Excisanin H, a Novel Cytotoxic 14,20-Epoxy-*ent*-Kaurene Diterpenoid, and Three New *ent*-Kaurene Diterpenoids from *Rabdosia excisa*

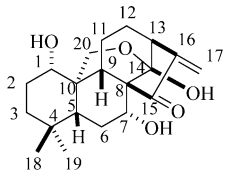
Ming-yu Gui,[†,‡] Yutaka Aoyagi,[†] Yong-Ri Jin,[‡] Xu-Wen Li,[‡] Tomoyo Hasuda,[†] and Koichi Takeya*[,†]

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan, and Department of Chemistry, JiLin University, No. 2 Xinmin Street, Changchun, JiLin 130021, People's Republic of China

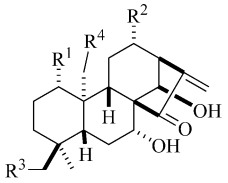
Received August 5, 2003

A novel 14,20-epoxy-*ent*-kaurene diterpenoid, excisanin H (**1**), and three new *ent*-kaurene diterpenoids, **2**−**4**, were isolated from aerial parts of *Rabdosia excisa* along with eight known *ent*-kaurene diterpenoids, **5**−**12**. The structural elucidations were made using spectral (HREIMS, IR, ^{1}H, ^{13}C, and 2D NMR) methods. The absolute configuration of **1** was determined by demonstrating that oxidation of kamebakaurin (**8**) produced excisanin H (**1**). These *ent*-kaurene diterpenoids all showed significant cytotoxic activity against P388 murine leukemia cells.

Phytochemical investigations for novel anticancer drugs from natural sources have been carried out in our laboratories over 20 years.[1] *Rabdosia excisa* Hara (Labiatae), which has been used as a folk medicine for treatment of fever and arthralgia in north China, is distributed widely in the world, especially in east Asia. A number of diterpenes have been isolated from *Rabdosia* plants.[2] Among these are *ent*-kaurene diterpenes having cytotoxic,[3] antibacterial,[4] NF-κB activation-inhibiting,[5] and apoptosis-inducing activities.[6] Eleven *ent*-kaurene diterpenes are known in *R. excisa*.[7−10] In our present chemical investigation of this plant, collected in Jing Yu County, Jinlin Province of China, we isolated four novel *ent*-kaurene diterpenoids and eight known ones. In this paper, we describe the isolation, structural elucidation, and cytotoxic activity of these *ent*-kaurenoids.



1



	R^1	R^2	R^3	R^4
2	H	OH	H	OH
3	H	H	OH	OH
4	OH	H	OH	H
5	OH	OH	H	H
6	OH	OAc	H	H
7	OH	H	OAc	H
8	OH	H	H	OH
9	OH	H	H	H
10	H	OH	OH	H
11	OH	OH	H	OH
12	OH	H	H	OAc

Results and Discussion

A hot water extract of 3 kg of the air-dried aerial parts of *R. excisa* yielded 16 g of *n*-BuOH extract. Silica gel column chromatography and ODS-HPLC (MeCN−H_2O and MeOH−H_2O) of the *n*-BuOH-soluble fraction gave excisanins H−K (**1**−**4**) and eight known diterpenes, **5**,[7] **6**,[7] **7**,[10] **8**,[7] **9**,[7] **10**,[11] **11**,[12] and **12**.[13]

Compound **1** was isolated as a colorless powder whose molecular formula was established as $C_{20}H_{28}O_5$ from its HRESIMS. The IR absorption spectrum indicated the presence of hydroxy (3432 cm^{-1}) and α,β-unsaturated carbonyl groups (1731 and 1647 cm^{-1}). On the basis of ^{1}H NMR, ^{13}C NMR, and DEPT spectral studies, **1** was shown to have 20 carbons assignable to four sp^3 and two sp^2 quaternary carbons, five sp^3 methines, one sp^2 and six sp^3 methylenes, and two methyl groups (Tables 1 and 2). The ^{1}H NMR spectrum exhibited two signals at δ_H 5.23 (1H, s) and 6.18 (1H, s), attributable to *exo*-cyclic methylene protons, two doublets at δ_H 5.22 (1H, d, J = 11.6 Hz) and 4.70 (1H, d, J = 11.6 Hz) each assignable to oxygen-bearing methylene protons, and two singlet signals at δ_H 0.95 (3H, s) and 0.84 (3H, s) due to two methyl groups attached to quaternary carbons. Since two out of the seven elements of unsaturations were accounted for, **1** had five rings. The characterization from the spectral data and the chemotaxonomic considerations on the *Rabdosia* species suggested that **1** was an *ent*-kaurene diterpene which possessed five ring systems. The cross-peaks observed in the HMBC of **1** revealed that two secondary hydroxy groups were at C-1 and C-7; the linkage between C-7 and C-20 via hemiacetal quaternary carbon C-14 (δ_C 103.1) was also suggested by HMBC, namely, the correlations between H-20 and C-14 and between H-7 and C-14. The relative configuration of **1** was elucidated by NOESY correlations as shown in the Platon drawing (Figure 1).[14,15] Namely, the hydroxyl groups at C-1 and C7 were both of α-orientation and that at C-14 was of β-orientation. On the basis of the correlations between Ha-20 and H-12α and between Hb-20, H-6α, and Me-19 as demonstrated in the NOESY spectrum, the methylene group at C-20 was shown to be α-oriented. Consequently, the structure of **1** was concluded to be 14α,20-epoxy-1α,7α,14β-trihydroxy-*ent*-kaur-16-en-15-one and given the trivial name excisanin H. This is the

* Corresponding author. Tel: +81-426-76-3007. Fax: +81-426-76-2201. E-mail: takeyak@ps.toyaku.ac.jp.
† Tokyo University of Pharmacy and Life Science.
‡ JiLin University.

10.1021/np030357r CCC: $27.50
Published on Web 02/05/2004

Table 1. ^{1}H NMR Data for Compounds **1**−**4** in Pyridine-d_5

proton	**1**[a]	**2**[a]	**3**[b]	**4**[b]
1a		2.67 (1H, d, 12.8)	2.40 (1H, m)	
1b	3.55 (1H, ddd, 11.5, 4.4, 4.4)	0.48 (1H, ddd, 12.8, 12.8, 3.1)	0.63 (1H, ddd, 12.9, 12.9, 3.9)	3.55 (1H, ddd, 9.8, 4.9, 4.9)
2a	1.80 (1H, m)	1.71 (1H, m)	2.06 (1H, m)	2.01 (1H, m)
2b	1.72 (1H, m)	1.41 (1H, m)	1.51 (1H, m)	1.91 (1H, m)
3a	1.34 (1H, m)	1.41 (1H, m)	1.69 (1H, m)	1.40 (1H, m)
3b	1.27 (1H, m)	1.14 (1H, m)	2.94 (1H, m)	1.99 (1H, m)
5b	1.03 (1H, dd, 12.6, 2.1)	1.10 (1H, dd, 12.4, 1.3)	1.96 (1H, dd, 12.4, 2.0)	1.80 (1H, dd, 12.4, 1.2)
6a	2.57 (1H, ddd, 12.6, 12.6, 12.6)	2.02 (1H, ddd, 12.5, 12.5, 12.5)	2.32 (1H, ddd, 12.4, 12.4, 12.4)	2.18 (1H, ddd, 12.4, 12.4, 12.4)
6b	2.31 (1H, ddd, 12.6, 5.6, 2.1)	2.14 (1H, ddd, 12.5, 1.9, 1.6)	2.41 (1H, m)	2.45 (1H, ddd, 12.4, 3.8, 1.2)
7b	4.74 (1H, ddd, 12.6, 5.6, 5.6)	4.97 (1H, ddd, 12.6, 4.9, 4.9)	5.11 (1H, ddd, 12.4, 4.7, 4.7)	4.96 (1H, m)
9b	1.84 (1H, m)	1.61 (1H, d, 10.5)	1.72 (1H, m)	1.97 (1H, d, 8.0)
11a	3.16 (1H, dd, 13.5, 11.9)	2.39 (1H, d, 16.5)	1.85 (1H, m)	3.68 (1H, m)
11b	1.63 (1H, m)	1.80 (1H, m)	1.51 (1H, m)	1.71 (1H, m)
12a	2.80 (1H, m)		1.82 (1H, m)	2.21 (1H, m)
12b	1.67 (1H, m)	4.37 (1H, ddd, 8.8, 4.4, 4.4)	1.42 (1H, m)	1.65 (1H, m)
13a	3.35 (1H, brs)	3.70 (1H, d, 4.4)	3.34 (1H, brs)	3.30 (1H, brs)
14a		6.06 (1H, s)	5.72 (1H, s)	5.33 (1H, s)
17	6.18 (1H, s)	6.35 (1H, s)	6.34 (1H, s)	6.28 (1H, s)
	5.23 (1H, s)	5.43 (1H, s)	5.39 (1H, s)	5.33 (1H, s)
18	0.84 (3H, s)	0.84 (3H, s)	3.68 (1H, dd, 10.5, 5.2)	3.67 (1H, dd, 10.5, 4.8)
			3.35 (1H, dd, 10.5, 5.2)	3.34 (1H, dd, 10.5, 4.8)
19	0.95 (3H, s)	0.88 (3H, s)	0.99 (3H, s)	0.92 (3H, s)
20	4.70 (1H, d, 11.8)	4.31 (1H, dd, 12.8, 4.4)	4.42 (1H, dd, 11.8, 4.4)	1.51 (3H, s)
	5.22 (1H, d, 11.8)	4.53 (1H, dd, 12.8, 8.0)	4.35 (1H, dd, 11.8, 4.4)	

[a] Recorded at 500 MHz at 300 K. [b] Recorded at 400 MHz at 300 K.

Table 2. ^{13}C NMR Data (δ) for Compounds **1**−**4** in Pyridine-d_5

carbon	**1**[a]		**2**[a]		**3**[b]		**4**[b]	
1	75.5	d	34.6	t	34.9	t	80.2	d
2	30.8	t	18.7	t	18.9	t	30.0	t
3	39.5	t	41.6	t	30.9	t	33.8	t
4	33.4	s	33.1	s	37.8	s	37.9	s
5	51.5	d	53.7	d	46.9	d	45.5	d
6	31.5	t	29.6	t	29.6	t	29.5	t
7	71.7	d	74.9	d	74.8	d	74.4	d
8	56.8	s	61.7	s	62.0	s	62.8	s
9	52.4	d	53.8	d	55.5	d	56.7	d
10	41.6	s	44.2	s	43.2	s	45.4	s
11	21.8	t	25.3	t	18.8	t	20.3	t
12	30.3	t	73.5	d	35.6	t	31.9	t
13	52.4	d	55.8	d	47.5	d	47.4	d
14	103.1	s	71.7	d	76.7	d	76.0	d
15	206.1	s	208.8	s	208.9	s	208.8	s
16	151.3	s	147.3	s	150.7	s	150.6	s
17	113.3	t	117.2	t	115.5	t	115.6	t
18	33.2	q	34.2	q	71.3	t	71.0	t
19	21.4	q	23.0	q	18.6	q	18.0	q
20	66.5	t	60.4	t	60.8	t	15.6	q

[a] Recorded at 125 MHz at 300 K. [b] Recorded at 100 MHz at 300 K.

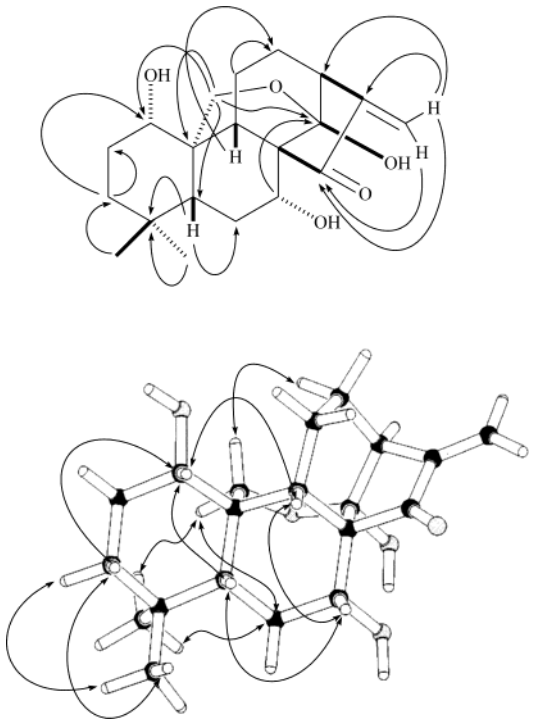
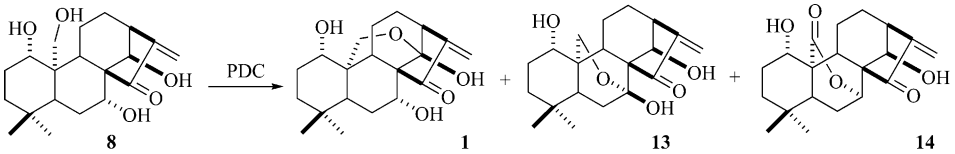


Figure 1. Selected HMBC (H → C) and NOESY correlations for **1**, which was minimized using Spartan 02 for Windows[15] and was drawn using Platon for Windows.[14]

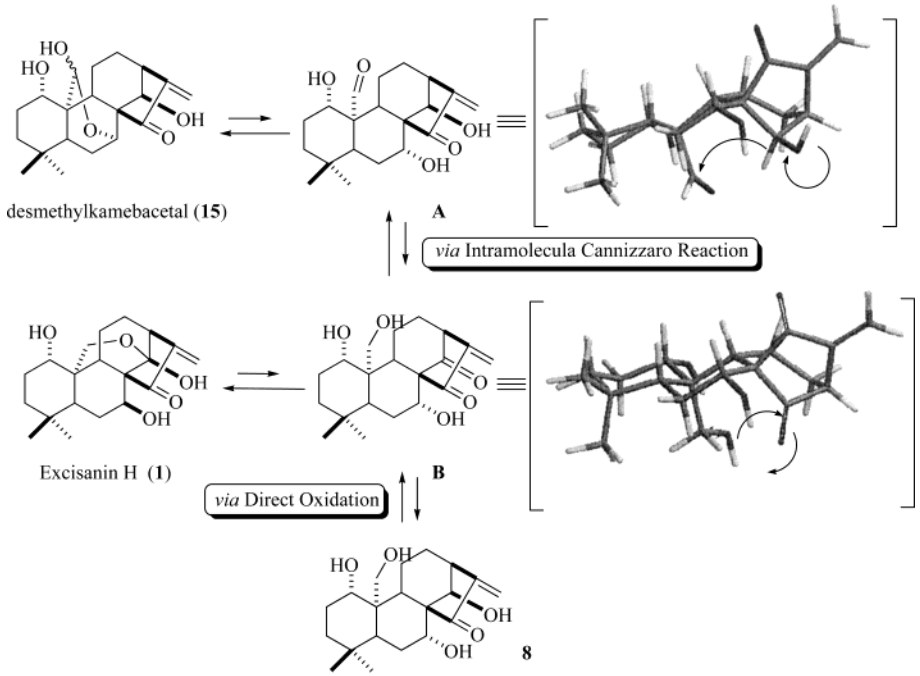
first *ent*-kaurene diterpenoid that has an epoxy linkage between C-14 and C-20. To elucidate the absolute configuration of excisanin H (**1**), kamebakaurin (**8**) was oxidized with pyridium dichromate (PDC) in dry $CHCl_3$ to give **1** in 0.84% yield, along with compound **13**[16] (0.70%) and compound **14**[17] (15.3%) (Scheme 1). The optical rotation ($[\alpha]_D$ −87.9° (*c* 0.07, MeOH)) of natural **1** was equivalent to that ($[\alpha]_D$ −90.7° (*c* 0.04, MeOH)) of the synthetic one. Hence, the absolute configuration of **1** was determined to be 1*S*, 7*R*, 8*S*, 9*S*, 10*R*, 13*S*, and 14*R*. The physical and spectral data of compounds **13** and **14** were identical to those reported for megathyrin A[16] and the known δ-lactone,[17] respectively.

Compound **2** was obtained as a colorless powder whose molecular formula was established as $C_{20}H_{30}O_5$ from its HRESIMS. The IR absorption spectrum implied the presence of hydroxy (3241 cm^{-1}) and α,β-unsaturated carbonyl (1728 and 1650 cm^{-1}) groups. ^{1}H, ^{13}C NMR, and DEPT spectra revealed 20 carbon signals assignable to three sp^3 and two sp^2 quaternary carbons, six sp^3 methines, one sp^2 and six sp^3 methylenes, and two methyl groups (Tables 1 and 2). The ^{1}H NMR and ^{13}C NMR spectral data of **2** were very similar to those of rabdoserrin B (**11**),[12] except for the lack of one hydroxy group, suggesting that **2** and **11** possessed the same basic structure. The remarkable upfield shifts of the signals for C-1 [δ_C 34.6 (t)] and C-2 [δ_C 18.7

Scheme 1. Oxidation of Kamebakaurin (**8**) with PDC



Scheme 2. Plausible Biogenetic Pathway of Excisanin H (**1**)



(t)] in **2** were observed. A detailed comparison of the NMR data including HMBC and NOESY spectral data of **2** and **11** revealed that **2** differed from **11** in that the hydroxy group at C-1 in **11** was missing in **2**, and thus **2** was 1-deoxyrabdoserrin B (Figures 2 and 3, Supporting Information). The structure of **2** was thus elucidated as 7α,12α,14*β*,20-tetrahydroxy-*ent*-kaur-16-en-15-one and given a trivial name, excisanin I.

Compound **3** was obtained as a colorless powder whose molecular formula was established as $C_{20}H_{30}O_5$ from its HRESIMS. The IR absorption spectrum implied the presence of hydroxy (3346 cm^{-1}) and α,*β*-unsaturated carbonyl (1718 and 1646 cm^{-1}) groups. On the basis of ^1H NMR, ^{13}C NMR, and DEPT spectral studies, **3** was shown to have 20 carbons ascribable to three sp^3 and two sp^2 quaternary carbons, five sp^3 methines, one sp^2 and eight sp^3 methylenes, and one methyl groups (Tables 1 and 2). The ^1H NMR and ^{13}C NMR spectral data of **3** were very similar to those of excisanin C[8] (7α,14α,18-trihydroxy-*ent*-kaur-16-en-15-one) except for one additional hydroxy group, suggesting that they possessed the same basic structure. The remarkable downfield shifts of the signals for C-20 [δ_C 60.8 (t)], C-1 [δ_C 34.9 (t)], and C-10 [δ_C 43.2 (s)] in **3** were observed. A detailed comparison of the NMR data of these two compounds revealed that **3** possessed one additional hydroxy group at C-20, which was missing in excisanin C.[8] Cross-peaks were observed between C-20 (δ_C 60.8) and H-5 (δ_H 1.96) and H-9 (δ_H 1.72), respectively, in the HMBC spectrum of **3** (Figure 2, Supporting Information). A NOESY spectrum showed that the stereochemistry of **3** was as shown in Figure 3 (Supporting Information). Accordingly, **3** was elucidated to be 7α,14*β*,18,20-tetrahydroxy-*ent*-kaur-16-en-15-one and given the trivial name excisanin J.

Compound **4** was obtained as a colorless powder whose molecular formula was established as $C_{20}H_{30}O_5$ from its HRESIMS. The IR absorption spectrum implied the presence of hydroxy (3333 cm^{-1}) and α,*β*-unsaturated carbonyl (1719 and 1647 cm^{-1}) groups. On the basis of ^1H NMR, ^{13}C NMR, and DEPT studies, **4** was shown to have 20 carbons assignable to three sp^3 and two sp^2 quaternary carbons, six sp^3 methines, one sp^2 and six sp^3 methylenes, and two methyl groups (Tables 1 and 2). The ^1H NMR and ^{13}C NMR spectral data of **4** were very similar to those of **7** (excisanin D)[10] except for the lack of an acetoxy group. Slight upfield shifts of the signals for C-18 [δ_C 71.0 (t)] and C-4 [δ_C 37.9 (s)] in **4** were observed. Comparison of the NMR data of these two compounds revealed that **4** and **7** were different in that C-18 of **4** had a hydroxy group whereas that of **7** was an acetate group. On the basis of 2D NMR spectral data, HMQC, HMBC, and NOESY (Figure 3, Supporting Information), **4** was shown to be 1α,7α,14*β*,18-tetrahydroxy-*ent*-kaur-16-en-15-one and was given the trivial name excisanin K.

We consider that excisanin H (**1**) is probably produced biogenetically from demethylkamebacetal (**15**) via an intramolecular Cannizzaro reaction or from kamebakaurin **8** via a direct oxidation of the 14-hydroxy group, followed by cyclization (Scheme 2). Kamebacetal B has been isolated from *R. excisa*,[7] suggesting the presence of **15** as a real metabolite.[17] On the other hand, Takeda et al. reported an intramolecular Cannizzaro reaction of *ent*-kaurene diterpenoid derivatives under mild basic conditions.[18] Of over 500 *ent*-kaurene diterpenoids isolated from the genus *Rabdosia*, only excisanin H (**1**) possesses the unique 14,20-epoxy type *ent*-kaurene skeleton.

Thus, we have isolated four new *ent*-kaurene diterpenoids, excisanins H (**1**), I (**2**), J (**3**), and K (**4**), from *R. excisa*.

Table 3. Cytotoxic Activities of Compounds **1**−**14** on P388 Murine Leukemia Cells

compound	IC_{50} (μg/mL)
1	0.96
2	0.87
3	0.92
4	0.92
5	1.11
6	0.63
7	0.72
8	0.82
9	0.69
10	1.06
11	1.01
12	0.58
13	0.77
14	0.77

Of them, excisanin H (**1**) is a unique *ent*-kaurene having a 14,20-epoxy skeleton. The IC_{50} values of **1**−**14** evaluated by an in vitro cytotoxic activity assay using P388 murine leukemia cells are shown in Table 3. All compounds tested showed significant cytotoxic activity (IC_{50} 0.72−1.11 μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO DIP-360 digital polarimeter, mass spectra on a VG AutoSpec E spectrometer, and IR spectra on a JASCO FT/IR 620 spectrophotometer. NMR spectra were obtained on Bruker DRX-500 and AM-400 spectrometers at 300 K. The chemical shifts (δ) are reported in ppm relative to the residual C_5D_4HN resonance at 7.21 ppm for ^{1}H NMR and to the C_5D_5N resonance at 135.4 ppm for ^{13}C NMR. Preparative HPLC was carried out on a JASCO PU-880 equipped with a UV-970 UV detector (λ 230 nm) and a Phenomenex Luna-ODS column (15 μm, 21.2 × 250 mm), by using a mixed solvent system of MeOH−H_2O (40:60, v/v) or of MeCN−H_2O (22/78, v/v) at a flow rate of 8 mL/min.

Plant Material. The leaves of *Rabdosia excisa* were collected in Jing Yu County, Jinlin Province of China, in August 2001. The botanical identification was made by Prof. Hang Xie, Department of Biology, Northeast Normal University, China. A voucher specimen has been deposited in the herbarium of Tokyo University of Pharmacy and Life Science (02JCP11).

Extraction and Isolation. The air-dried aerial parts of the *R. excisa* (3 kg) were extracted with hot H_2O (25 L × 3). The combined H_2O extract was passed through an AB-8 resin column (Nankai Co. Ltd., 3 kg) and washed with H_2O and EtOH, successively. The EtOH washings were evaporated in vacuo to give a residue (74 g), which was partitioned between H_2O and AcOEt, and then the H_2O layer was treated with *n*-BuOH. The *n*-BuOH phase (3 L) was evaporated in vacuo to give a residue (16 g), which was applied to HP-20 resin column chromatography (Mitsubishi Chemical Co. Ltd., 150 g) eluting with a H_2O−MeOH gradient system. The fraction eluted with H_2O−MeOH (40:60, v/v) was concentrated in vacuo to give a residue (5.1 g), which was applied to a silica gel column (silica gel 60N, Kanto Chemical Co. Ltd., 220 g, 63−210 μm) and eluted with $CHCl_3$ containing an increasing amount of MeOH to yield fractions I−IV. Fraction II (1.0 g) was further purified by repeated ODS-HPLC using eluting systems MeOH−H_2O (40:60, v/v) and MeCN−H_2O (22:78, v/v) to afford **1** (2.0 mg), **2** (2.7 mg), **6** (38.0 mg), **7** (3.0 mg), **8** (600.0 mg), **9** (68.0 mg), **11** (16.0 mg), and **12** (1.0 mg). Fraction III (0.72 g) was further purified by repeated ODS-HPLC using MeOH−H_2O (30:70, v/v) and MeCN−H_2O (15:85, v/v), to afford **3** (2.8 mg), **4** (4.0 mg), **5** (206.0 mg), and **10** (71.0 mg).

Compound 1 (Excisanin H): colorless powder (MeOH); mp 206−207 °C; $[\alpha]_D$ −87.9° (*c* 0.07, MeOH); IR (film) ν_{max} 3432, 2927, 1731, 1647, 1457, 1255, 1107, 1027 cm^{-1}; ^{1}H NMR and ^{13}C NMR, Tables 1 and 2; HRESIMS *m/z* 371.1830 (calcd for $C_{20}H_{28}O_5Na$ 371.1834).

Compound 2 (Excisanin I): colorless powder (MeOH); mp 142−144 °C; $[\alpha]_D$ −110.3° (*c* 0.06, MeOH); IR (film) ν_{max} 3241, 2923, 1728, 1650, 1456, 1363, 1256, 1094 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, Tables 1 and 2; HRESIMS *m/z* 373.1985 (calcd for $C_{20}H_{30}O_5Na$ 373.1991).

Compound 3 (Excisanin J): colorless powder (MeOH); mp 116−118 °C; $[\alpha]_D$ −125.0° (*c* 0.17, MeOH); IR (film) ν_{max} 3346, 2927, 1718, 1646, 1457, 1258, 1092 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, Tables 1 and 2; HRESIMS *m/z* 373.1964 (calcd for $C_{20}H_{30}O_5Na$ 373.1991).

Compound 4 (Excissanin K): colorless powder (MeOH); mp 128−129 °C; $[\alpha]_D$ −109.2° (c 0.23, MeOH); IR (film) ν_{max} 3333, 2933, 1719, 1647, 1456, 1363, 1256, 1029 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, Table 1 and Table 2; HRESIMS *m/z* 373.1980 (calcd for $C_{20}H_{30}O_5Na$ 373.1991).

Oxidation of 8 to 1. PDC (235 mg, 0.625 mmol) was added to a solution of **8** (50 mg, 0.143 mmol) in dry $CHCl_3$ (15 mL) at 0 °C under an Ar atmosphere. After stirring the mixture at room temperature for 1 h, it was filtered through a short column of Celite 545, which was washed with $CHCl_3$−acetone (1:1). The filtrate was evaporated in vacuo to give a residue, which was subjected repeatedly to ODS-HPLC using MeCN−H_2O (20:80−40:60, v/v) to give compounds **1** (0.42 mg, 0.84%), **13**[16] (0.35 mg, 0.70%), and **14**[17] (7.64 mg, 15.3%). The physical and spectral data of synthetic **1** ($[\alpha]_D$ −87.9° (*c* 0.07, MeOH)) were identical with those of **1** isolated from the plant ($[\alpha]_D$ −90.7° (*c* 0.037, MeOH)).

Acknowledgment. This study was supported in part by Japan-China Sasakawa Medicinal Fellowship (to M.-Y.G.). This work was supported by a Grant for Private Universities Provided by the Ministry of Education, Culture, Sports, Science and Technology and the Promotion and Mutual Aid Corporation for Private Schools of Japan (to K.T.) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (to Y.A.).

Supporting Information Available: Figures 2 and 3, selected NOESY and HMBC data for compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Itokawa, H.; Takeya, K.; Hitotsuyanagi, Y.; Morita, H. *Yakugaku Zasshi* **1999**, *119*, 529−583.
(2) Takeda, Y.; Otsuka, H. Recent advances in the chemistry of diterpenoids from *Rabdosia* species. In *Studies in Natural Products Chemistry;* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1995; Vol. 15, pp 111−185.
(3) Fujita, E.; Nagao, Y.; Node, M.; Kaneko, K.; Nakazawa, S.; Kuroda, H. *Experientia* **1976**, *32*, 203−206.
(4) Fujita, T.; Takeda, Y.; Shingu, T. *J. Chem. Soc., Chem. Commun.* **1980**, 205−7.
(5) Castrillo, A.; De las Heras, B.; Hortelano, S.; Rodriguez, B.; Villar, A.; Bosca, L. *J. Biol. Chem.* **2001**, *276*, 15854−15860.
(6) Nagashima, F.; Kondoh, M.; Kawase, M.; Simizu, S.; Osada, H.; Fujii, M.; Watanabe, Y.; Sato, M.; Asakawa, Y. *Planta Med.* **2003**, *69*, 377−379.
(7) Sun, H.-D.; Sun, X.-C.; Lin, Z.-W.; Xu, Y.-L.; Minami, Y.; Marunaka, T.; Fujita, T. *Chem. Lett.* **1981**, 753−756.
(8) Chang, R.; Kim, D.; U, Z.; Shen, X.; Chen, Y.; Sun, H. *Phytochemistry* **1992**, *31*, 342−343.
(9) Wang, Y.-H.; Chen, Y.-Z.; Kim, D.-S.; Sun, H.-D. *J. Nat. Prod.* **1997**, *60*, 1161−1162.
(10) Wang, Y.; Chen, Y.; Kim, D.; Sun, H. *Phytochemistry* **1997**, *45*, 1015−1017.
(11) Zhang, H.; Sun, H. *Phytochemistry* **1989**, *28*, 3405−2409.
(12) Wang, Z. Q.; Node, M.; Xu, F.; Hu, H.; Fuji, K. *Chem. Pharm. Bull.* **1989**, *37*, 2683−2686.
(13) Wang, X.; Wang, Z.; Dong, J.; Wang, X. *Zhiwu Xuebao* **1986**, *28*, 292−298.
(14) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C34; Platon for windows software.
(15) The 3D model was minimized by MM calculations with MMFF force field using Spartan 02 for Windows software (Wavefunction, Inc., Irvine, CA).
(16) Sun, H.-D.; Lin, Z.-W.; Niu, F.-D.; Lin, L.-Z.; Chai, H.; Pezzuto, J. M.; Cordell, G. A. *J. Nat. Prod.* **1994**, *57*, 1424−1429.
(17) Takeda, Y.; Ichihara, T.; Takaishi, Y.; Fujita, T.; Shingu, T.; Kusano, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2403−2409.
(18) Takeda, Y.; Ichihara, T.; Takaishi, Y.; Fujita, T. *Chem. Pharm. Bull.* **1988**, *36*, 1886−1889.

NP030357R