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Synthesis and Structure Determination of Cryptomanhydride, an Uncommon Natural Terpenic Anhydride

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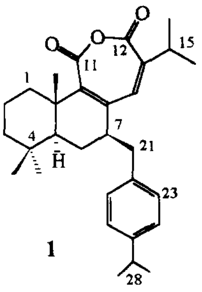
***Abstract*:** A novel terpenic anhydride, namely cryptomanhydride, was isolated from the leaves of *Cryptomeria japonica*; its absolute configuration was determined by a partial synthesis from hinokiol.

The Japanese cedar, *Cryptomeria japonica* D. Don., is a widely distributed conifer called 'sugi' in Japanese.[1] From the ethyl acetate-soluble part of the acetone extract of the leaves, we isolated a novel terpenic anhydride **1**, namely cryptomanhydride.[2] This compound has a unique skeleton incorporating an abietane diterpene and a *p*-cymene monoterpene. This is the first report of such uncommon terpenic anhydride in nature.[3]



1

Oil, $[\alpha]_D^{30}$ +370° (MeOH; *c* 0.4)

TLC (Merck silica gel 60F, CH_2Cl_2/hexane = 1:2) R_f 0.37

UV (MeOH) : 255 nm (ε 8500), 236 nm (ε 7000),
219 nm (ε 15200), 217 nm (ε 15000)

CD (MeOH) : $[\theta]_{266}$ +61900, $[\theta]_{236}$ +38300,
$[\theta]_{223}$ +32300, $[\theta]_{205}$ +22000

HRMS for $C_{30}H_{40}O_3$ requires 448.2979; found 448.2977

The structure of **1** was determined by analysis of its spectral properties. The parent peak appearing at *m*/*z* 448.298 indicated the molecular formula $C_{30}H_{40}O_3$. The anhydride moiety was inferred from the IR absorptions at 1775 and 1733 cm^{-1} as well as from the ^{13}C signals at δ 161.6 (C-11) and 162.0 (C-12). The ^1H and ^{13}C resonances (Table 1) were assigned by assistance of the C-H COSY and HMBC spectra. Four aromatic protons on the *para*-disubstituted phenyl ring occurred at δ 7.04 (*d*, *J* = 8 Hz) and 7.15 (*d*, *J* = 8 Hz). The olefinic proton (H-14) occurring at a low field δ 6.16 (*s*) was attributable to the conjugated system. The cymenyl group is on equatorial position as the axial H-7 at δ 2.60 exhibited a large coupling constant $J_{6\beta,7}$ = 13 Hz.

Compound **1** exhibited a positive Cotton effect in the CD spectrum. Its absolute configuration was determined by a partial synthesis from hinokiol (**3**), a constituent of known configuration isolated from the same plant *C. japonica*. The phenol moiety of hinokiol was selectively methylated (Scheme I). The product **4**

Table 1. ^{1}H and ^{13}C NMR spectral data of 1 ($CDCl_3$ solution, δ value in ppm, *J* values in Hz)*

	C	H		C	H
1	36.4	1.23 (*ddd*, *J* 3.5, 12, 12.5)	14	133.1	6.16 (*s*)
		1.83 (*ddd*, *J* 3, 5, 12.5)	15	32.2	2.82 (*sept*, *J* 7)
2	18.6	1.50 (*m*), 1.64 (*m*)	16	20.6	1.07 (*d*, *J* 7)
3	41.5	1.20 (*m*)	17	22.1	1.09 (*d*, *J* 7)
		1.46 (*ddd*, *J* 3, 4.5, 12.5)	18	33.4	0.89 (*s*)
4	33.2		19	21.4	0.81 (*s*)
5	46.1	1.19 (*dd*, *J* 4,12)	20	20.2	1.33 (*s*)
6	21.7	1.58 (*ddd*, *J* 2.5, 4, 12)	21	40.3	2.44 (*dd*, *J* 9, 13)
		1.60 (*ddd*, *J* 12, 12, 13)			2.67 (*dd*, *J* 3.5, 13)
7	41.5	2.60 (*dddd*, *J* 2.5, 3.5, 9, 13)	22	136.9	
8	138.2		23,27	129.1	7.04 (*d*, *J* 8)
9	142.9		24,26	126.6	7.15 (*d*, *J* 8)
10	39.3		25	147.1	
11	161.6		28	33.7	2.83 (*sept*, *J* 7)
12	162.0		29,30	24.0	1.22 (*d*, *J* 7)
13	141.9				

* The assignments of ^{1}H (300 MHz) and ^{13}C (75 MHz) signals were confirmed by the H-H COSY, C-H COSY, HMBC and *J*-resolved spectra as well as by the nOe experiments.

was treated with PBr_3 to give the corresponding bromides **5** (two 3-epimers), which were subsequently reduced with Bu_3SnH/Et_3B to afford ferruginol methyl ether (**6**). The (5*S*,10*S*)-configuration of ferruginol methyl ether has been determined.[4] The optical rotation of **6**, $[\alpha]^{20}_D$ +37.5° ($CHCl_3$; *c* 3.3), was in agreement with the reported value, $[\alpha]_D$ +35.9° ($CHCl_3$).

Direct introduction of cymenyl group at C-7 of compound **6** by means of metalation-alkylation may be complicated by side-products derived from *ortho*-metalations. Wittig reaction of ketone **7** with the phosphorus ylide, prepared from 7-bromocymene, Ph_3P and BuLi, failed. Cymenyl substituent was successfully introduced by a three-step sequence: (i) oxidation of **6** with pyridinium chlorochromate, giving ketone **7** (sugiol methyl ether, 95%) along with a small amount of enone **8**; (ii) addition of the Grignard reagent prepared from 7-bromocymene onto ketone **7**, giving **9** as a single product (90%)[5]; and (iii) catalytic hydrogenation of **9** in the presence of hydrochloric acid, giving **11** (two 7-epimers). Alternatively, **9** was dehydrated to give alkene **10**, which underwent hydrogenation to yield **11**. By analysis of the ^{1}H NMR spectrum, compound **11** consisted of two 7-epimers (3:2) inseparable by HPLC.

According to the reported method,[6] the isomeric mixture of **11** was treated with *m*-chloroperbenzoic acid (3 equiv) in darkness for 5 days to give cryptomanhydride **1** (15%) having (5*S*,7*R*,10*S*)-configuration and the 7*S*-epimer **2**[7] (10%) along with recovery of **11** (30%).

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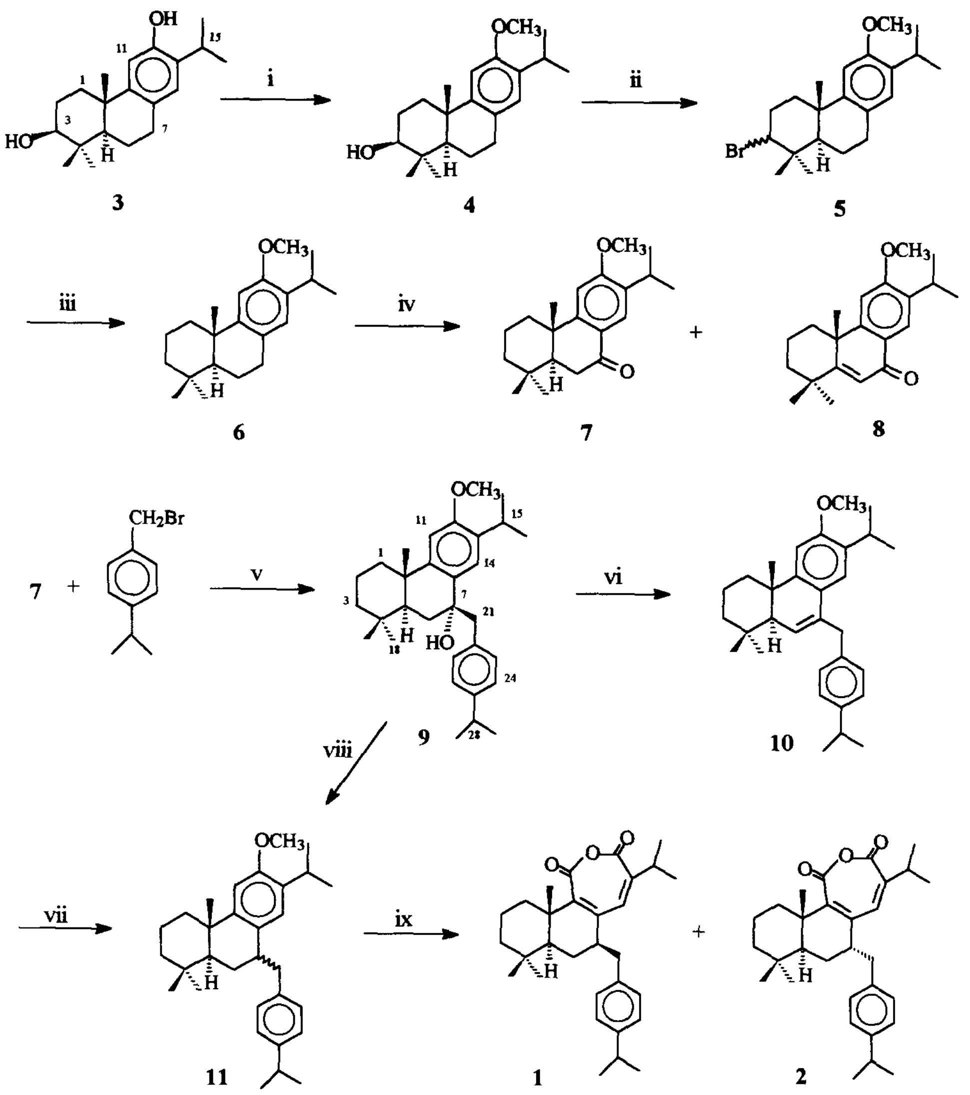
Scheme I



Reagents and conditions: (i) CH_3I, Me_2CO, K_2CO_3, H_2O, reflux, 16 h; 95%. (ii) PBr_3, Et_2O, 20 °C, 16 h; then 5% $NaHCO_3$; 96%. (iii) Et_3B, benzene, Bu_3SnH, 20 °C, 6 h; then Et_3N; 96%. (iv) PCC, benzene, reflux, 16 h; 95%. (v) Mg, THF, 0 °C to 20 °C, 2 h; then NH_4Cl, H_2O; 90%. (vi) p-$CH_3C_6H_4SO_3H$, benzene, reflux, 16 h; 100%. (vii) 10% Pd/C, MeOH, H_2, 20 °C, 16 h; 100%. (viii) 10% Pd/C, MeOH, H_2, 10% HCl, 20 °C, 16 h; 95%. (ix) MCPBA, CH_2Cl_2, 20 °C, 5 days; **1** (15%), **2** (10%).

REFERENCES AND NOTES

1. Gan, W. S. (1958) *Manual of Medicinal Plants in Taiwan.* Nat. Res. Inst. Chin. Med.: Taipei, **1958**, Vol. 1, 54-55. A voucher specimen is deposited in our laboratory. We previously isolated a series of sesquiterpenes, diterpenes (abietane-, kaurane- and labdane-types) and triterpenes from this plant, see Su, W.-C.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1993**, *34*, 779; *ibid.* **1994**, *35*, 1279; *ibid.* **1994**, *37*, 1109.
2. The system name of **1** is (6*R*,7a*S*,11a*S*)-4-isopropyl-6-(4-isopropylphenyl)methyl-6,7,7a,8,9,10,11,11a-octahydro-8,8,11a-trimethylnaphth[1,2-*c*]oxepin-1,3-dione. We use the numbering of abietanes for **1** in this manuscript.
3. Three norabietane anhydrides have been found in the Chinese drug Danshen, *Salvia multiorrhiza.* see Chang, H. M.; Choang, T. F.; Chui, K. Y.; Hon, P. M.; Lee, C. M.; Mak, T. C. W.; Wong, H. N. C. *J. Chem. Res. (S)* **1990**, 114.
4. Matsumoto, T.; Usui, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 212.
5. Compound 9 ($C_{31}H_{44}O_2$), $[\alpha]^{20}_{D}$ -31.5° ($CHCl_3$; *c* 3.3), was homogenous in the ^1H and ^{13}C NMR spectra. The 7-hydroxyl group of 9 was considered to be on the axial position as evidenced by (i) irradiation of H-21 causing a 7% NOE of H-14; (ii) an intense fragment $[M-H_2O]^+$ at *m/z* 430 occurring in the mass spectrum of 9 without appearance of the parent peak.
6. Bendall, J. G.; Cambie, R. C.; Grimsdale, A. G.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1992**, *45*, 1063.
7. Compound 2: Oil, $[\alpha]^{15}_{D}$ +110° ($CDCl_3$; *c* 0.3). TLC (CH_2Cl_2/ hexane = 1:2) *Rf* 0.32. IR υ^{neat}_{max} cm^{-1} : 1775, 1734, 1507, 1455. UV λ^{MeOH}_{max} nm (ε) : 252 (8400), 236 (7600), 219 (15400). ^1H NMR ($CDCl_3$, 300 MHz) : δ 0.80 (*s*, H-18), 0.82 (*s*, H-19), 1.00 (*d*, *J* = 7 Hz, H-16), 1.02 (*d*, *J* = 7 Hz, H-17), 1.11 (*s*, H-20), 1.22 (*d*, *J* = 7 Hz, H-29, 30), 2.64 (*m*, H-7), 2.72 (*dd*, *J* = 7, 13.5 Hz, H-21), 2.82 (*sept*, *J* = 7 Hz, H-28), 2.87 (*sept*, *J* = 7 Hz, H-15), 2.90 (*dd*, *J* = 6, 13.5 Hz, H-21), 6.34 (*s*, H-14), 7.06 (*d*, *J* = 8 Hz, H-23, 27), 7.15 (*d*, *J* = 8 Hz, H-24, 26). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 18.5 (C-2), 21.0 (C-20), 21.2 (C-16, 17), 21.6 (C-19), 24.0 (C-29, 30), 25.6 (C-6), 32.4 (C-15), 32.8 (C-18), 33.3 (C-4), 33.7 (C-28), 36.9 (C-1), 38.2 (C-10), 40.4 (C-7), 40.7 (C-21), 41.5 (C-3), 49.7 (C-5), 126.7 (C-24, 26), 128.9 (C-23, 27), 130.7 (C-14), 136.3 (C-8), 136.8 (C-22), 141.7 (C-13), 143.4 (C-9), 147.2 (C-25), 161.4 (C-11), 162.3 (C-12). EIMS (70eV) *m/z* (rel. int.) 448 $[M]^+$ (5), 315 (25), 271 (10), 243 (4), 133 (100), 117 (18), 105 (17). HRMS for $C_{30}H_{40}O_3$ requires 448.2979; found 448.2975.

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