O_6$: 370.1417, Found: 370.1429.

(*E*)-3-[(2*R*,3*S*)-2,3-Dihydro-3-hydroxymethyl-7-methoxy-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propen-1-ol (19b)

Compound **18b** (25 mg, 0.07 mmol) was converted to **19b** using the same procedure as described for the preparation of **19a**. The resulting residue was purified by column chromatography on silica gel (2 g, hexanes/ethyl acetate 2:3) to give **19b** as a colorless oil (21 mg, 84%); $[\alpha]_D^{23}$ -12.5° (*c* 0.35, $CHCl_3$); ^1H NMR δ 3.60-3.65 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.88-3.95 (m, 2H), 3.89 (s, 3H), 4.27-4.30 (m, 2H), 5.59 (d, *J* = 7 Hz, 1H), 6.17-6.28 (dt, *J* = 15.8 Hz, 5.8 Hz, 1H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.80-6.96 (m, 5H); ^{13}C NMR δ 53.44, 55.9, 56.04, 63.5, 63.98, 87.95, 109.60, 110.83, 111.37, 114.93, 118.54, 126.43, 128.37, 130.84, 131.07, 133.67, 144.28, 148.24, 149.08; MS *m/e* 372 (M^+). Accurate mass calcd for $C_{21}H_{24}O_6$: 372.1573, Found: 372.1572.

[(2*R*,3*S*)-3-Hydroxymethyl-7-methoxy-2,3-dihydro-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-propan-1-ol (20b)[17-19]

Compound **19b** (30 mg, 0.1 mmol) was converted to **20b** using the same procedure as described for the preparation of **20a**. The product **20b** was obtained by column chromatography on silica gel (3 g, hexanes/ethyl acetate 2:3) as a yellowish oil (26 mg, 74%); $[\alpha]_D^{23}$ -10° (*c* 0.4, $CHCl_3$); ^1H NMR δ 1.85-1.94 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 7.7 Hz, 2H), 3.44-3.62 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 6.3 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.88-3.96 (m, 2H), 5.56 (d, *J* = 7.5 Hz, 1H), 6.67-6.98 (m, 5H); ^{13}C NMR δ 31.97, 34.57, 53.77, 55.92, 55.92, 62.25, 63.92, 87.73, 109.39, 111.04, 112.52, 115.97, 118.66, 127.74, 133.73, 135.38, 144.17 146.57, 149.13, 149.13; MS *m/e* 374 (M^+).

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References and Notes

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§ Crystal data of **10b**. $C_{30}H_{32}O_9$ = 536.6, monoclinic, space group $P2_1$, *a* = 6.272(1) Å, *b* = 16.831(2) Å, *c* = 13.405(1) Å, β = 93.69(1)°, *V* = 1412.2(7) $Å^3$, Z = 2, D_c = 1.262 Mg/m^3, *F*(000) = 568, MoK_α radiation λ = 0.71073 Å. Intensity data were collected on a Rigaku RAXIS IIC diffractometer: 4844 reflections in the range $3.0 < 2\theta < 55.0°$, $0 \le h \le 7$, $-21 \le k \le 21$, $-16 \le l \le 16$; 4632 independent (R_{int} =

2.16%). Anisotropic thermal parameters were used for all nonhydrogen atoms. The hydrogen atoms were located in difference Fourier maps and refined isotropically. The final agreement was $R_F = 0.073$ for 2955 observed data [$F > 6\sigma(F)$]. Tables of fractional atomic coordinates, thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom.

1. (a) Taken in part from the Ph.D. Thesis of M.S.M.Y., The Chinese University of Hong Kong, 1997. (b) To whom correspondence concerning the X-ray crystallographic study should be adderssed. (c) To whom other correspondence should be addressed.
2. Hartwell, J. R. *Cancer Treat. Rep.* **1976**, *60*, 1031.
3. Barclay, A. S.; Perdue, Jr., R. E. *Cancer Treat. Rep.* **1976**, *60*, 1081.
4. Badawi, M. M.; Seida, A. A.; Kinghorn, A. D.; Cordell, G. A.; Farnsworth, R. *J. Nat. Prod.* **1981**, *43*, 331.
5. Kato, A.; Hashimoto. Y.; Kidokoro, M. *J. Nat. Prod.* **1979**, *42*, 159.
6. Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, U.; Nishibe, S.; Hisada, S. *Chem. Pharm. Bull.* **1981**, *29*, 3586.
7. Namba, T.; Tsunezuka, M.; Hattori, M. *Planta Medica* **1982**, *44*, 100.
8. Kumada, Y.; Naganawa, H.; Tinuma, H.; Matsuzaki, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1976**,*29*, 8821.
9. Kumada, Y.; Naganawa, H.; Takeuchi, T.; Yamashita, H.; Watanabe, K. *J. Antibiot.* **1978**, *31*, 105.
10. Markkanen, T.; Makinen, M. L.; Maunuksela, E.; Himanen, P. *Drug Exp. Clin. Res.* **1981**, *7*, 711.
11. Mabry, T. J.; Ulubelen, A. *J. Agric. Food Chem.* **1980**, *28*, 188.
12. Haruna, M.; Koube, T.; Ito, K.; Murata, H. *Chem. Pharm. Bull.* **1982**, *30*, 1525.
13. Fukuyama, Y.; Miauta, K.; Nakagawa, K.; Qin, W.; Wa, X. *Planta Medica* **1986**, 501.
14. Agrawal, P. K.; Thakur, R. S. *Magnetic Resonance in Chemistry* **1985**, *23*, 389.
15. Salama, O.; Chaudhuri, R. K.; Sticher, O. *Phytochemistry* **1981**, *20*, 2603.
16. (a) Hartwell, J. L. *Plants Used Against Cancer. A Survey*; Quarterman Publications: Lawrence, Massachusetts, 1982; p 194. (b) Weinges, K.; Müller, R.; Kloss, P.; Jaggy. H. *Liebigs Ann. Chem.* **1970**, *736*, 170. (c) Wang, M. Y.; Wu, A. X.; She, X. G.; Pan, X. F. *Hecheng Huaxue* **1997**, *5* (Supplement), 325.
17. Pieters, L. A. C.; van den Berghe, D. A.; Vlietinck, A. J. *Phytochemistry* **1990**, *29*, 348.
18. Pieters, L.; de Bruyne, T.; Claeys, M.; Vlietinck, A. *J. Nat. Prod.* **1993**, *56*, 899.
19. Lemière, G.; Gao, M.; de Groot, A.; Dommisse, R.; Lepovire, J.; Pieters, L.; Buss, V. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1775.
20. Donnelly, B. J.; Donnelly, D. M. X.; O'Sullivan, A. M.; Prendergast, J. P.*Tetrahedron* **1969**, *25*, 4409.
21. Aiba, C. J.; Campos Corrêa, R. G.; Gottlieb, O. R. *phytochemistry* **1973**, 12, 1163.
22. Antus, S.; Gottsegen, Á.; Kolonits, P.; Wagner, H. *Liebigs Ann. Chem.* **1989**, 598.
23. Gerlach, H.; Kappes, D.; Boeckman, R. K. Jr.; Maw, G. N. *Org. Synth.* **1992**, *71*, 48.
24. Cotton, A. *Compt. Rend.* **1895**, *220*, 1044.
25. Mitchell, S. *The Cotton Effect*; G. Bell & Sons Ltd: London, 1933.
26. Tamada, M.; Endo, K.; Hikino, H.; Kabuto, C. *Tetrahedron* **1979**, *10*, 873.
27. Schlessinger, R. H.; Iwanowicz, E. J. *J. Org. Chem.* **1986**, *51*, 3070.
28. Corey, E. J.; Gilman, N. W.; Ganem, B. E.; *J. Am. Chem. Soc.* **1968**, *90*, 5616.