New Phenolic Tricyclic Diterpenoids from Rhizomes of *Isodon hispida* (BENTH.) HARA

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Three new phenolic tricyclic diterpenoids, including two sempervirane diterpenoids, hispidanols A and B (**1** and **2**, resp.), and one totarane diterpenoid, totara-8,11,13-triene-13 → 16-hemiacetal (**3**), along with 14 known compounds, **4**–**17**, were isolated from the AcOEt-soluble fraction of the 70%-acetone extract of rhizomes of *Isodon hispida*. Their structures were elucidated based on the analyses of extensive spectroscopic data and physicochemical properties.

Introduction. – Plants from the genus *Isodon* (*Rabdosia*) were often used as folk medicine in China, and a large number of reports on the studies of *Isodon* plants has been published during the past several decades, and more than 600 new diterpenoids, mainly of the *ent*-kaurane-type, with antibacterial, cytotoxic, *etc.*, activities, were reported [1][2]. Since the aerial parts (stems and leaves) of most *Isodon* plants are the primary officinal parts used for medicinal purposes, it is not surprising that almost all studies have been focused on aerial parts of the plants so far [3][4]. However, some *Isodon* species like *Isodon hispida* have swollen rhizomes, and these underground parts of *Isodon* plants often have medicinal records and utilizations as well [4]. In this study, the rhizomes of *I. hispida* were collected from Dali, China, and their major chemical constituents were intensively investigated. As a result, three new phenolic tricyclic diterpenoids, **1**–**3**, together with 14 known compounds, **4**–**17**, were isolated from the AcOEt-soluble portion of the 70%-acetone extract of rhizomes of *I. hispida*. The new compounds were identified as hispidanols A and B (**1** and **2**, resp.) and totara-8,11,13-triene-13 → 16-hemiacetal (**3**; *Fig. 1*). Their structures were elucidated based on the analyses of extensive spectroscopic data and their physicochemical properties. Herein, we report the isolation and structure elucidation of the new tricyclic diterpenoids.

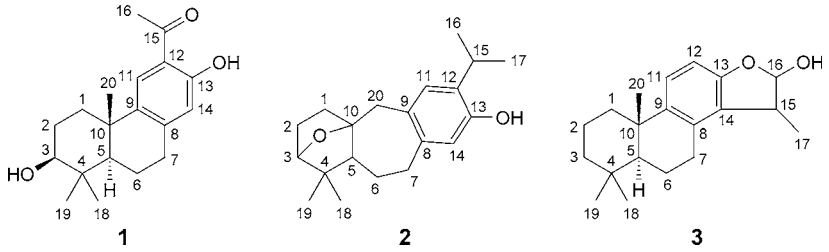

Fig. 1. *Compounds* **1**–**3**, *isolated from* Isodon hispida

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Results and Discussion. – The 70%-acetone extract of *I. hispida* was concentrated and suspended in H_2O, and then partitioned successively with AcOEt and BuOH. The AcOEt-soluble portion was subjected to column chromatography (silica gel, *RP-18*, and *Sephadex LH-20*) to give three new phenolic tricyclic diterpenoids, **1**–**3**, along with 14 known compounds, **4**–**17**.

Compound **1** was isolated as colorless needles from acetone. The molecular formula was established as $C_{19}H_{26}O_3$ (seven degrees of unsaturation) according to its EI-MS (*m*/*z* 302 (M^+)) and NMR data (*Tables 1* and *2*). The IR spectrum indicated the presence of OH groups (3431 cm^{-1}), a conjugated C=O group (1643 cm^{-1}), and an aromatic ring (1617, 1490, and 887 cm^{-1}). The UV spectrum (λ_{max} 216.6, 264.4, and 334.2 nm) also evidenced the presence of a conjugated benzene ring. The ^{1}H-NMR spectrum (*Table 1*) of **1** displayed signals of four Me groups at δ(H) 2.59, 1.18, 1.07, and 0.90 (4*s*), of two aromatic H-atoms at 7.56 and 6.64 (2*s*), of one O-bearing CH group at 3.32 (*dd*, *J* = 11.4, 4.6, H–C(3)), and of a H-bonded OH group at 11.96 (*s*, HO–C(13)). Moreover, analysis of the ^{13}C-NMR spectrum with the aid of DEPT experiments revealed the presence of 19 C-atoms (*Table 2*) including three sp^3 Me (δ(C) 28.1, 25.2, and 15.3), one Ac (203.9 (C=O) and 26.5 (Me)), two sp^3 CH (78.5 and 49.6), four sp^3 CH_2 groups (37.2, 30.9, 27.8, and 18.4), and six olefinic C-atoms (including two sp^2 CH groups at 126.5 and 117.3 and four sp^2 C_q-atoms at 159.5, 145.8, 140.9, and 118.1). Since the structural units mentioned above accounted only for five degrees of unsaturation, **1** should possess two alkane rings. The correlations in the ^{1}H,^{1}H-COSY spectrum suggested two segments, CH_2(1)CH_2(2)CH(3) and CH(5)CH_2(6)CH_2(7) (shown in bold in *Fig. 2*). Long-range correlations of the H-atom with a signal at δ(H) 3.32 (*dd*, *J* = 11.4, 4.6, H–C(3)) with C(1), C(5), C(18), and C(19) in the HMBC spectrum indicated that a OH group was linked to C(3). HMBCs of Me(18,19) with C(3–5) and of Me(20) with C(1), C(5), and C(9) suggested that three Me groups were connected to C(4) and C(10) (*Fig. 2*), respectively. Furthermore, the HMBCs Me(16)/C(12,15) and HO–C(13)/C(12–14) indicated that an Ac group was located at C(12) and a phenolic OH group at C(13) (*Fig. 2*). The spatial structure of **1** was confirmed by the key ROESY correlations H–C(3)/Me(18) and H–C(5); Me(18)/H–C(5); and Me(19)/Me(20), as well as by comparing the specific-rotation data ($[\alpha]_D^{18} = +72.4$ (*c* = 0.09, MeOH)) of **1** with those of known sempervirane-type diterpenoids [5–7]. Thus, **1** was identified as 3β-hydroxy-15-oxo-17-norsempervirol and named hispidanol A.

Compound **2** was obtained as colorless needles from petroleum ether (PE)/acetone. Its molecular formula, $C_{20}H_{28}O_2$ (seven degrees of unsaturation), was deduced from its EI-MS (*m*/*z* 300 (M^+)) and NMR data (*Tables 1* and *2*). The IR spectrum indicated the presence of a OH group (3240 cm^{-1}) and an aromatic ring (3020, 1618, and 1518 cm^{-1}). The UV spectrum (λ_{max} 206.4 and 283.0 nm) also evidenced the presence of an aromatic ring. ^{1}H- and ^{13}C-NMR data (*Tables 1* and *2*) of **2** were highly similar to those of 1β-hydroxypisiferanol [8]. The correlations from the ^{1}H,^{1}H-COSY spectrum suggested three segments, CH_2(1)CH_2(2)CH(3), CH(5)CH_2(6)CH_2(7), and Me(16)CH(15)Me(17) (shown in bold in *Fig. 2*). Long-range correlations of the H-atom with the signal at δ(H) 3.81 (*d*, *J* = 5.2, H–C(3)) with C(1), C(5), and C(10), and of the H-atoms of Me(18,19) with C(3–5) in the HMBC spectrum revealed that C(3) was connected with C(10) *via* an O-bridge, and that the two sp^3 Me groups were located at C(4) (*Fig. 2*). Furthermore, the HMBCs H–C(15)/C(11–13) and

Table 1. *^{1}H-NMR Data* (400 MHz, in $CDCl_3$) *of* **1**–**3**. δ in ppm, J in Hz.

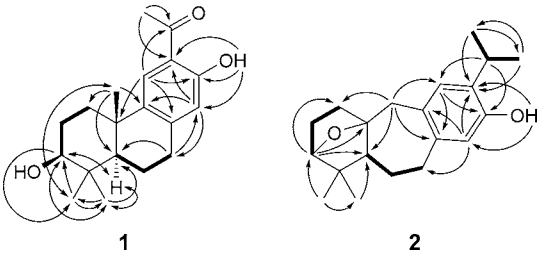
Position	**1**	**2**	**3**
1	2.31 (*dt*, *J* = 13.0, 3.3), 1.57 (*td*, *J* = 13.0, 3.9)	1.49 (*td*, *J* = 11.8, 4.1), 1.32–1.37 (*m*)	2.25 (br. *d*, *J* = 12.0), 1.40 (*dd*, *J* = 13.2, 3.9)
2	1.84 (overlapped), 1.80 (overlapped)	1.79–1.84 (*m*), 1.67 (overlapped)	1.72 (overlapped), 1.60 (overlapped)
3	3.32 (*dd*, *J* = 11.4, 4.6)	3.81 (*d*, *J* = 5.2)	1.48 (br. *d*, *J* = 13.1), 1.25 (overlapped)
5	1.28 (*dd*, *J* = 12.3, 2.3)	1.27 (*dd*, *J* = 13.5, 2.2)	1.35 (br. *d*, *J* = 12.2)
6	1.90 (overlapped), 1.76 (overlapped)	1.86 (overlapped), 1.66 (overlapped)	1.87–1.92 (*m*), 1.68 (overlapped)
7	2.99 (*dd*, *J* = 17.9, 6.2), 2.84 (*dd*, *J* = 10.8, 7.8)	3.12 (*dd*, *J* = 14.1, 7.1), 2.70 (*dd*, *J* = 18.3, 9.4)	2.73–2.85 (*m*)
11	7.56 (*s*)	6.87 (*s*)	7.10 (*d*, *J* = 8.4)
12			6.67 (*d*, *J* = 8.4)
14	6.64 (*s*)	6.46 (*s*)	
15		3.10–3.16 (*m*)	3.17 (*q*, *J* = 7.2)
16	2.59 (*s*)	1.25 (*d*, *J* = 6.9)	5.55 (*s*)
17		1.23 (*d*, *J* = 6.9)	1.24 (*d*, *J* = 7.2)
18	1.07 (*s*)	0.98 (*s*)	0.96 (*s*)
19	0.90 (*s*)	0.98 (*s*)	0.93 (*s*)
20	1.18 (*s*)	3.46 (*d*, *J* = 13.1), 2.65 (*d*, *J* = 13.1)	1.15 (*s*)
13-OH	11.96 (*s*)	4.62 (*s*)	

Table 2. *^{13}C-NMR Data* (100 MHz, in $CDCl_3$) *of* **1**–**3**

Position	**1**	**2**	**3**	Position	**1**	**2**	**3**
1	37.2 (*t*)	36.0 (*t*)	39.2 (*t*)	11	126.5 (*d*)	127.9 (*d*)	124.7 (*d*)
2	27.8 (*t*)	23.1 (*t*)	19.4 (*t*)	12	118.1 (*s*)	131.5 (*s*)	107.7 (*d*)
3	78.5 (*d*)	86.1 (*d*)	41.6 (*t*)	13	159.5 (*s*)	151.2 (*s*)	154.3 (*s*)
4	39.0 (*s*)	44.7 (*s*)	33.4 (*s*)	14	117.3 (*d*)	116.8 (*d*)	127.5 (*s*)
5	49.6 (*d*)	53.6 (*d*)	50.7 (*d*)	15	203.9 (*s*)	26.7 (*d*)	44.0 (*d*)
6	18.4 (*t*)	25.5 (*t*)	18.7 (*t*)	16	26.5 (*q*)	22.7 (*q*)	107.2 (*d*)
7	30.9 (*t*)	32.5 (*t*)	27.9 (*t*)	17	–	22.6 (*q*)	16.3 (*q*)
8	145.8 (*s*)	137.5 (*s*)	132.5 (*s*)	18	28.1 (*q*)	25.7 (*q*)	33.4 (*q*)
9	140.9 (*s*)	128.4 (*s*)	143.6 (*s*)	19	15.3 (*q*)	23.7 (*q*)	21.6 (*q*)
10	37.0 (*s*)	89.1 (*s*)	37.7 (*s*)	20	25.2 (*q*)	38.1 (*t*)	25.4 (*q*)

HO–C(13)/C(12–14) indicated that an ^{i}Pr group was located at C(12) and a phenolic OH group at C(13) (*Fig. 2*). Therefore, **2** was deduced as 3,10-epoxy-9(10 → 20)*abeo*-sempervirol and named hispidanol B.

Compound **3** was isolated as colorless oil. The molecular formula was determined as $C_{20}H_{28}O_2$ (seven degrees of unsaturation) based on its EI-MS (*m*/*z* 300 (M^+)) and NMR data (*Tables 1* and *2*). The IR spectrum indicated the presence of an OH group (3425 cm^{-1}) and an aromatic ring (1598, 1472, and 808 cm^{-1}). The UV spectrum (λ_{max} 202.8 and 283.0 nm) also evidenced the presence of a benzene ring. ^{1}H- and ^{13}C-NMR spectra (*Tables 1* and *2*) of **3** were very similar to those of a known



1 **2**

Fig. 2. *Key* $^1H,^1H$*-COSY* (—), *HMB* (H → C), *and ROESY* (H ↔ H) *correlations of* **1** *and* **2**

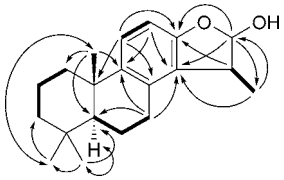


Fig. 3. *Key* $^1H,^1H$*-COSY* (—), *HMB* (H → C), *and ROESY* (H ↔ H) *correlations of* **3**

compound, totarol [9], except for the disappearance of a Me signal and the observation of an O-bearing tertiary C-atom resonance at δ(C) 107.2. The correlations in the $^1H,^1H$-COSY spectrum suggested four segments, $CH_2(1)CH_2(2)CH_2(3)$, $CH(5)CH_2(6)CH_2(7)$, CH(11)CH(12), and CH(15)Me(17) (shown in bold in *Fig. 3*). The HMBCs H–C(15)/C(13), H–C(16)/C(13,14), and Me(17)/C(14,16) indicated that C(16) was linked to C(13) by an O-bridge (*Fig. 3*). Thus, **3** was elucidated as totara-8,11,13-triene-13 → 16-hemiacetal.

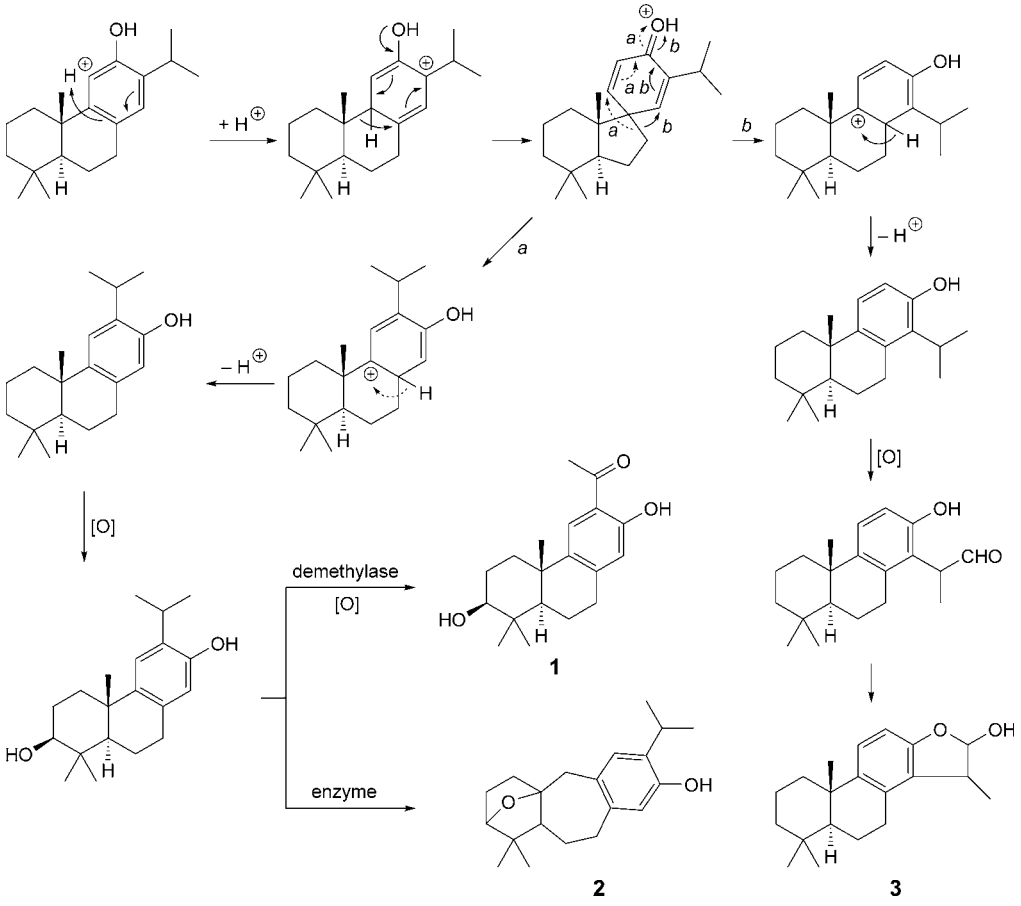
By analyses of their spectral data, as well as by comparison of their physicochemical properties with those reported in the literature, the 14 known compounds were identified as hinokiol (**4**) [10], lambertic acid (**5**) [11], 6,12,15-trihydroxyabieta-5,8,11,13-tetraen-7-one (**6**) [12], taraxasterol (**7**) [13], oleanolic acid (**8**) [14], hyptadienic acid (**9**) [15], ursolic acid (**10**) [14], β-sitosterol (**11**) [16][17], 7β-hydroxysitosterol (**12**) [18], 6-hydroxystigmasta-4,22-dien-3-one (**13**) [19], tetracosyl ferulate (**14**) [20], trilinolein (**15**) [21], 1-monolinolein (**16**) [22], and linoleic acid (**17**) [23].

Hispidanols A and B (**1** and **2**, resp.) are two sempervirane-type diterpenoids which are quite rare in nature. In fact, the first sempervirane diterpenoid, sempervirol, was discovered in *Cupressus sempervirens* in 1967 [24], and its derivatives were isolated from plants of the genera *Salvia* [25][26] and *Podocarpus* [6], as well as from feces of *Trogopterus xanthipes* [27]. Recently, a sempervirane-type diterpenoid, 3β-hydroxysempervirol, was reported from *Isodon lophanthoides* var. *graciliflorus* [5] as well. Totarane diterpenoids represent also a diterpenoid type, which is seldom found in nature. It is very interesting that the three types of phenolic tricyclic diterpenoids, sempervirane, totarane, and abietane, were all found in *I. hispida*. This is actually the first report about these three types of diterpenoids found in a plant together. According to '*Flora Reipublicae Popularis Sinicae*', *Isodon* plants in China can be divided into four sections, and both *I. hispida* and *I. lophanthoides* belong to the same section and series

(ser. *Gerardianae*, sect. *Rabdosia*) [3]. The fact that sempervirane-type diterpenoids were found in both *I. hispida* and *I. lophanthoides* further confirms the plant morphotaxonomy. However, it remains unknown if this kind of diterpenoids can be used as marker for plant morphotaxonomy.

According to the biosynthetic relationship, sempervirane and totarane diterpenoids in *Isodon* plants should originate from abietane-type diterpenoids [28]. A possible biosynthetic pathway for **1**–**3** is proposed in the *Scheme*.

Scheme



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Experimental Part

General. TLC: Precoated silica-gel GF_{254} plates (SiO_2; *Qingdao Marine Chemical Ltd.*, Qingdao, P. R. China). Column chromatography (CC): SiO_2 (200–300 or 300–400 mesh; *Qingdao Marine*

Chemical Ltd.), *RP-18* (*Fuji*, Nagoya, Japan), and *Sephadex LH-20* (*Amersham Biosciences*, SE-Uppsala). Optical rotations: *Jasco P-1020* digital polarimeter (*Jasco*, Tokyo, Japan). UV Spectra: *Shimadzu UV-2401PC* UV/VIS spectrophotometer (*Shimadzu*, Kyoto, Japan); λ_{max} (log ε) in nm. IR Spectra: *Bruker Tensor 27* FT-IR spectrophotometer (*Bruker*, DE-Bremen); KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AM-400*, *DRX-500*, or *Avance III-600* instrument (*Bruker*, CH-Faellanden); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *Waters AutoSpec Premier P776* mass spectrometer (*Waters Co.*, Milford, MA, USA); in *m*/*z*.

Plant Material. Rhizomes of *I. hispida* were collected in October 2010 from Cangshan Mountain, Dali, Yunnan Province, P. R. China. The plant material was identified by Dr. *Chun-Lei Xiang* (Kunming Institute of Botany, Chinese Academy of Sciences) as *I. hispida* (BENTH.) HARA. A voucher specimen (No. 20101003-2b) has been deposited with the College of Pharmacy and Chemistry (research group of Prof. *Bei Jiang*), Dali University, Dali, P. R. China.

Extraction and Isolation. Air-dried rhizomes of *I. hispida* (5.5 kg) were milled and extracted with acetone/H_2O 70:30 (5 × 20 l). Then, the solns. were combined and concentrated under reduced pressure, and the resulting residue (610 g) was suspended in H_2O and partitioned with AcOEt and BuOH, successively. The AcOEt-soluble portion (115 g) was subjected to CC (SiO_2; $CHCl_3$/acetone 1:0 → 0:1) to yield eight fractions, *Frs. 1–8*. *Fr. 1* (42 g) was subsequently separated by CC (SiO_2; PE/AcOEt 100:1 → 2:1) to give ten subfractions, *Frs. 1.1–1.10*. *Fr. 1.1* (6 g) was subjected to repeated CC (SiO_2, PE/AcOEt 50:1, PE/acetone 40:1; then *Sephadex LH-20*, $CHCl_3$/MeOH 1:1), followed by recrystallization to give **4** (20 mg), **11** (4 g), **13** (28.2 mg), **17** (1.5 g), **2** (20 mg), **15** (200 mg), and **3** (20 mg). *Fr. 1.2* (2 g) was subjected to CC (SiO_2, PE/acetone 40:1; *RP-18*, MeOH/H_2O 80:20 → 100:0; *Sephadex LH-20*, $CHCl_3$/MeOH 1:1, successively) to give **7** (50 mg), **8** (4 mg), and **14** (7 mg). *Fr. 1.3* was further purified by CC (SiO_2, PE/AcOEt 30:1; *Sephadex LH-20*, $CHCl_3$/MeOH 1:1) to give **10** (50 mg) and **1** (20 mg). *Fr. 1.4* was further separated by CC (SiO_2, PE/acetone 30:1; *Sephadex LH-20*, $CHCl_3$/MeOH 1:1) to give **12** (10 mg) and **9** (7.6 mg). *Fr. 2* (4 g) was subjected to repeated CC (SiO_2, PE/AcOEt 40:1, $CHCl_3$/MeOH 100:1; *Sephadex LH-20*, $CHCl_3$/MeOH 1:1) to give **5** (56 mg) and **16** (100 mg). *Fr. 3* was purified by CC (*RP-18*; MeOH/H_2O 70:30 → 95:5) to give **6** (3 mg).

Hispidanol A (=*1-[(4bS,7S,8aR)-4b,5,6,7,8,8a,9,10-Octahydro-2,7-dihydroxy-4b,8,8-trimethylphenanthren-3-yl]ethanone*; **1**). Colorless needles (acetone). $[\alpha]_D^{18} = +72.4$ ($c = 0.09$, MeOH). UV (MeOH): 216.6 (4.58), 264.4 (4.40), 334.2 (3.83). IR: 3431, 2964, 2926, 2854, 1643, 1617, 1490, 1368, 1327, 1266, 1212, 1091, 1021, 887. ^1H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 302 (M^+).

Hispidanol B (=*1,2,3,4,5,10,11,11a-Octahydro-1,1-dimethyl-7-(1-methylethyl)-2,4a-epoxy-4a*H*-dibenzo[*a,d*]cyclohepten-8-ol*; **2**). Colorless needles from PE/acetone. $[\alpha]_D^{24} = +16.5$ ($c = 0.27$, $CHCl_3$). UV (MeOH): 206.4 (3.70), 283.0 (2.90). IR (KBr): 3240, 3020, 2959, 1618, 1518, 1424, 944, 713. ^1H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 300 (M^+).

Totara-8,11,13-triene-13 → 16-hemiacetal (=*(5aS,9aS)-2,3,4,5,5a,6,7,8,9,9a-Decahydro-3,6,6,9a-tetramethylphenanthro[2,1-b]furan-2-ol*; **3**). Colorless oil. $[\alpha]_D^{18} = -98.1$ ($c = 0.09$, MeOH). UV (MeOH): 202.8 (4.78), 283.0 (3.65). IR (KBr): 3425, 2924, 2852, 1630, 1598, 1472, 1374, 1245, 1051, 940, 808. ^1H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 300 (M^+).

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