Triterpenes from *Garcia parviflora.* Cytotoxic Evaluation of Natural and Semisynthetic Friedelanes

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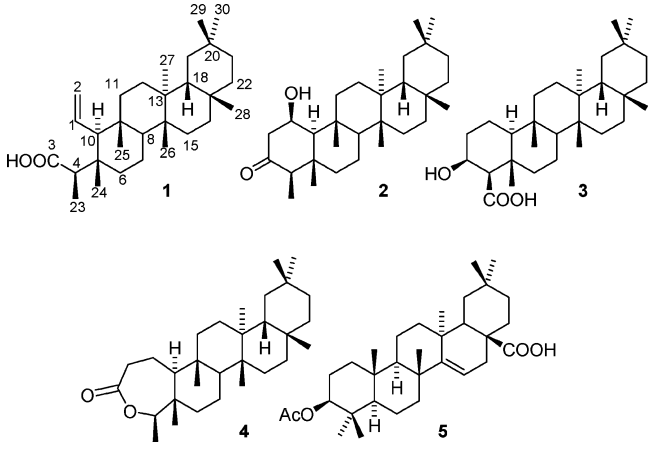
Three new friedelane-type triterpenes, 1,2-dehydro-2,3-secofriedelan-3-oic acid (**1**), 1β-hydroxyfriedelin (**2**), and 3β-hydroxyfriedelan-23-oic acid (**3**), and the known compounds friedelin-3,4-lactone (**4**), acetyl aleuritolic acid (**5**), 4-hydroxy-5-propionyl-1,3-di-*O*-methylpyrogallol, elemicin, and (−)-syringaresinol were isolated from the leaves of *Garcia parviflora*. The structures of **1**−**3** were elucidated by spectroscopic methods, including 1D and 2D NMR, HREIMS, X-ray, and CD analysis. Some derivatives of **2** (**6**−**14**) were prepared via oxidation, reduction, and esterification. The natural triterpenes and the semisynthetic friedelane derivatives were tested for cytotoxic activity against human cancer cell lines U251, PC-3, K562, HCT-15, MCF-7, and SKLU-1. Compound **5** was cytotoxic against U251 cells.

Members of the plant family Euphorbiaceae have provided various bioactive metabolites,[1] including pro-inflammatory,[2] anti-inflammatory,[3] antiviral,[4] and cytotoxic[5] compounds, represented by cytotoxic triterpenes,[6,7] diterpenes,[8] and sesquiterpenes.[7,9] *Garcia parviflora* Lundell (Euphorbiaceae) is a tree endemic to Mexico,[10] and its chemical constituents have not been investigated previously. Three new friedelanes (**1**−**3**) have been isolated and characterized from this material, together with some known compounds. Previous publications[11,12] have reported the preparation of several compounds by modifying the A ring of friedelane triterpenes, which afforded derivatives with cytotoxic activity. Therefore, we prepared some selected derivatives of **2** (**6**−**14**) via oxidation, reduction, and esterification. The natural triterpenes and the semisynthetic friedelane derivatives were tested for cytotoxicity against breast (MCF-7), leukemia (K562), central nervous system (U251, Glia), prostate (PC-3), colon (HCT-15), and lung (SKLU-1) cancer cell lines.



Results and Discussion

The hexane, ethyl acetate, and methanol extracts obtained from the aerial parts of *G. parviflora* were evaluated in a cytotoxicity assay using the sulforhodamine B colorimetric method.[13] In this assay, the hexane and ethyl acetate extracts inhibited growth of cells in the U251, PC3, K562, SKLU-1, and MCF-7 cancer cell lines (between 60% and 100% at 50 μg/mL), which encouraged us to investigate their bioactive principles. Fractionation of the hexane extract led to the isolation and characterization of the new triterpene 1,2-dehydro-2,3-secofriedelan-3-oic acid (**1**) and the known compounds friedelin-3,4-lactone (**4**),[14] acetyl aleuritolic acid (**5**),[15,16] and β-sitosterol. The new natural products 1β-hydroxyfriedelin (**2**) and 3β-hydroxyfriedelan-23-oic acid (**3**) and the known compounds 4-hydroxy-5-propionyl-1,3-di-*O*-methylpyrogallol[17] and elemicin[18,19] were isolated from the ethyl acetate extract. The methanol extract yielded the known compounds (−)-syringaresinol[20,21] and β-sitosteryl-β-D-glucopyranoside.

Compound **1** was obtained as a white solid. Its molecular formula was established as $C_{30}H_{50}O_2$ from the HRFABMS (*m*/z 443.3886 $[M + H]^+$), indicating six degrees of unsaturation. The IR spectrum showed absorptions indicating OH (3375 cm^{-1}) and carbonyl (1693 cm^{-1}) groups. Analysis of the ^{13}C NMR (Table 1) spectrum, with the aid of DEPT and HSQC experiments, revealed the presence of 30 signals involving eight methyl (δ_C 34.9, 32.1, 31.8, 20.8, 20.3, 18.9, 18.7, and 11.7), nine sp^3 methylene (δ_C 39.3, 36.6, 36.0, 35.3, 34.3, 32.8, 32.3, 30.3, and 17.7), one sp^2 methylene (δ_C 118.7), four sp^3 methine (δ_C 60.6, 52.4, 47.8, and 42.8) with one sp^2 (δ_C 135.2), and seven quaternary carbons including the carbonyl group of a carboxylic acid (δ_C 179.5, 39.7, 38.6, 38.5, 37.0, 30.0, and 28.2). The ^1H NMR spectrum (Table 1) showed seven tertiary methyl singlets and one secondary methyl doublet; these data were in agreement with the structure of a friedelane skeleton, ascribing the signal at δ_H 1.09 (J = 7.0 Hz) to H-23. The signals at δ_H 5.74 (ddd, J = 10.0, 10.5, 17.0 Hz), 5.13 (dd, J = 10.0, 2.5 Hz), and 4.98 (dd, J = 17.0, 2.5 Hz) indicated a terminal double bond, attributed to H-1, H-2a, and H-2b, respectively, in agreement with the assignments from the HSQC spectrum for the signals at δ_C 135.2 (C-1) and 118.7 (C-2). The olefinic hydrogens exhibited HMBC correlations with a methine carbon at δ_C 60.6 (C-10) and its corresponding hydrogen exhibited a resonance at δ_H 1.72 (d, J = 10.5 Hz, H-10α), confirming that the vinylic residue was at C-10. The ^1H NMR spectrum revealed a quartet at δ_H 2.48 (J = 7.0 Hz), which corresponded to the hydrogen attached to C-4 (δ_C 47.8), and this signal showed HMBC correlations with the quaternary carbons at δ_C 179.5 (C-3) and 38.6 (C-5), with a methylene carbon at δ_C 34.3 (C-6), with a methine carbon at δ_C 60.6 (C-10), and with the methyl carbons at δ_C 11.7 (C-23) and 20.8 (C-24). The H-23 methyl protons (δ_H 1.09) showed HBMC correlations with the carboxylic acid carbon C-3 (δ_C 179.5) and with the quaternary carbon C-5 (δ_C 38.6). These correlations confirmed the location of the carboxylic group, and the additional ^1H and ^{13}C NMR signals (Table 1) were similar to those of friedelin. Thus, **1** was 1,2-dehydro-2,3-secofriedelan-3-oic acid, and the configuration at C-4 was proposed as *R* considering analogy with other naturally occurring friedelanes.

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Table 1. $^{1}H^{a}$ and $^{13}C^{b}$ NMR Spectroscopy Data for **1**−**3** (δ in ppm)

	1		**2**		**3**	
position	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)
1	135.2, CH	5.74, ddd (17.0, 10.5, 10.0)	71.4, CH	4.84, br s	16.0, CH_2	1.50[c]
2a	118.7, CH_2	5.13, dd (10.0, 2.5)	52.7, CH_2	2.66, dd (14.0, 4.5)	33.5, CH_2	1.94, m
2b		4.98, dd (17.0, 2.5)		2.38, dd (14.0, 2.5)		1.50[c]
3	179.5, qC		211.3, qC		68.2, CH	4.15, ddd (2.5,2.5,2.5)
4	47.8, CH	2.48, q (7.0)	59.1, CH	2.30, q (6.5)	59.5, CH	2.20, d (2.5)
5	38.6, qC		43.9, qC		38.5, qC	
6a	34.3, CH_2	1.64, ddd (13.5, 3.5, 3.0)	34.3, CH_2	1.78, ddd (13.5, 3.5, 3.5)	42.9, CH_2	1.76, br d (12.5)
6b		1.53[c]				1.37[c]
7	17.7, CH_2	1.47[c]	18.8, CH_2		18.0, CH_2	1.45[c]
8	52.4, CH	1.20[c]	53.9, CH	1.33[c]	53.7, CH	1.36[c]
9	37.0, qC		38.6, qC		37.9, qC	
10	60.6, CH	1.72, d (10.5)	61.6, CH	1.47, br s	61.0, CH	0.98, br s
11a	36.6, CH_2	1.19[c]	35.7, CH_2	1.64, ddd (13., 3.0, 3.0)	36.0, CH_2	1.45[c]
11b		1.14, m				
12a	30.3, CH_2	1.28, m	30.4, CH_2	1.39, m	31.0, CH_2	1.34, m
12b						
13	39.7, qC		39.8, qC		40.2, qC	
14	38.5, qC		38.5, qC		38.8, qC	
15a	32.3, CH_2	1.50[c]	32.7, CH_2	1.55[c]	32.8, CH_2	1.52, m
15b		1.30[c]		1.29, m		1.31, m
16a	36.0, CH_2	1.55[c]	36.2, CH_2		36.5, CH_2	1.57[c]
16b		1.36[c]				1.36[c]
17	30.0. qC		30.1. qC		30.5. qC	
18	42.8, CH	1.53[c]	43.0, CH	1.58, dd (11.0, 6.0)	43.4, CH	1.57, dd (11.0, 6.0)
19a	35.3, CH_2	1.36[c]	35.5, CH_2		35.8, CH_2	1.38[c]
19b		1.19[c]				1.22, dd (14.0, 6.0)
20	28.2, qC		28.2, qC		28.5, qC	
21a	32.8, CH_2	1.46[c]	33.0, CH_2	1.50[c]	33.3, CH_2	1.50[c]
21b		1.25[c]				1.28, m
22a	39.3, CH_2	1.49, m	39.3, CH_2	1.50, m	39.7, CH_2	1.49[c]
22b		0.93[c]				0.94[c]
23	11.7, CH_3	1.09, d (7.0)	6.9, CH_3	0.94, d (6.5)	177.8, qC	
24	20.8, CH_3	1.11, s	17.4, CH_3	1.08, s	18.40, CH_3	1.19, s
25	18.9, CH_3	0.95, s	19.2, CH_3	1.31, s	18.43, CH_3	0.89, s
26	20.3, CH_3	0.995, s	20.2, CH_3	1.04, s	20.4, CH_3	1.01, s
27	18.7, CH_3	1.02, s	18.7, CH_3	1.05, s	18.9, CH_3	1.04, s
28	32.1, CH_3	1.17, s	32.2, CH_3	1.19, s	32.2, CH_3	1.19, s
29	31.8, CH_3	0.990, s	31.8, CH_3	1.01, s	32.4, CH_3	1.00, s
30	34.9, CH_3	0.94, s	34.9, CH_3	0.96, s	35.2, CH_3	0.95, s

[a] Recorded in $CDCl_3$ (**1**, **2** [50 °C]), $CDCl_3$−CD_3OD (1:1) (**3**) at 500 MHz. [b] Recorded in $CDCl_3$ (**1**, **2** [50 °C]), $CDCl_3$−CD_3OD (1:1) (**3**), at 125 MHz (**1**, **3**) and 75 MHz (**2**). [c] Overlapping signals.

Compound **2** was isolated as colorless needles. Its IR spectrum exhibited bands for OH (3370 cm^{-1}) and carbonyl (1703 cm^{-1}) groups. The molecular formula was established as $C_{30}H_{50}O_2$ from the HRFABMS ion at m/z 443.3884 $[M + H]^+$, indicating six degrees of unsaturation. The ^{13}C NMR spectrum (Table 1) had 30 resonances, and the DEPT spectra showed the presence of eight methyl, 10 methylene, five methine including one carbinol (δ_C 71.4), and seven quaternary carbons with one carbonyl group at δ_C 211.3. The ^{1}H NMR spectrum (Table 1) showed eight methyl signals, seven singlets (δ_H 1.31, 1.19, 1.08, 1.05, 1.04, 1.01, and 0.96), and a doublet at δ_H 0.94 (J = 6.5 Hz), similar to those described for **1**. This last signal was ascribed to H-23 since it showed a HSQC correlation with the shielded methyl carbon resonance at δ_C 6.9 and HMBC correlations with a methine carbon at δ_C 59.1 (C-4) and with the quaternary carbons at δ_C 43.9 (C-5) and 211.3 (C-3), establishing a ketone group at C-3. A secondary OH group was evident in the ^{1}H NMR spectrum by a broad signal located at δ_H 4.84, which corresponded to the carbinol methine proton H-1. The existence of this group was supported by the signal of an oxygenated carbon at δ_C 71.4 in the ^{13}C NMR spectrum. Two doublets of doublets [δ_H 2.66 (J = 14.0, 4.5 Hz) and 2.38 (J = 14.0, 2.5 Hz)] were assigned to methylene protons H-2a and H-2b, respectively, attached to C-2 (δ_C 52.7). The quartet signal at δ_H 2.30 (J = 6.5 Hz) corresponded to the axial proton H-4α. The OH group was assigned a β-orientation from the NOESY experiments, which exhibited interactions of equatorial proton H-1α with H-10α, H-8α, and H-2a and H-2b. The additional ^{1}H and ^{13}C NMR signals were similar to those reported for friedelane trierpenes. The structure of **2** was confirmed by X-ray diffraction analysis of crystals grown from ethyl acetate (Figure 1). Its absolute configuration was determined as depicted in **2** from a circular dichroism spectrum that showed a negative Cotton effect at 295 nm ($\Delta\varepsilon$ −50.41) due to the n → π^* transition of the carbonyl group.[22] This configuration is characteristic for naturally occurring friedelanes.

Compound **3** was obtained as white crystals. Its molecular formula, $C_{30}H_{50}O_3$ (HRFABMS, m/z 459.3841 $[M + H]^+$), indicated six degrees of unsaturation. IR absorptions at 3508 and 1717 cm^{-1} and the ^{13}C signals at δ_C 68.2 and 177.8 established the presence of OH and carbonyl groups. The ^{13}C NMR and DEPT spectra exhibited 30 signals involving seven methyl, 11 methylene, five methine, and seven quaternary carbons. The ^{1}H NMR spectrum showed six tertiary methyl singlets, of which two were overlapping methyls (H_3-24 and H_3-28). The signal at δ_H 4.15 (ddd, J = 2.5, 2.5, 2.5 Hz, H-3α) placed a secondary OH at C-3 in **3**, supported by an oxygenated carbon at δ_C 68.2 in the ^{13}C NMR spectrum that correlated with H-1 (δ_H 1.50) in the HMBC spectrum. The doublet at δ_H 2.20 (J = 2.5 Hz) was assigned to the hydrogen attached to C-4 (δ_C 59.5), since it showed HMBC correlations with the carboxylic acid group at C-23 (δ_C 177.8), with C-5 (δ_C 38.5), and with C-24 (δ_C 18.4), and a COSY correlation with H-3α. The coupling constant between H-3 and H-4 (2.5 Hz) established the β-orientation of the OH and carboxylic groups, and this was confirmed by NOESY interactions of H-4α with H-3α and H-10α.

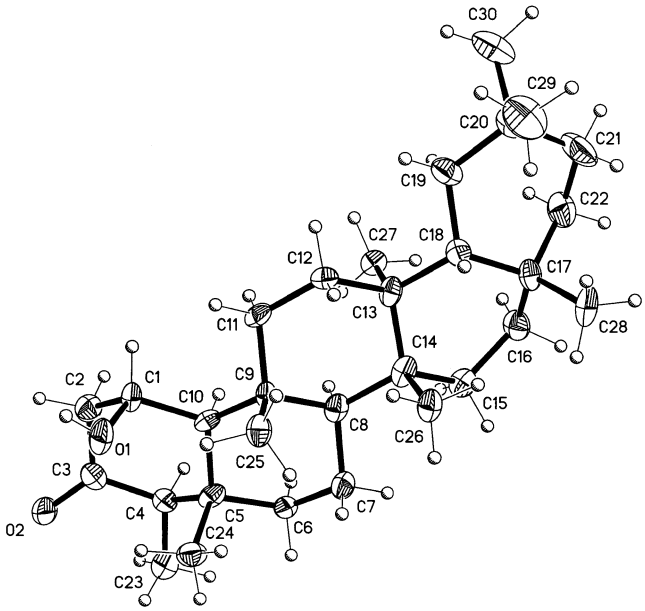


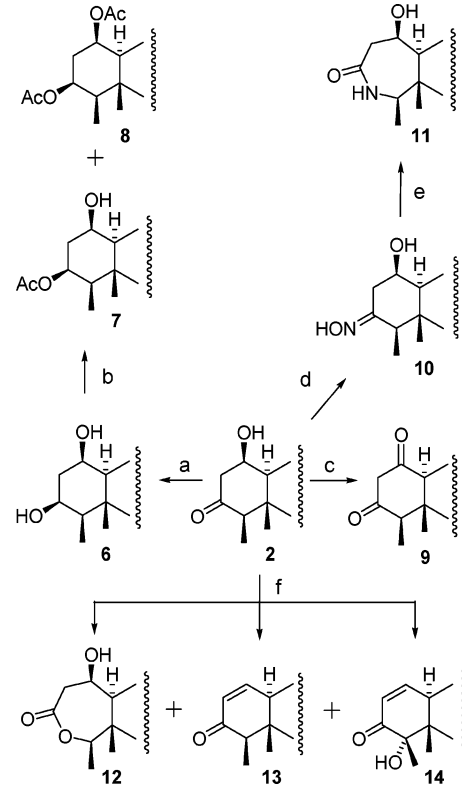
Figure 1. ORTEP drawing of **2** with atom labeling.

The additional ^{1}H and ^{13}C NMR (Table 1) signals were similar to those reported for friedelane trierpenes, verifying structure **3**.

Friedelanes functionalized at ring A possess a variety of biological activities,[23] and we considered that compound **2** offered the possibility of various structural modifications. Therefore, some derivatives were prepared in order to explore the cytotoxic potential of the resulting semisynthetic friedelane derivatives. Reduction of **2** with $NaBH_4$ in $THF-H_2O$[24] under reflux afforded 1β,3β-dihydroxyfriedelane (**6**) in good yield, which was subjected to acetylation with Ac_2O−pyridine, yielding the monoacetyl (**7**) and diacetyl (**8**) derivatives. Oxidation of **2** by Jones's reagent[25] at room temperature produced the previously reported 1,3-diketone **9** in moderate yield.[26,27] Reaction of **2** with hydroxylamine chloride[28] afforded oxime **10**, which was treated with *p*-TsCl,[28] producing the lactam **11**. Treatment of **2** with *m*-CPBA in $CHCl_3$[29] under reflux afforded **12**−**14**. Compound **13** has been reported previously.[30] The structures of the compounds obtained by these transformations (Scheme 1) were determined by conventional spectroscopic analyses (Tables 2 and 3).

The cytotoxicity of compounds **1**−**14** was tested against six human tumor cell lines. Compound **5** was cytotoxic against the U251 cell line, with IC_{50} 8.4 μM. Compounds **1**, **4**, and **6** exhibited weak activity in the same cell line, with IC_{50} 36.8, 17.1, and 22.8 μM, respectively, when compared to the positive control adriamycin (IC_{50} 0.3 μM). Compound **14** exhibited weak cytotoxicity against the HCT-15 cell line (IC_{50} 41.8 μM compared with adriamycin (IC_{50} 0.23 μM). Friedelin-3,4-lactone (**4**) and acetyl aleuritolic acid (**5**) were more cytotoxic than 1,2-dehydro-2,3-secofriedelan-3-oic acid (**1**). All other compounds were noncytotoxic against the tested cell lines.

Scheme 1. Friedelane Derivatives[a]



[a] Reagents: (a) $NaBH_4$; (b) Ac_2O, Py; (c) Jones reagent; (d) NH_2OH; (e): *p*-TsCl, Py; (f) *m*-CPBA.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher Johns apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer 341 polarimeter using a sodium lamp at the wavelength 589 nm. UV data were measured on a Shimadzu UV-160 spectrophotometer. The CD spectrum was measured with a JASCO J-720 spectrometer. IR spectra were recorded on a Nicolet Magna FT-IR 750 spectrometer. ^{1}H (500 MHz),^{13}C (125.0 MHz), and 2D NMR spectra (in $CDCl_3$, DMSO, and CD_3OD) were obtained on a Varian Inova 500, and ^{13}C NMR (75.0 MHz) were obtained on a Varian Unity 300 spectrometer. Chemical shifts were expressed in parts per million (δ) relative to TMS as internal standard. EI and HRFAB mass spectra were measured on JEOL JMS-AX 505 HA and JEOL JMX-SX 102 A mass spectrometers, respectively. Analytical TLC was carried out on precoated silica gel 60 F_{254} sheets (Merck). Column chromatography (CC) was performed using silica gel (230−400). All solvents were dried and distilled before use.

Plant Material. Aerial parts of *G. parviflora* were collected in Zacatal, Veracruz, México, during April 2003, and identified by Francisco Ramos Marchena. A voucher specimen was deposited at the National Herbarium (MEXU, voucher 1104455), Instituto de Biología, Universidad Nacional Autónoma de México.

Extraction and Isolation. The air-dried plant material (leaves and branches, 5.7 kg) was powdered and extracted at room temperature consecutively with *n*-hexane (24 L × 3), ethyl acetate (24 L × 3), and methanol (24 L × 2), and the extracts were concentrated to dryness in vacuo to obtain 27.7, 57.4, and 54.0 g of residues, respectively. The hexane extract was chromatographed on a silica gel (90 g) column with a gradient solvent system of hexane−EtOAc. The fractions (100 mL each) were monitored by TLC and pooled into seven main fractions. Fraction 3 (38.0 mg) was separated by preparative TLC using benzene−EtOAc (9:1) to yield 1,2-dehydro-2,3-secofriedelan-3-oic acid (**1**, 25 mg) and acetyl aleuritolic acid (**5**, 8 mg). Fraction 4 was subjected to CC using mixtures of *n*-hexane and EtOAc of increasing polarity. Five subfractions were collected. Subfraction 3 (87 mg) was purified by preparative chromatography using benzene−EtOAc (98:2) to obtain compound **1** (50 mg), friedelin-3,4-lactone (**4**, 6 mg), and β-sitosterol (19 mg). The ethyl acetate extract was suspended in acetone, filtered, and washed with a mixture of hexane−ethyl acetate (1:1), yielding 1β-hydroxyfriedelin (**2**, 2.0 g). The filtrate was evaporated to dryness, and this residue (55.0 g) was chromatographed on a silica gel column eluted with mixtures of *n*-hexane, *n*-hexane−EtOAc, and *n*-EtOAc−MeOH of increasing polarity to afford 11 main fractions. Fraction 2 (1.48 g) was fractionated by silica gel CC eluted with *n*-hexane−EtOAc mixtures to give eight subfractions. (8.1−8.8). Subfraction 8.6 (82 mg) was purified by preparative TLC using toluene−EtOAc (7:3) to afford 63 mg of elemicin. Fraction 6 (3.7 g) was subjected to silica gel CC and eluted with a gradient of *n*-hexane−EtOAc to give 13 subfractions (13a−13m). Subfraction 13g (0.97 g) was subjected to CC over silica gel using an *n*-hexane−EtOAc mixture of increasing polarity to yield seven fractions. Fraction 13g-4 (46 mg) was purified by preparative

Table 2. ^{1}H NMR Data of Compounds **6**−**8**, **10**−**12**, and **14** (δ in ppm, J in Hz)[a]

position	6	7	8	10	11	12	14
1	4.48, br s	4.38, br s	5.47, br s	4.66, s	4.61, d (8.0)	4.66, br s	6.96, dd (10.5, 2.0)
2a	2.21, ddd (15.0, 3.0, 2.5)	2.12, ddd (15.5, 2.5, 2.5)	2.21, ddd (16.0, 2.5, 2.0)	2.53, dd (13.0, 3.0)	2.79, d (14.0)	2.92, d (14.0)	6.01, dd (10.0, 3.0)
2b	1.69, ddd (15.0, 3.5, 3.0)	1.80, ddd (15.5, 4.0, 4.0)	1.71, ddd (16.0, 4.0, 4.0)	2.06, dd (13.0, 4.0)	2.56, dd (14.0, 7.5)	2.83, dd (14.0, 7.0)	
3	3.87, br s	5.15, ddd (3.0, 3.0, 3.0)	4.94, br s				
4	1.32, br s	1.45[b]	1.44[b]	2.26, q (6.5)	2.37, q (7.0)	2.24, q (6.0)	
6a	1.76, ddd (13.0, 3.5, 3.0)	1.77, ddd (13.0, 3.0, 3.0)	1.81, ddd (13.0, 3.0, 3.5)	1.75, ddd (13.0, 3.0, 3.0)	1.45, q (3.5)	1.45, m	1.81, m
6b	0.96[b]	1.01[b]	1.01[b]	1.23[b]	1.11[b]	1.05, m	1.53[b]
7a	1.41[b]	1.49[b]	1.45[b]	1.48[b]	1.52, m	1.51	1.58[b]
7b		1.43, m					
8	1.21[b]	1.21[b]	1.21[b]	1.25[b]	1.26, m	1.21[b]	1.42, dd (11.0, 4.00)
10	0.88, br s	0.88, br s	1.05, br s	1.18[b]	0.99, br s	1.00[b]	2.84, br s
11a	1.58, m	1.62, ddd (13.0, 3.5, 3.0)	1.45[b]	1.61, br d (13.0)	1.64, ddd (13.0, 3.0, 3.0)	1.60, m	1.62 dd (13.0, 3.5, 3.0)
11b	1.19[b]	1.37[b]	1.34[b]	1.31, br d (13.5)		1.34, m	1.32[b]
12a	1.41[b]	1.44[b]	1.33[b]	1.38[b]	1.41[b]	1.41, m	1.38[b]
12b	1.35[b]	1.35[b]				1,37[b]	
15a	1.49, m	1.49, m	1.49, m	1.50[b]		1.50, m	1.32[b]
15b	1.25[b]	1.24[b]	1.24[b]	1.24[b]		1.24[b]	
16a	1.52, m	1.53, m	1.53, m	1.54, m	1.56[b]	1.53[b]	1.54[b]
16b	1.34[b]	1.35[b]	1.35[b]	1.35[b]	1.37 br s	1.37[b]	1.34, m
18	1.54[b]	1.56, dd (12.0, 6.0)	1.54 dd (11.0, 6.0)	1.55, dd (11.0, 6.0)	1.58, dd (11.0, 6.0)	1.57, dd (11.0, 6.0)	1.57, dd (11.0, 6.0)
19a	1.35[b]	1.37[b]	1.34[b]	1.37[b]	1.40[b]	1.38[b]	1.38[b]
19b	1.23[b]	1.21[b]	1.20[b]	1.21, dd (14.0, 6.0)	1.23, dd (14.0, 6.0)	1.21[b]	1.20, dd (13.5, 6.0)
21a	1.44, m	1.47[b]	1.47, m	1.46[b]	1.46[b]	1.47[b]	1.46, m
21b	1.26, m	1.26[b]	1.23, m	1.25[b]	1.25[b]	1.26[b]	1.27[b]
22a	1.45[b]	1.47[b]	1.47[b]	1.48[b]	1.50, br s	1.49, m	1.47[b]
22b	0.92, br s	0.91[b]	0.93[b]	0.93[b]	0.93, br s	0.94[b]	0.93, br d
23	1.04, d (7.0)	0.90, d (7.0)	0.91, d (7.0)	1.08, d (6.5)	1.12, d (7.0)	1.24, d (6.5)	1.26, s
24	1.28, s	1.27, s	1.28, s	1.09, s	1.17, s	1.25, s	0.91, s
25	1.29, s	1.32, s	1.07, s	1.27, s	1.30, s	1.29, s	0.96, s
26	1.03, s	1.03, s	1.00, s	1.01, s	1.037, s	1.03, s	1.01, s
27	0.99, s	0.99, s	0.98, s	1.02, s	1.031, s	1.00, s	1.04, s
28	1.17, s	1.18, s	1.17, s	1.17, s	1.19, s	1.18, s	1.19, s
29	1.00, s	1.00, s	0.99, s	1.00, s	1.00, s	1.00, s	1.00, s
30	0.94, s	0.94, s	0.94, s	0.95, s	0.95, s	0.95, s	0.95, s
OH-1	2.64, d (7.0)						
OH-3	2.32, d (6.0)						
OAc-1			2.00, s				
OAc-3		2.07, s	2.02, s				

[a] Recorded in $CDCl_3$ (**6**−**8**, **12**, **14**), $CDCl_3$−DMSO (3:1) (**10**), $CDCl_3$−MeOH (1:1) (**11**) at 500 MHz. [b] Overlapping signals.

Table 3. ^{13}C NMR Data of Compounds[a] **6**−**8**, **10**−**12**, and **14** (δ in ppm)

position	6	7	8	10	11	12	14
1	68.4	67.2	68.1	68.1	64.7	65.5	150.7
2	41.9	39.8	36.1	37.6	45.0	43.7	127.4
3	74.1	74.8	72.8	166.6	177.4	172.6	198.3
4	49.5	48.3	48.0	51.2	60.3	85.2	78.4
5	38.1	37.6	37.8	42.5	41.2	41.7	45.5
6	44.4	44.4	43.7	42.6	41.4	40.4	32.7
7	17.8	18.0	17.9	18.1	19.2	18.4	17.3
8	53.8	53.8	53.9	52.9	53.9	53.4	51.6
9	39.3	38.2	37.8	38.5	40.0	39.3	36.3
10	61.8	61.4	60.4	60.7	67.2	66.2	52.9
11	35.5	35.3	35.3	34.5	36.0	35.6	34.9
12	30.5	30.4	30.3	29.6	31.2	30.5	30.2
13	39.7	39.7	39.6	38.9	39.9	39.5	39.7
14	38.4	38.4	38.4	37.6	39.2	38.6	38.2
15	32.4	32.4	32.4	31.7	33.0	32.6	32.1
16	36.1	36.0	36.0	35.3	36.6	36.1	35.9
17	30.0	30.0	30.0	29.3	30.6	30.0	30.0
18	42.8	42.8	42.8	42.1	43.5	42.9	42.8
19	35.3	35.3	35.3	34.6	35.9	35.4	35.4
20	28.2	28.2	28.1	27.5	28.6	28.2	28.1
21	32.8	32.8	32.8	32.2	33.4	32.9	32.7
22	39.3	39.3	39.3	38.5	39.8	39.3	39.2
23	12.0	11.6	11.5	8.1	15.7	15.2	16.4
24	18.4	18.2	17.2	16.2	15.8	16.2	17.2
25	19.4	19.2	18.8	18.3	19.4	19.2	20.3
26	20.0	20.0	20.1	19.4	20.4	20.0	19.9
27	18.7	18.7	18.6	18.1	19.0	18.6	18.7
28	32.1	32.1	32.1	31.5	32.4	32.1	32.1
29	31.8	31.8	31.8	31.3	32.1	31.8	31.7
30	35.0	35.0	34.9	34.4	35.2	34.9	35.0
acetate-1							
C=O			170.0				
CH_3			21.6				
acetate-3							
C=O		170.2	170.5				
CH_3		21.3	21.2				

[a] Recorded in $CDCl_3$ (**6**−**8**, **12**, **14**), $CDCl_3$−DMSO (3:1) (**10**), $CDCl_3$−MeOH (1:1) (**11**) at 125 MHz (**6**−**8**, **10**−**12**) and 75 MHz (**14**).

TLC using *n*-hexane−EtOAc (6:4) to yield 36.8 mg of 4-hydroxy-5-propionyl-1,3-di-*O*-methylpyrogallol. Subfraction 13i (0.38 g) was suspended in a mixture of hexane−CH_2Cl_2 (1:1), the suspension was filtered, and the solids were washed with hexane−CH_2Cl_2 (1:1) and crystallized from $CHCl_3$−MeOH to obtain 7.8 mg of compound **3**. The methanol extract of *G. parviflora* (54 g) was chromatographed on a silica gel column with mixtures of *n*-hexane−EtOAc and EtOAc−MeOH of increasing polarity, yielding 15 main fractions. The 13th fraction (152 mg) was purified by preparative chromatography using *n*-hexane−EtOAc−MeOH (40:55:5) to afford 43 mg of a yellow oil, which was further purified by analytical TLC using CH_2Cl_2−EtOAc−MeOH (80:15:5) to yield (−)-syringaresinol (21 mg). The last fraction from chromatography of the MeOH extract yielded β-sitosterol-β-D-glucopyranoside (10 mg).

1,2-Dehydro-2,3-secofriedelan-3-oic acid (1): white solid (from $CHCl_3$); mp 205−208 °C; $[\alpha]^{25}_D$ +16.8 (*c* 0.095, $CHCl_3$); IR (KBr) ν_{max} 3375, 2928, 2860, 1693, 1463, 1388, 1231, 1079, 1007, 919, 674 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 442 $[M]^+$ (31), 427 (32), 245 (39), 205 (96), 191 (55), 163 (49), 137 (53), 109 (79), 95 (100), 69 (81), 57 (61), 43 (40), 29 (7); HRFABMS *m*/*z* $[M + H]^+$ 443.3886 (calcd for $C_{30}H_{51}O_2$, 443.3889).

1β-Hydroxyfriedelin (2): colorless needles (from EtOAc) relatively insoluble in solvents such as acetone, ethyl acetate, THF, and CH_2Cl_2. This limited solubility could be explained by two intermolecular hydrogen bonds (identified by X-ray analysis) between the carbonyl and OH groups that enhance the crystalline stability.[31] Mp >300 °C; $[\alpha]^{25}_D$ −38.0 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 243 (2.42) nm; CD ($CHCl_3$) λ_{max} $\Delta\varepsilon_{295}$ −50.41; IR (KBr) ν_{max} 3370, 2938, 2865, 1704, 1454, 1384, 1235, 1174, 1121, 1024, 917, 651 cm^{-1}; ^1H and ^{13}C NMR, see Table 1 (the spectra were recorded at 50 °C due to the low solubility of **2** in $CDCl_3$ at rt); EIMS *m*/*z* 442 $[M]^+$ (5), 424 (4), 344 (100), 289 (7), 258 (41), 230 (14), 205 (11), 193 (77), 184 (22), 135 (39), 129 (27), 90 (33), 77 (20), 57 (50), 18 (57); HRFABMS *m*/*z* $[M + H]^+$ 443.3884 (calcd for $C_{30}H_{51}O_2$, 443.3889).

3β-Hydroxyfriedelan-23-oic acid (3): white crystals (from CH_3Cl_3:MeOH), mp 237−240 °C; $[\alpha]^{25}_D$ +37.7 (*c* 0.13 $CHCl_3$); IR (KBr) ν_{max} 3508, 2934, 2867, 1717, 1453, 1385, 1235, 1188, 1002, 687 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; FABMS *m*/*z* 459 $[M + H]^+$ (2), 441 (3), 391 (4), 307 (11), 289 (13), 165 (22), 154 (80), 136 (72), 107 (40), 77 (100), 63 (56), 39 (62), 27 (32), 14 (8); HRFABMS *m*/*z* $[M + H]^+$ 459.3841 (calcd for $C_{30}H_{51}O_3$, 459.3838).

Preparation of 1β,3β-Dihydroxyfriedelane (6). 1β-Hydroxyfriedelin (**2**) (50.0 mg, 0.11 mmol) was suspended in THF−H_2O (3:0.1 mL), and $NaBH_4$ (9.4 mg, 0.25 mmol) was added. The resulting mixture was stirred under reflux and monitored by TLC (hexane−EtOAc, 7:3). After completion of the reaction (3 h), distilled water (3 mL) was added to the reaction mixture, and it was then stirred for an additional 5 min at rt. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by CC (silica gel, hexane−EtOAc, 8:2), affording compound **6** (47.8 mg, 95.2% yield).

1β,3β-Dihydroxyfriedelane (6): white needles ($CHCl_3$−MeOH), mp 217−219 °C; $[\alpha]^{25}_D$ +7.0 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3428, 2937, 2867, 1459, 1385, 1145, 1055, 976, 848, 578 cm^{-1}; ^1H and ^{13}C NMR, see Tables 2 and 3, respectively; EIMS *m*/*z* 444 $[M]^+$ (7), 429 (21), 291 (22), 260 (27), 220 (18), 205 (35), 191 (33), 163 (28), 137 (38), 123 (68), 95 (100), 83 (95), 69 (95), 55 (82), 43 (83), 18 (77); HRFABMS *m*/*z* 444.3973 $[M]^+$ (calcd for $C_{30}H_{51}O_2$, 444.3967).

Acetylation of 1β,3β-Dihydroxyfriedelane (6). Compound **6** (30.5 mg) was treated with Ac_2O (1.5 mL) in pyridine (1.0 mL) at room temperature for 72 h. The formation of products was monitored by TLC using *n*-hexane−CH_2Cl_2−EtOAc (8:1:1). The reaction mixture was worked up as usual, and the residue was subjected to CC over silica gel. Elution with an *n*-hexane−CH_2Cl_2−EtOAc solvent system afforded **7** (12.5 mg, 41%), **8** (3.6 mg, 9.9%), and recovered starting material (**6**, 10.7 mg, 35.1%).

3β-Acetoxy-1β-hydroxyfriedelane (7): colorless needles (CH_2Cl_2), mp 213-215 °C; $[\alpha]^{25}_D$ −5.45 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2934, 2865, 1731, 1462, 1378, 1251, 1230, 1139, 1019, 978 cm^{-1}; ^1H and ^{13}C NMR, see Tables 2 and 3; EIMS *m*/*z* 486 $[M]^+$ (3), 471 (10), 426 (9), 333 (8), 273 (14), 260 (18), 229 (15), 218 (31), 205 (21), 191 (26), 149 (27), 121 (60), 109 (73), 95 (100), 69 (82), 55 (62), 43 (45), 41 (27), 29 (6); HRFABMS *m*/*z* 486.4065 $[M]^+$ (calcd for $C_{32}H_{54}O_3$, 486.4073).

1β,3β-Diacetoxyfriedelane (8): colorless needles (CH_2Cl_2), mp 219−221 °C; $[\alpha]^{25}_D$ +9.2 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2939, 2867, 1726, 1462, 1371, 1268, 1242, 1140, 1022, 977 cm^{-1}; ^1H and ^{13}C NMR, see Tables 2 and 3; EIMS *m*/*z* 528 $[M]^+$ (6), 468 (4), 426 (9), 408 (8), 393 (9), 376 (11), 273 (17), 260 (26), 205 (48), 149 (40), 137 (44), 123 (90), 109 (97), 95 (100), 81 (75), 69 (98), 55 (52), 43 (68); HRFABMS *m*/*z* 528.4186 $[M]^+$ (calcd for $C_{34}H_{56}O_4$, 528.4179).

Preparation of Friedelane-1,3-dione (9). 1β-Hydroxyfriedelin (**2**) (14.0 mg, 0.03 mmol) was suspended in THF (5 mL). Jones reagent was added dropwise until the orange color remained. The reaction mixture was stirred (30 min) at room temperature, and then it was quenched with MeOH, producing a blue-green solution. The solvents were eliminated under vacuum, and water was added. The product was extracted with $CHCl_3$ (3 × 3 mL), washed with aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The product was purified by CC (silica gel, hexane−EtOAc, 8:2) to afford 1,3-diketofriedelane (**9**) (9.0 mg, 64% yield) and recovered 1β-hydroxyfriedelin (**2**) (2.0 mg, 14.3% yield). Compound **9** was identified by direct comparison with data reported in the literature,[26,27] $[\alpha]^{25}_D$ −5.0 (*c* 0.12, $CHCl_3$), lit.[27] $[\alpha]^{25}_D$ −4.2.

Preparation of 1β-Hydroxyfriedelin-3-oxime (10). Compound **2** (100 mg, 0.22 mmol) and hydroxylamine hydrochloride (39.3 mg) were dissolved in a mixture of anhydrous pyridine (1.5 mL) and absolute ethanol (1.5 mL), and the reaction mixture was refluxed for 30 min and cooled to rt.[28] Then, a solution of HCl (10%, 2 mL) was added, obtaining a precipitate, which was filtered. The solid was washed with EtOAc to obtain **10** (98.9 mg, 95.6%).

1β-Hydroxyfriedelin-3-oxime (10): colorless crystals, mp 242−244 °C; $[\alpha]^{25}_D$ +18.4 (*c* 0.10, $CHCl_3$); IR (KBr) ν_{max} 3611, 3289, 2933, 2867, 1674, 1460, 1385, 936 cm^{-1}; ^1H and ^{13}C NMR, see Tables 2 and 3; EIMS *m*/*z* 457 $[M]^+$ (17), 439 (33), 422 (100), 408 (19), 205 (96), 191 (21), 166 (38), 138 (44), 123 (68), 109 (76), 95 (96), 69

(79), 55 (50), 41 (22), 18 (35); HRFABMS *m/z* [M + H]$^+$ 458.3997 (calcd for $C_{30}H_{52}O_2N$, 458.3998).

Preparation of 1β-Hydroxyfriedelin-3,4-lactam (11). Compound **10** (42.0 mg, 0.09 mmol) and *p*-toluenesulfonyl chloride (14.0 mg, 0.07 mmol) were dissolved in pyridine (1 mL), and the mixture was refluxed for 5 h. Then, the reaction mixture was cooled and diluted with water (3 mL), and the product was extracted with $CHCl_3$ (3 × 5 mL). The organic phases were combined, washed with HCl (10%) and brine, and dried over anhydrous Na_2SO_4. Concentration of the organic phase afforded **11** (39.4 mg, 93.8%).

1β-Hydroxyfriedelin-3,4-lactam (11): white powder, mp 262−264 °C; $[\alpha]^{25}_D$ −13.3 (*c* 0.10, $CHCl_3$); IR (KBr) ν_{max} 3422, 3257, 3938, 2868, 1667, 1452, 1192 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 2 and 3; EIMS *m/z* 457 [M]$^+$ (25), 439 (8), 424 (32), 218 (21), 205 (48), 191 (36), 163 (22), 137 (29), 123 (39), 109 (48), 95 (56), 81 (47), 69 (45), 55 (31), 44 (100), 28 (11); HRFABMS *m/z* [M + H]$^+$ 458.4000 (calcd for $C_{30}H_{52}O_2N$, 458.3998).

Reaction of 1β-Hydroxyfriedelin (2) with *m*-CPBA. Compound **2** (30 mg, 0.06 mmol) was dissolved in $CHCl_3$ (15 mL), and then *m*-CPBA[29] (29.3 mg, 0.16 mmol) was added. The mixture was refluxed for 6 h. The reaction mixture was diluted with $CHCl_3$, and the solution was washed successively with 5% Na_2SO_3(aq), saturated $NaHCO_3$, and brine and dried with Na_2SO_4. The solution was evaporated in vacuo, and the residue was separated by silica gel CC eluted with mixtures of *n*-hexane and EtOAc, to afford compounds **12** (4.2 mg, 13.5%), **13** (4.8 mg, 16.6%), and **14** (3.7 mg). Compound **13** was identified by direct comparison with data reported in the literature.[12,30]

1β-Hydroxyfriedelin-3,4-lactone (12): amorphous solid ($CHCl_3$); $[\alpha]^{25}_D$ +17.1 (*c* 0.10, $CHCl_3$); IR (KBr) ν_{max} 3364, 2939, 2867, 1720, 1447, 1384, 1306, 1265, 1183, 1076 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 2 and 3; EIMS *m/z* 458 [M]$^+$ (1), 173 (12), 83 (100), 55 (35), 43 (7), 18 (5); HRFABMS *m/z* 459.3832 [M + H]$^+$ (calcd for $C_{30}H_{51}O_3$, 459.3838).

4α-Hydroxyfriedel-1-en-3-one (14): white crystals ($CHCl_3$); mp 266−268 °C; $[\alpha]^{25}_D$ −90 (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 238 (3.84) nm; IR ($CDCl_3$) ν_{max} 2931, 2866, 2867, 1674, 1463, 1388, 1235, 1172, 1073 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 2 and 3; EIMS *m/z* 440 [M]$^+$ (43), 412 (12), 397 (13), 218 (13), 205 (26), 152 (30), 109 (31), 95 (73), 69 (100), 67 (42), 55 (29), 18 (87); HRFABMS *m/z* 440.3651 [M]$^+$ (calcd for $C_{30}H_{48}O_2$, 440.3654).

Cytotoxic Assays. Human tumor cell lines leukemia (K562), central nervous system (U251, Glia), colon (HCT-15), breast (MCF-7), lung (SKLU-1), and prostate cancer (PC-3) were supplied by the National Cancer Institute. The cytotoxic activities of **1**−**14** and of the *n*-hexane and ethyl acetate extracts on tumor cells were determined using the protein-binding dye sulforhodamine B (SRB) in a microculture assay to measure cell growth.[13] The cells were cultured in RPMI-1640 (Sigma Chemical Co., Ltd., St. Louis, MO), supplemented with 10% fetal bovine serum, 2 μM L-glutamine, 100 IU/mL penicillin G, 100 μg/mL streptomycin sulfate, and 0.25 μg/mL amphotericin B (Gibco). They were maintained at 37 °C in a 5% CO_2 atmosphere with 95% humidity. For the assay, 5 × 10^4 cells/mL (K562, MCF-7), 7.5 × 10^4 cells/mL (U251, PC-3, SKLU-1), and 10 × 10^4 cells/mL (HCT-15) with 100 μL/well of the cell suspensions were seeded in 96-well microtiter plates and incubated to allow cell attachment. After 24 h, 100 μL of each test compound, extract, or positive control was added (all test substances were dissolved in DMSO). After 48 h, adherent cell cultures were fixed in situ by adding 50 μL of cold 50% (w/v) aqueous trichloroacetic acid (TCA) and incubated for 60 min at 4 °C. The supernatant was discarded, and the plates were washed three times with H_2O and then air-dried. Cultures fixed with TCA were stained for 30 min with 100 μL of 0.4% SRB solution. Protein-bound dye was extracted with 10 μM unbuffered Tris base, and the optical densities were read on an Ultra microplate reader ($E1_x$ 808, Bio-Tek Instruments, Inc.), at a wavelength of 515 nm. Results were expressed as concentration giving 50% inhibition (IC_{50}). The data were calculated according to the protocol of Monks,[13] where a dose−response curve was plotted for each compound; the IC_{50} values were estimated from linear regression equations. The IC_{50} values (mean ± standard error) for **1**, **4**−**6**, **14**, and the positive control (adriamycin) are reported in the text.

X-ray Structure Determination of 1β-Hydroxyfriedelin (2).[31] The X-ray crystallographic data were measured on a Bruker Smart Apex automatic diffractometer with a CCD area detector at 173(2) K using graphite- monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the program SHELXS-97.[32] The crystal data are summarized as follows: empirical formula $C_{30}H_{50}O_2$; formula weight 442.70 amu; crystal color and habit, colorless prism, orthorhombic, crystal size 0.268 × 0.056 × 0.038 mm, space group $P2_12_12_1$, $Z = 4$, $a = 6.230(3)$ Å, $b = 14.029(8)$ Å, $c = 29.261(16)$ Å, $V = 2557(2)$ Å^3; $D_{calcd} = 1.150$ Mg/m^3; $F(000) = 984$, $\mu = 0.069$ mm^{-1}; 18 537 collected reflections ($2.01° \le \theta \le 25.44°$), $-7 \le h \le 7$, $-16 \le k \le 16$, $35 \le l \le 35$; 2723 independent reflections ($R_{int} = 0.0877$); goodness-of-fit on F^2 is 1.020, final *R* indices for $I > 2\sigma(I)$, $R_1 = 0.0877$, $wR_2 = 0.1724$, *R* indices for all data $R_1 = 0.1560$, $wR_2 = 0.2023$; refining 301 parameters and no restraints; the largest difference peak and hole was 0.289 and −0.266 e Å^{-3}; completeness to θ (25.44°) 99.2%, maximum transmission 0.9999, minimum transmission 0.9811.

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Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **1**−**3**, **6**−**8**, **10**−**12**, and **14**, CD curve, and X-ray crystallographic data for **2** are provided. This information is available free of charge via the Internet at http://pubs.acs.org.

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(31) Crystallographic data for the structure of compound **2** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 766372). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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