Abietane Diterpenoids from the Barks of *Cryptomeria japonica*

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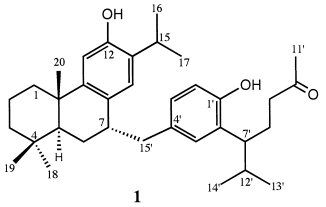
Received November 1, 2005; accepted December 12, 2005

From the bark of *Cryptomeria japonica* were isolated sugikurojins I (1) and J (2), and an abietane derivative (3) was obtained for the first time as a natural product. These structures were elucidated primarily through extensive NMR experiments. Sugikurojin I (1) has a unique skeleton incorporating an abietane diterpene and a 1,10-secocadinane sesquiterpene. Sugikurojin J (2) is a peroxyester of hydroxyabietane diterpene and isopimarane acid diterpene. Compound 3 was *p*-quinone acid, which occurred by cleavage between C-7 and C-8 of sugiol; it was deduced to [4′-isopropyl-1(*S*),3,3-trimethyl-3′,6′-dioxo-bicyclohexyl-1′,4′-dien-2(*R*)-yl]-acetic acid. Also obtained in this investigation were three known diterpenes (4—6).

Key words *Cryptomeria japonica*; bark; abietane; seco-abietane; isopimarane; seco-cadinane

The Japanese cedar, *Cryptomeria japonica* D. DON. (Taxodiaceae), is one of the important forestry resources of Japan with a hinoki. It is planted in large quantities, and is widely used as a building material, thus a large quantity of its bark is meanwhile ejected in the production process of obtaining raw wood logs. Cedar bark was formerly used roof material thatching, for the exterior siding of houses, and in fencing but now is mainly burned without being used. Furthermore, in recent years incineration disposal itself has become difficult as Japan tightens controls on waste disposal. Therefore, we conducted a study of the ingredients of cedar bark aimed at determining new uses for the bark. We previously investigated an acetone extract from this bark and reported three new abietane diterpenes, sugikurojins D, E, and F, and two new abietanes incorporated with cadinanes, sugikurojins G and H, along with nine known compounds.[1)] In this paper, we report our continued study of cedar bark and the isolation, purification, and structural elucidation of compound **1** having a unique skeleton which incorporates an abietane diterpene, and a 1,10-seco-cadinane, a peroxyester (**2**) composed of diterpene peroxy acid and diterpene alcohol, and an abietane derivative (**3**) obtained for the first time as a natural product.

The air-dried bark of *C. japonica* was milled and exhaustively extracted with acetone at room temperature for 6 weeks. The acetone extract was fractionated into seven fractions by column chromatography (silica gel), followed by repeated separation of their four portions by chromatography over silica gel and reversed-phase silica gel furnished sugikurojins I (**1**), J (**2**), and an abietane derivative (**3**), along with 8β-hydroxy-9(11),13-abietadiene-12-one (**4**),[2)] 6α-hydroxysuginyl methyl ether (**5**),[3)] and 16-pyhllocladanol (**6**).[4)]



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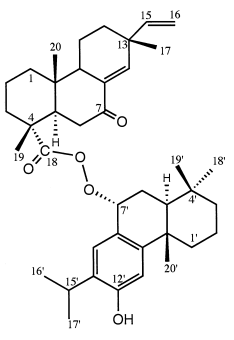

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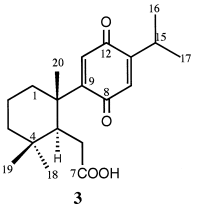

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Sugikurojin I (**1**), $[\alpha]_D^{25}$ +16.8° was obtained as a colorless solid and was considered to have the molecular formula $C_{35}H_{50}O_3$ based on the positive HR-EI-MS of the molecular ion at *m*/*z* 518.3743 $[M]^+$, suggesting the presence of eleven degrees of uasaturation. The IR spectrum of **1** showed absorption bands at 3400 (OH), 1700 (C=O), 1610 and 1500 cm^{-1} (aromatic). The presence of the aromatic group was supported by the UV data (λ_{max} 226, 282 nm). The 35 carbon signals observed in the ^{13}C-NMR spectrum (Table 1) and distortionless enhancement by polarization transfer (DEPT) experiment showed the presence of an acetyl group at δ 210.7 (s) and 30.1 (q); 12 olefinic carbons at δ 152.3 (s), 151.0 (s) 148.7 (s), 133.6 (s), 131.6 (s), 130.8 (s), 129.0 (s), 128.8 (d), 127.6 (d), 127.3 (d), 115.8 (d), and 110.8 (d), suggesting that **1** contains four rings. The EI-MS displayed fragment ions at *m*/*z* 286 (35%), 285 (100%), 233 (2%), 229 (7%), 201 (17%), and 189 (25%). The HR-EI-MS exhibited fragment ions at *m*/*z* 285 (observed 285.2210; calcd. 285.2218 for $C_{20}H_{29}O$) and 233 (observed 233.1559; calcd. 233.1542 for $C_{15}H_{21}O_2$), indicating that compound **1** is composed of a diterpene constituent-1 [$C_{20}H_{30}O-H$] and a sesquiterpene constituent-2 [$C_{15}H_{22}O-H$] (Fig. 1). Its NMR data (Table 1) showed that the diterpene constituent-1 was ferruginol. We also observed an isopropyl group at δ 0.73, 0.91 (d, J=7.0 Hz), and 1.87 (m), an allylic methylene at δ 2.91 (2H, dd, J=11.0, 3.5 Hz), and an acetyl group at δ 2.08 (s), in addition to signals attributed to a 1,2,4-substituted benzene ring at δ 6.75 (d, J=8.0 Hz), 6.87 (d, J=2.0 Hz), and 6.98 (dd, J=8.0, 2.0 Hz), suggesting constituent-2 to be a 1,10-seco-calamenene[5,6)] or a 1,10-seco-cadinane-type sesquiterpene derived from cadinane-like α-cadinol,[7)] T-cadinol,[8)] cubenol,[8)] and epi-cubenol.[9,10)] The gross structure of **1** was determined by analysis of the NMR data, including heteronuclear multiquantum coherence (HMQC), heteronuclear multiple bond connectivity (HMBC), and rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments. The HMBC experiment (Fig. 1) of **1** showed long-range couplings from H-2′ to C-1′, C-3′, C-4′, and C-6′; H-3′ to C-1′, C-2′, C-4′, and C-5′; from H-5′ to C-1′, C-3′, and C-6′; and from H_2-15′ to C-3′, C-4′ and C-5′. Thus, the aromatic moiety due to the sesquiterpenoid of **1** was deduced to be 1-

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Table 1. NMR Data on Compounds **1**—**3** in $CDCl_3$

C No.	**1**		**2**		**3**	
	^{13}C δ (mult.)	^{1}H δ (mult. J in Hz)	^{13}C δ (mult.)	^{1}H δ (mult. J in Hz)	^{13}C δ (mult.)	^{1}H δ (mult. J in Hz)
1	38.7 (t)	H-α 1.36 (ddd, 13.0, 13.0, 4.0) H-β 2.17 (ddd, 13.0, 4.0, 4.0)	37.8 (t)	H-α 1.02 (m) H-β 1.74 (br d, 13.0)	36.4 (t)	H-α 2.45 (ddd, 13.0, 13.0, 3.5) H-β 1.27 (m)
2	19.3 (t)	H-α 1.58 (m) H-β 1.72 (m)	17.7 (t)	H-α, -β 1.48 (2H, m)	18.6 (t)	H-α 1.49 (m) H-β 1.63 (br dd, 13.0, 13.0)
3	41.7 (t)	H-α 1.22 (ddd, 13.0, 13.0, 4.0) H-β 1.48 (br d, 13.0)	36.8 (t)	H-α 1.38 (m) H-β 1.50 (m)	40.6 (t)	H-α, -β 1.43—1.58 (2H, m)
4	33.3 (s)		46.1 (s)		34.0 (s)	
5	45.0 (d)	1.42 (dd, 13.0, 2.0)	43.8 (d)	2.05 (dd, 14.5, 6.0)	44.1 (d)	2.77 (dd, 7.0, 4.5)
6	21.7 (t)	H-α, -β 1.60 (2H, m)	38.6 (t)	H-α, -β 2.17—2.20 (2H, m)	32.3 (t)	2.26 (dd, 16.5, 4.5) 2.04 (dd, 16.5, 7.0)
7	39.7 (d)	3.08 (m)	199.0 (s)		179.9 (s)	
8	130.8 (s)		135.0 (s)		187.8 (s)	
9	148.7 (s)		51,2 (d)	*ca.* 1.94 (m)	154.4 (s)	
10	37.9 (s)		35.4 (s)		43.1 (s)	
11	110.8 (d)	6.63 (s)	18.9 (t)	H-α 1.70 (m) H-β 1.33 (m)	134.5 (d)	6.52 (s)
12	151.0 (s)		34.1 (t)	H-α 1.62 (m) H-β 1.50 (m)	187.8 (s)	
13	131.6 (s)		38.7 (s)		152.4 (s)	
14	127.3 (d)	6.97 (s)	144.5 (d)	6.70 (d, 1.5)	133.2 (d)	6.41 (d, 1.0)
15	26.9 (d)	3.12 (sept, 7.0)	146.5 (d)	5.82 (dd, 17.5, 10.5)	26.1 (d)	2.91 (dsept, 7.0, 1.0)
16	22.7 (q)	1.25 (d, 7.0)	111.7 (t)	5.01 (dd, 17.5, 1.5) 4.99 (dd, 10.5, 1.5)	21.5 (q)	1.10 (d, 7.0)
17	22.6 (q)	1.27 (d, 7.0)	25.9 (q)	1.08 (s)	20.9 (q)	1.10 (d, 7.0)
18	33.7 (q)	0.86 (s)	175.3 (s)		33.2 (q)	0.92 (s)
19	21.5 (q)	0.82 (s)	16.3 (q)	1.04 (s)	22.7 (q)	0.99 (s)
20	24.9 (q)	1.12 (s)	14.2 (q)	0.79 (s)	20.0 (q)	1.18 (s)
1′	152.3 (s)		40.8 (t)	H-α 1.82 (ddd, 12.5, 12.5, 7.0)		
2′	115.8 (d)	6.75 (d, 8.0)		H-β 1.94 (m)		
			18.6 (t)	H-α, -β 1.60 (2H, m)		
3′	127.6 (d)	6.98 (dd, 8.0, 2.0)				
			42.8 (t)	H-α 1.28 (m)		
				H-β 1.48 (m)		
4′	133.6 (s)		34.5 (s)			
5′	128.8 (d)	6.87 (d, 2.0)	43.4 (d)	1.64 (dd, 12.0, 3.0)		
6′	129.0 (s)		32.9 (t)	H-α 1.82 (ddd, 12.5, 3.0, 3.0)		
				H-β 2.24 (ddd, 12.5, 12.0, 3.0)		
7′	44.2 (d)	2.62 (m)	94.1 (d)	H-β 6.25 (dd, 3.0, 3.0)		
8′	26.8 (t)	2.13 (m) 1.72 (m)	146.0 (s)			
9′	41.8 (t)	2.28 (m) 2.22 (m)	141.8 (s)			
10′	210.7 (s)		40.6 (s)			
11′	30.1 (q)	2.08 (s)	113.6 (d)	6.71 (s)		
12′	33.0 (d)	1.87 (m)	148.8 (s)			
13′	21.2 (q)	0.73 (d, 7.0)	132.4 (s)			
14′	20.9 (q)	0.91 (d, 7.0)	121.4 (d)	6.66 (s)		
15′	43.9 (t)	2.91 (2H, dd, 11.0, 3.5)	26.8 (d)	3.01 (sept, 7.0)		
16′			22.4 (q)	1.20 (d, 7.0)		
17′			22.4 (q)	1.19 (d, 7.0)		
18′			33.4 (q)	0.88 (s)		
19′			23.1 (q)	0.95 (s)		
20′			21.4 (q)	1.31 (s)		

hydroxy-4-methylene-6-substituted benzene with a partial structure **a**. Additional HMBC correlations between H-13′ (14′) and C-7′ and C-12′, H-8′ and C-9, H-9′ and C-8, and H_3-11′ and C-9′ and -10′ established the connectivity between partial structure **b** and an acetyl group. Furthermore, an NOE (Fig. 2) was detected between H-5′ and H-7′ confirming the structure of the sesquiterpenoid moiety of **1**. Namely, constituent-2 was deduced to be 5-(2-hydroxy-5-methyl-phenyl)-6-methyl- heptan-2-one. The HMBC correlations between H_2-15′ and C-6, -7, and -8 and the NOEs between H-7 and H_2-15′ confirmed that the structure of **1** included ferruginol and 5-(2-hydroxy-5-methyl-phenyl)-6-methyl-heptan-2-one joined together by C atoms, which connected C-7 to C-15′. The α-substituted group at C-7 could be assigned from the NOEs between H_2-6 and H-7, H-5 and H_2-15′ (Fig. 2). Hence, the structure of sugikurojin I was established to be that shown as **1**. The biosynthetic pathways of sugikutojin I (**1**) are proposed as shown in Chart 1. Aldol condensation of 6-ketosugiol (**A**)[11] occurred in *Cryptomeria japonica* and 15-oxo-α-cadinol (**B**)[12] occurred in *Chamae-*

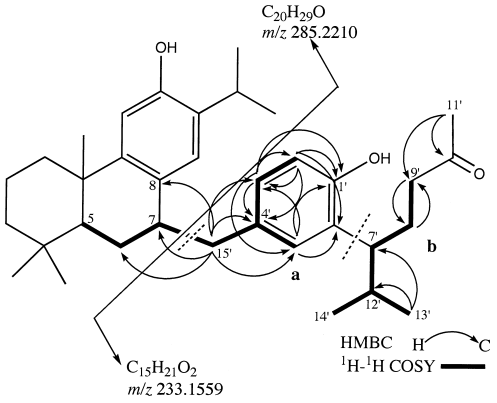

Fig. 1. Some Key HMBC and HR-EI-MS for Compound **1**

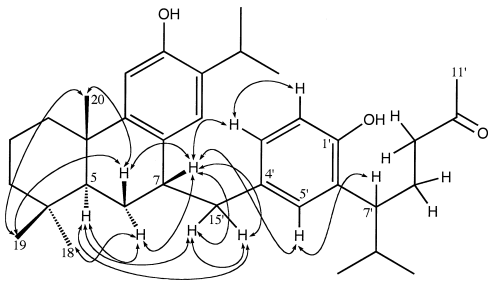

Fig. 2. Some Key ROESY Correlations for Compound **1**

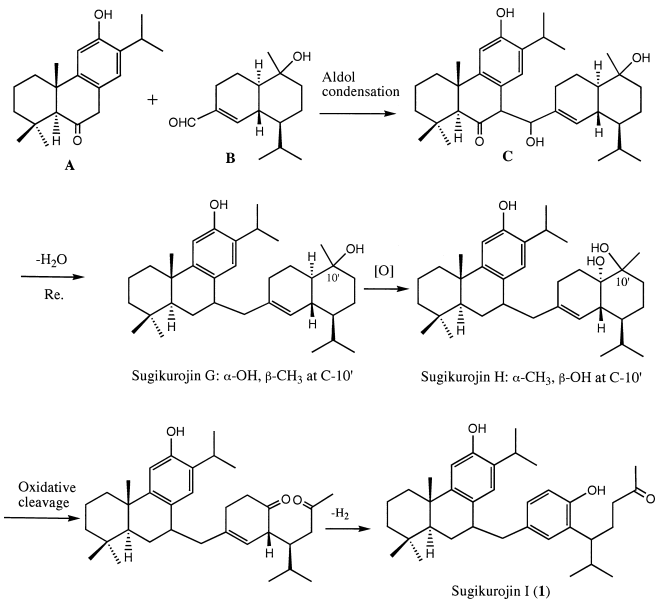

Chart 1. Proposed Biogenetic Pathway of **1** *via* Sugikurojins G and H Isolated from *Cryptomeria japonica*

cyparis obutusa var. *formosana* belong to Cupressaceae, which is very near to Taxodiaceae in systematics, would lead to the formation of intermediate (**C**). Dehydration and the subsequent reduction of **C** would afford sugikurojin G, which was oxygenated to give sugikurojin H and sugikurojin I.

Sugikurojin J (**2**), $[\alpha]_D^{25}$ −3.4° an amorphous solid, had the molecular formula $C_{40}H_{56}O_5$ based on HR-EI-MS, with absorption maxima at 3400, 1740, 1685 cm^{-1} due to hydroxy and carbonyl groups in the IR spectrum. The EI-MS of **2** displayed fragment ions at *m/z* 318 (11%), 316 (11%), 301 (14%), 300 (48%), 285 (7%), 271 (9%), 229 (9%), 203 (20%), and 189 (100%). The HR-EI-MS exhibited fragment ions at *m/z* 318 (observed 318.2180; calcd. 318.2195 for $C_{20}H_{30}O_3$), 316 (observed 316.4360; calcd. 316.4345 for $C_{20}H_{28}O_3$), 301 (observed 301.2150; calcd. 301.2150 for $C_{20}H_{29}O_2$), 300 (observed 300.2078; calcd. 300.2089 for $C_{20}H_{28}O_2$), 285 (observed 285.2220; calcd. 285.2218 for $C_{20}H_{29}O$), and 271 (observed 271.2050; calcd. 271.2062 for $C_{19}H_{27}O$), indicating that compound **2** is a peroxyester dimer of pimarane carboxylic acid (constituent-1) (Fig. 3) and a hydroxyferruginol (constituent-2) (Fig. 4). The HMBC experiments (Fig. 5) of **2** showed long-range couplings from H_3-19 to an ester carbonyl group at δ 175.3, and from H_2-6 and H-14 to a carbonyl group at δ 199.0. Additional HMBC correlations between H_3-17 to an olefinic carbon at δ 144.5 and a vinyl carbon at δ 146.5, established that **2** had a double bond at C-8 (14) and a vinyl group at C-13. Thus, the diterpene peroxy carboxylic acid moiety of **2** was 7-oxo-8(14)-en-peroxy-18 or -19 oic acid of isopimarane or pimarane. The NOEs between H-11β/H_3-17 and H_3-20, and H_3-19/H_3-20 enabled the relative configuration of the three methyl groups to be determined as β (Fig. 5). Furthermore, from cedar, many isopimarane diterpenes[13,14] have been obtained, but no pimarane diterpenes had been reported. From the aforementioned data, the diterpene acyloxy moiety of sugikurojin J was 7-oxo-8(14),15-isopimaradien peroxy-18-oate.[15] While, in the NMR spectra due to a hydroxyferruginol moiety of **2**, a carbinol proton was assigned to H-7′ by the ^{1}H–^{1}H COSY (H-5′–H-7′) and by the HMBC correlation of H-6′ to C-5′

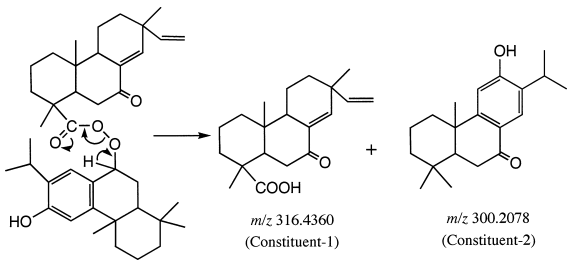

Fig. 3. Some Key HR-EI-MS for Compound **2**

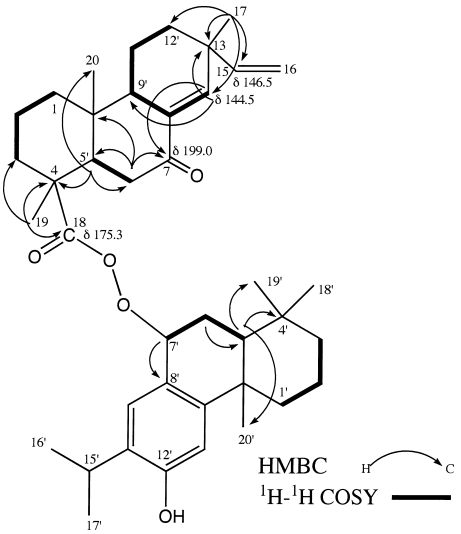

Fig. 4. Some Key HMBC for Compound **2**

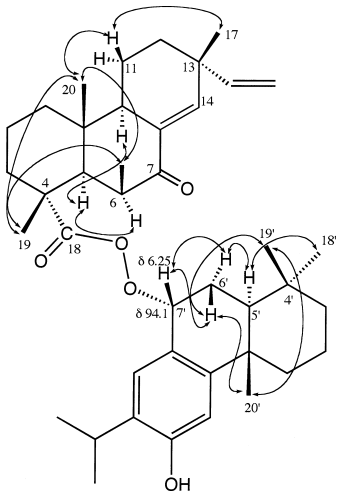

Fig. 5. Some Key ROESY Correlations for Compound **2**

and H-7′ to C-8′. The *α-O* function at C-7′ could be assigned from the observed coupling constants for H-7′ at δ 6.25 (dd, J=3.5, 3.5 Hz) and the NOEs between H-7′/H-6′α and -6′β. Unusual downfield shifts of H-7′ at δ 6.25 and C-7′ at δ 94.1 indicated that **2** possesses a peroxy ester group at C-7′ instead of the usual ester function. Thus the structure of sugikurojin J was established as to be **2**.

Compound **3**, $[\alpha]_D^{25}$ +8.1° was obtained as a pale yellow solid. The molecular formula $C_{20}H_{28}O_4$, which was determined based on HR-EI-MS, suggested the presence of seven degrees of unsaturation. The IR spectrum of **3** showed absorption bands at 3300, 1710 and 1640 cm^{-1}. Further, the presence of two carbonyl groups at δ 187.8 (s) and two double bonds at δ 154.4 (s), 152.4 (s), 134.5 (d), and 133.2 (d) in the ^{13}C-NMR spectrum (Table 1) and the UV maximum at 258 (log ε 3.9), 312 (log ε 2.9), and 335 nm (log ε 2.8), indicated that **3** should include a di-substituted *p*-quinone moiety.[16] The HMBC experiment revealed long-range couplings from H-5 to C-3, -4, -6, -7, -9, -10, -18, -19, and -20, and from H_2-6 to C-4, -5, and -7, establishing the connectivity between the A ring and carboxymethyl group. Additional HMBC correlations between H-11 and C-8, -9, -10, -12, and -13, and between H-14 and C-8, -9, -12, -13, -15, and -16 revealed the connectivity among the A ring, *p*-benzoquinone moiety, and isopropyl group. Further, the NOEs between H-5/H_3-18, H_2-6/H_3-19 and -20 established the β-orientation of the carboxymethyl group. Hence, the structure of **3** was determined to be [(*rel*-1*S*,2*R*)-(4′-isopropyl-1,3,3-trimethyl-3′,6′-dioxo-bicyclohexyl-1′,4′-dien-2-yl)-acetic acid, which has been reported as a synthetic intermediate of coleon U from ferruginol methyl ether or abietatriene-7-one. However, the physicochemical data were not reported for synthetic **3**.[17—19] Compound **3** is an initial example of a natural product.

Experimental

General Experimental Procedures Optical rotations were recorded on a JASCO DIP-140 digital polarimeter. IR spectra were measured on a JASCO FT/IR-5300 instrument. UV spectra were recorded with a Shimadzu UV-6000 spectrophotometer. NMR spectra were recorded on a Varian UNITY 600 spectrometer. The chemical shifts are given in δ (ppm) in $CDCl_3$ solution using tetramethylsilane (TMS) as an internal standard. NMR experiments included ^{1}H–^{1}H COSY, HMQC, HMBC, and ROESY. Coupling constants (*J* values) are given in Hertz (Hz). HR-EI-MS were measured on a JEOL JMS-700 MS station. Kieselgel 60 (230—400 mesh, Merck) was used for column chromatography, and silica gel 60F-254 (Merck) for TLC. HPLC was carried out on a JASCO-PU 1580 instrument using a COSMOSIL C18 P-MS (4.6×150, 20×250 mm) column.

Plant Material The air-dried bark of the black heartwood of *C. japonica* trees, aged 70 to 80 years, from Kaifu, Tokushima, was collected in October 2003. A voucher specimen (3002) is deposited in the Herbarium of the Department of Pharmacognosy, Tokushima Bunri University, Tokushima, Japan.

Extraction and Isolation The powdered bark (2.0 kg) of *C. japonica* was exhaustively extracted with acetone at room temperature for 4 weeks. The acetone extract was evaporated under a vacuum to yield a brown residue (70 g), which was subjected to silica gel column chromatography with hexane–acetone (30 : 1→0 : 10) to afford fractions 1—7. Fraction 2 (6.6 g) was passed through silica gel with hexane–acetone (5 : 1→1 : 3) and purified by preparative HPLC (80% MeOH, flow rate 8 ml/min), and to yield 6α-hydroxysugiyl methyl ether (**5**, 14 mg). Fraction 6 (8.96 g) was passed through silica gel with hexane–acetone (2 : 1→1 : 5) and purified by preparative HPLC (75% MeOH, flow rate 8 ml/min) to afford sugikurojin J (**2**, 4 mg) and 8β-hydroxy-9(11),13-abietadiene-12-one (**4**, 7 mg), and 16-phyllocladanol (**6**, 420 mg). Fraction 7 (3.5 g) was passed through silica gel with hexane–acetone (1 : 1—1 : 10) and purified by preparative HPLC (70% MeOH, flow rate 8 ml/min) to afford sugikurojin I (**1**, 22 mg) and [4′-isopropyl-1(*S*),3,3-trimethyl-3′,6′-dioxo-bicyclohexyl-1′,4′-dien-2(*R*)-yl]-acetic acid (**3**, 14 mg).

Sugikurojin I (**1**): A colorless solid; $[\alpha]_D^{25}$ +16.8° (c=0.77, $CHCl_3$); FT-IR (dry film) 3400, 1700, 1610, 1500 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 226 (4.04), 282 (3.72); ^{1}H- and ^{13}C-NMR, see Table 1; selected HMBC, see Fig. 1; selected ROESY, see Fig. 2; EI-MS: 518 (M^+, 6%), 286 (35%), 285 (100%), 233 (2%), 229 (7%), 201 (17%), 189 (25%); CI-MS *m/z*: 519 $(M+H)^+$; positive FAB-MS *m/z*: 541 $(M+Na)^+$, 557 $(M+K)^+$; HR-EI-MS *m/z*: 518.3743 (Calcd for $C_{35}H_{50}O_3$, 518.3760).

Sugikurojin J (**2**): A colorless solid; $[\alpha]_D^{25}$ −3.4° (c=0.51, $CHCl_3$); FT-IR (dry film) 3400, 1740, 1685, 1590 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 205 (4.60), 248 (3.50), 280 (3.60); ^{1}H- and ^{13}C-NMR, see Table 1; selected HMBC, see Fig. 4; selected ROESY, see Fig. 5. EI-MS: 616 (M^+, 15%), 318 (11%), 316 (11%), 301 (14%), 300 (48%), 285 (7%), 271 (9%), 229 (85%), 203 (20%), 189 (100%); CI-MS *m/z*: 617 $(M+H)^+$; HR-EI-MS *m/z*: 616.4138 (Calcd for $C_{40}H_{56}O_5$, 616.4128).

Compound (**3**): A colorless solid; $[\alpha]_D^{25}$ +8.1° (c=1.38, $CHCl_3$); FT-IR (dry film) 3300, 1710, 1640 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 258 (3.90), 312 (2.90), 335 (2.80); ^{1}H- and ^{13}C-NMR, see Table 1; selected HMBC (H/C) 5/4, 5/6, 5/7, 5/9, 5/10, 5/18, 5/19, 5/20, 6/4, 6/5, 6/7, 6/10, 11/8, 11/9, 11/10, 11/12, 11/13, 14/8, 14/9, 14/12, 14/13, 14/15, 15/12, 15/13, 15/14, 15/16, 15/17, 20/1, 20/5, 20/9, 20/10. Selected ROESY data, 2β/19, 2β/20, 3α/5α, 3α/18, 5α/18, 5α/7α, 6a/18, 6a/20, 6b/18, 6b/20, 14/15, 14/16, 14/17, 16/15. 16/17, 18/19; EI-MS: 332 (100%), 317 (28%), 272 (69%), 248 (36%), 217 (46%), 203 (84%), 179 (47%), 163 (79%); CI-MS *m/z*: 333 $(M+H)^+$; HR-EI-MS *m/z*: 332.1993 (Calcd for $C_{20}H_{28}O_4$, 332.1987) ; HR-CI-MS *m/z*: 333.2065 (Calcd for $C_{20}H_{28}O_4$+H, 333.2065).

Acknowledgment This work was supported by Japan Science and Technology Corporation.

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