A New *Lycopodium* Alkaloid, Lycoposerramine-R, with a Novel Skeleton and Three New Fawcettimine-Related Alkaloids from *Lycopodium serratum*

by **Kazuaki Katakawa**[a]), **Noriyuki Kogure**[b]), **Mariko Kitajima**[b]), and **Hiromitsu Takayama***[b])

[a]) Department of Pharmaceutical Sciences, International University of Health and Welfare, 2600-1 Kitakanemaru, Ohtawara, Tochigi 324-8501, Japan

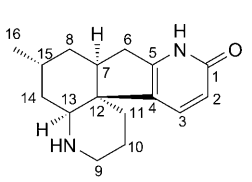
[b]) Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan (phone and fax: +81-43-290-2901; e-mail: htakayam@p.chiba-u.ac.jp)

A new *Lycopodium* alkaloid, lycoposerramine-R, possessing an unusual tetracyclic ring system, was isolated from *Lycopodium serratum*. Its structure as well as those of three new co-existing fawcettimine-related alkaloids were elucidated by means of extensive spectroscopic analysis.

Introduction. – The club moss, *Lycopodium*, is a rich source of complex alkaloids and has attracted the interest of many chemists [1][2]. The discovery of huperzine A [3], a compound that shows potent acetylcholine esterase inhibitory activity, has sparked further investigations of the alkaloidal constituents of *Lycopodium* [4]. As a part of our continuing research of structurally unique and biologically active alkaloids in medicinal plants, we have embarked on a quest for novel *Lycopodium* alkaloids and our efforts have resulted in the discovery of many alkaloids [5]. In this work, we describe the structure elucidation of a new alkaloid, lycoposerramine-R with a new skeleton, and three new fawcettimine-related alkaloids from *Lycopodium serratum*.

Results and Discussion. – An alkaloid fraction was obtained by a conventional procedure from MeOH extract as previously reported [5c]. The alkaloid fraction was separated and purified by repeated chromatography to afford four new alkaloids: lycoposerramines-R and -T (**1** and **2**, resp.), and *N*-methyl and *N*-formyl derivatives of **2** (**3** and **4**, resp.), together with the known alkaloids *N*-demethyl-β-obscurine (**5**) [6], lycodine (**6**) [7], and fawcettimine (**7**) [2c][8].

Lycoposerramine-R (**1**) was obtained as a colorless amorphous solid, and its molecular formula was established as $C_{16}H_{22}N_2O$ by HR-FAB-MS analysis. The UV spectrum indicated the presence of a pyridinone ring system (λ_{max} 322 and 236 nm) and constituent signals in the ^{1}H- and ^{13}C-NMR spectra were the same as those of **5** (*i.e.*, five sp^2 C-atoms, two aromatic H-atoms, one Me group, six sp^3 CH_2 groups, three sp^3 CH groups, and one sp^3 quaternary C-atom). Comparison of 1D-NMR data of **1** and **5** led to the conclusion that these two compounds are not stereoisomers, because almost all aliphatic C-atom chemical shifts differed from each other (*Table 1*). Extensive 2D-NMR analysis allowed to confirm the structure of **1** as indicated in the formula. ^{1}H,^{1}H-COSY and HMQC analyses indicated three fragments, **a**–**c** (*Fig. 1*). HMBC



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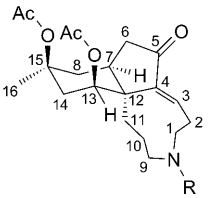

2 R = H[1])
3 R = Me[1])
4 R = CHO[1])

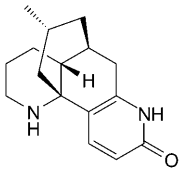

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Table 1. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$, 400 and 100 MHz) *of Compounds* **1** *and* **5**[1]). δ in ppm, J in Hz.

Position	**1**		**5**	
	δ(H)	δ(C)	δ(H)	δ(C)
1		165.8		164.8
2	6.34 (*d*, *J* = 9.2)	115.0	6.47 (*d*, *J* = 9.5)	117.4
3	8.33 (*d*, *J* = 9.2)	143.3	7.61 (*d*, *J* = 9.2)	139.9
4		124.5		117.9
5		150.4		144.8
6a	3.17 – 3.23 (*m*)	36.2[a])	2.95 (*dd*, *J* = 18.9, 7.0)	29.8
6b	2.33 (*d*, *J* = 17.0)		2.46 (*d*, *J* = 18.6)	
7	2.19 (*ddd*, *J*= 6.9, 6.9, 6.9)	42.0	2.03 (br. *d*, *J* = 3.1)	33.2
8a	1.47 – 1.55 (*m*)	36.0[a])	1.72 (br. *d*, *J* = 13.1)	43.1
8b	1.20 – 1.25 (*m*)		1.25 – 1.31 (*m*)	
9a	3.17 – 3.23 (*m*)	47.8	2.79 (br. *d*, *J* = 13.7)	41.4
9b	2.80 (*ddd*, *J* = 11.6, 11.6, 3.0)		2.44 (*ddd*, *J* = 12.7, 12.7, 3.2)	
10a	1.41 – 1.59 (*m*)	22.7	1.58 – 1.61 (*m*)	27.7
10b	1.41 – 1.59 (*m*)		1.47 – 1.53 (*m*)	
11a	1.66 – 1.69 (*m*)	38.1	1.47 – 1.53 (*m*)	25.8
11b	1.39 – 1.50 (*m*)		1.24 – 1.29 (*m*)	
12		49.4	1.47 – 1.53 (*m*)	44.5
13	2.92 (*dd*, *J* = 12.1, 4.8)	57.1		54.6
14a	1.42 – 1.50 (*m*)	34.6	1.47 – 1.53 (*m*)	49.6
14b	1.20 – 1.25 (*m*)		1.06 (*dd*, *J* = 11.7, 11.7)	
15	1.72 – 1.79 (*m*)	25.6	1.38 – 1.46 (*m*)	25.9
16	0.96 (*d*, *J* = 6.9, 3 H)	20.6	0.82 (*d*, *J* = 6.4, 3 H)	21.9

[a]) Assignment may be reversed.

Correlations between the terminal H-atom in fragment **b** (δ(H) 3.17 – 3.23 (H–C(6)[1]))) and two aromatic C-atoms (δ(C) 124.5 (C(4)) and 150.4 (C(5))) indicated that fragment **b** was connected to the pyridinone ring system *via* C(6). HMBC Correlations between the CH group at δ(H) 2.19 (H–C(7)) and two C-atoms (C(4) and a quaternary C-atom at δ(C) 49.4 (C(12))) indicated the presence of a ring system with condensed cyclopentene and pyridinone moieties. An octahydroquinoline

[1]) Arbitrary numbering. For systematic names, see *Exper. Part.*

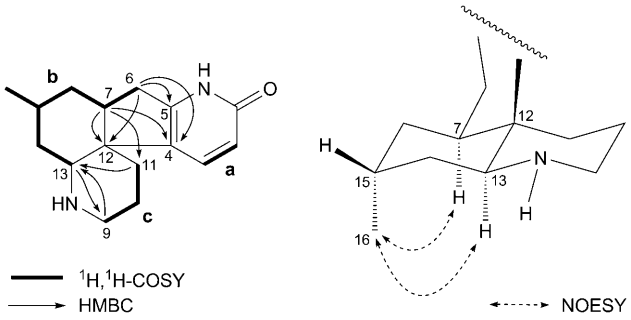


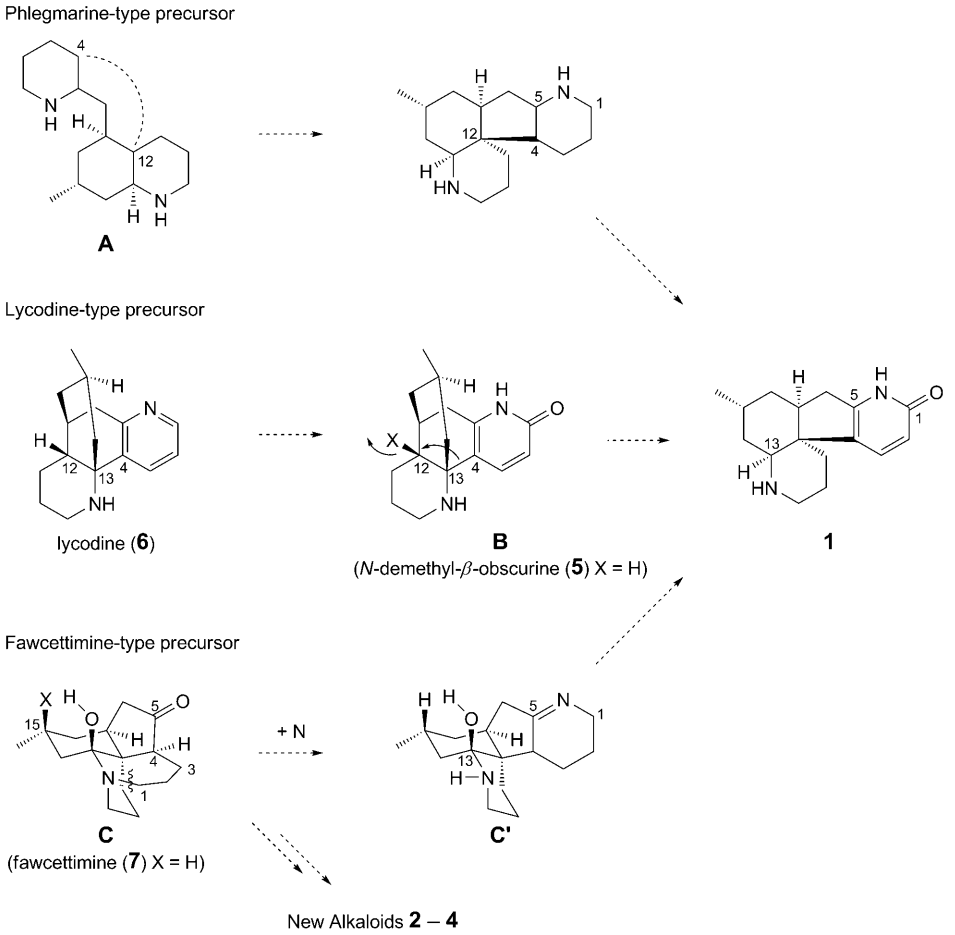
Fig. 1. *2D-NMR Analyses of* **1**[1])

ring system (C(7)–C(8), C(9)–C(15)) was elucidated based on HMBC correlations, particularly H–C(7)/C(11), H–C(9)/C(13), and H–C(11)/C(13). The relative configuration was elucidated based on NOESY correlations between Me H-atoms and two CH groups (H–C(7) and H–C(13)); thus, this Me group and the two CH groups were located on the same face in the cyclohexane ring (C(7,8) and C(12)–C(15)). On the basis of the above data, we proposed lycoposerramine-R as a novel tetracyclic alkaloid with a uniquely rearranged skeleton.

The plausible biogenetic route to **1** is shown in *Scheme 1*. As **1** possesses structural properties related to lycodine- and fawcettimine-type skeletons, it could be generated from at least three precursors, **A**–**C**. In the first route from the phlegmarine-type precursor **A**, C–C bond formation between C(4) and C(12), followed by oxidation of piperidine ring (C(1)–C(5) and an N-atom), would occur to produce **1**. In the second route from lycodine-type precursor **B**, **1** would be formed by direct bond migration to rearrange from a cyclohexene ring system to a cyclopentene ring system. In the third route from fawcettimine-type precursor **C**, bond scission between C(1) and the N-atom and subsequent incorporation of one external N-atom would give the tetracyclic core structure **C′**. Further metabolism including removal of the O-atom on C(13) and formation of pyridinone ring would give **1**.

Lycoposerramine-T (**2**) was isolated as a colorless amorphous solid and its molecular formula was established as $C_{20}H_{29}NO_5$ by HR-FAB-MS analysis. IR absorption bands at 1732 and 1717 cm^{-1} indicated the presence of ketone and ester functionalities. ^{1}H- and ^{13}C-NMR data implied the presence of two AcO groups (δ(H) 1.81 (*s*, 3 H), 1.95 (*s*, 3 H), δ(C) 169.4 and 170.1), one ketone (δ(C) 205.8 (C(5)[1]))), one tri-substituted olefinic group (δ(H) 6.72 (H–C(3)), δ(C) 138.1 (C(3)) and 141.7 (C(4))), and one tertiary Me group (δ(H) 1.52 (*s*, Me(16)), besides eight CH_2 groups, two CH groups, and two quaternary C-atoms. The gross structure of **2** was elucidated by 2D-NMR analysis (*Fig. 2*). Four fragments (**a**–**d**) were analyzed by HSQC and DQF-COSY. Fragments **a** and **b** should be connected through the conjugated enone moiety (C(3)–C(5)) based on HMBC correlations between the olefinic H-atom (H–C(3)) and two C-atoms (olefinic C-atom (141.7, C(4)) and CO C-atom (δ(C) 205.8, C(5))) as well as correlations between a CH_2 group (δ(H) 3.08–3.11 and 2.33–2.36 (CH_2(6))) and the CO C-atom (C(5)). Fragments **b** and **d** should be connected through a quaternary C-atom with a Me substituent (C(15)), based on HMBC

Scheme 1. *Plausible Biogenetic Route to* **1**[1])



correlations between the Me group (δ(H) 1.52 (Me(16))) and three C-atoms (δ(C) 33.7 (C(8)), 32.7 (C(14)), and 78.6 (C(15))). The three fragments **b**–**d** must be connected through a quaternary C-atom (δ(C) 47.2 (C(12))) as determined from HMBC correlations between three H-atoms (δ(H) 2.29–2.36 (H–C(7)), 1.85–1.93 (H_b–C(11)), and 5.40 (H–C(13))), and the quaternary C-atom (C(12)), aside from correlations H–C(7)/C(11), H–C(11)/C(13), and H–C(13)/C(7). The connection of fragment **a** to **c** through the N-atom was inferred from HMBC correlations between N–CH_2 H-atoms (δ(H) 3.03–3.05 and 2.78–2.85 (CH_2(1))) and N–CH_2 C-atom (δ(C) 47.2 (C(9))), and the hexahydro azonine ring system (C(1)–C(4), C(9)–C(12)) was elucidated from HMBC correlations between H–C(3) and C(12). Finally, the locations of two acetoxy functionalities on C(13) and C(15) were determined based on the HMBC between H–C(13) and one AcO CO C-atom (δ(C) 169.4), besides consideration of the chemical shifts at C(13) and C(15) (δ(C) 74.7 (C(13)) and 78.6

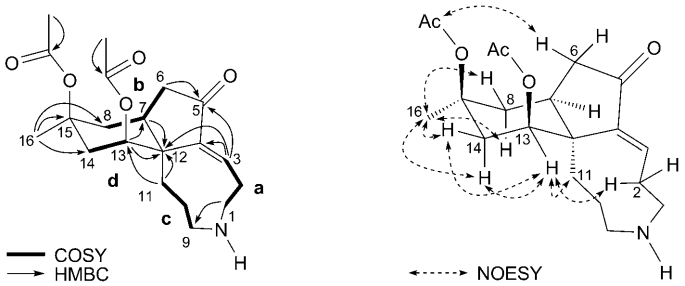


Fig. 2. *2D-NMR Analyses of* **2**[1])

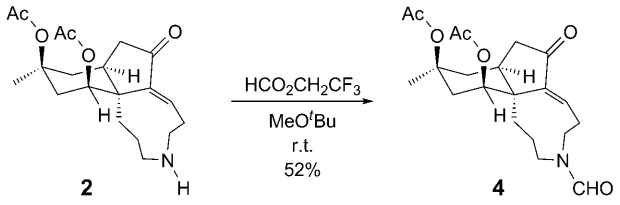
(C(15))). The configuration of **2** was elucidated by NOESY correlations, particularly H–C(11)/H–C(13), Me(16)/CH_2(8), and Me(16)/CH_2(14).

Biogenetically, **2** and related alkaloids **3** and **4** (described below) would be generated from a fawcettimine-type precursor such as **C** in *Scheme 1* by dehydrogenation at C(3)[1]) and C(4), and oxidation at C(15). The 3,4-dehydro fawcettimine-type skeleton is unusual and only a few alkaloids possessing this type of structure have been reported [6a][9]. To the best of our knowledge, this is the first report of an enone functional group at this position (C(3)–C(5)) in *Lycopodium* alkaloids.

The new compound **3** was isolated as a colorless amorphous solid and its molecular formula was established as $C_{21}H_{31}NO_5$ by HR-EI-MS analysis. The spectral data of **3** resembled those of **2** except for the NMR signals derived from a Me function (δ(H) 2.35 (*s*, 3 H) and δ(C) 47.7). Extensive NMR analysis indicated that **3** should have the same structural properties as **2**, and the additional Me function described above should be located at the N-atom based on HMBC between the Me group (δ(H) 2.35) and two N–CH_2 C-atoms (δ(C) 55.0 (C(1)) and 55.4 (C(9))). Thus, we proposed that **3** is an *N*-Me derivative of **2**.

The new compound **4** was isolated as a colorless amorphous solid and its molecular formula was established as $C_{21}H_{29}NO_6$ by HR-EI-MS analysis. The IR absorption band at 1667 cm^{-1} indicated that **4** has an additional amide function besides ketone and ester functionalities (1732 and 1719 cm^{-1}), compared to **2**. As with the case of **3**, ^{1}H- and ^{13}C-NMR data of **4** resembled those of **2** except for the presence of a formyl H-atom and the amide CO C-atom (δ(H) 8.03 and δ(C) 162.9). Extensive NMR analysis also supported the structure of **4** to be an *N*-formyl derivative of **2**. To prove this, we conducted *N*-formylation of **2** (*Scheme 2*). Compound **2** was reacted with 2,2,2-

Scheme 2. *Formylation of* **2**



trifluoroethyl formate [10] at room temperature, and *N*-formyl derivative was obtained as the sole product. NMR, MS, and optical-rotation data of the reaction product were completely identical with those of **4**. Thus, **4** was confirmed to be an *N*-formyl derivative of **2**.

We thank Prof. *W. A. Ayer* of the University of Alberta for providing a sample of *N*-demethyl-*β*-obscurine (**5**). This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Experimental Part

General. Column chromatography was performed on silica gel (SiO_2; *Merck*; 70–230 mesh for open column (CC), 230–400 mesh for flash column chromatography (FC)). Optical rotations: *JASCO P-1020* polarimeter. IR Spectra: *JASCO FT/IR-4200* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$, on a *JEOL ECX-400* spectrometer at 400 and 100 MHz, resp. EI-MS and HR-EI-MS: *JEOL JMS GC-mate* spectrometer with direct probe insertion; in *m*/*z* (rel. %). HR-FAB-MS: *JEOL HX110* spectrometer; in *m*/*z*.

Plant Material. The club moss *Lycopodium serratum* THUNB. was collected in Boso Peninsula, Chiba Prefecture in May 2000, and identified by Mr. *Tamotsu Nose*, a member of the Botanical Society of Chiba Prefecture, Japan. A voucher specimen was deposited with the Herbarium of the Faculty of Pharmaceutical Sciences, Chiba University.

Extraction and Isolation. The air-dried club moss (1.45 kg) was extracted with MeOH (7.7 l) four times and filtered. The combined filtrates were concentrated under reduced pressure to give a crude extract (336 g), which was then dissolved in 2% tartaric acid and filtered. The aq. layer was extracted with petroleum ether (PE), alkalinized with $NaHCO_3$ (pH 10), and exhaustively extracted with 5% MeOH/$CHCl_3$. The org. layer was dried ($MgSO_4$) and evaporated to give a crude alkaloid fraction (3.32 g). A portion of the crude mixture (3.18 g) was roughly separated by SiO_2 FC using a $CHCl_3$ to 30% MeOH/$CHCl_3$ gradient, 30% MeOH in $CHCl_3$ (sat. with NH_4OH), and finally MeOH to afford five fractions (*A*–*E*). The 5% MeOH/$CHCl_3$ fraction (*Fr. B*) was rechromatographed over SiO_2 using 5–10% MeOH/AcOEt to afford **4** (3.6 mg), together with **6** (13.6 mg). The 10–20% MeOH/$CHCl_3$ fraction (*Fr. C*) was rechromatographed over SiO_2 using 5–15% MeOH/AcOEt to afford **1** (2.3 mg) and **3** (2.0 mg) together with **5** (3.3 mg). The 30% MeOH/$CHCl_3$ sat. with NH_4OH fraction (*Fr. D*) was rechromatographed over SiO_2 using 20% MeOH/AcOEt to afford **2** (1.4 mg), together with **7** (14.6 mg).

Lycoposerramine-R (=*(4a*S*,6*R*,7a*S*,12b*S*)-1,2,3,4,4a,5,6,7,7a,8-Decahydro-6-methylpyrido[2′,3′:4,5]-cyclopenta[1,2-*e*]quinolin-10(9*H*)-one*; **1**). Colorless amorphous solid. $[\alpha]_D^{25} = -23.9$ ($c = 0.21$, $CHCl_3$). IR ($CHCl_3$): 1649. ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 258 (82, M^+), 215 (39), 200 (55), 187 (100), 173 (51), 160 (82). HR-FAB-MS: 259.1828 ($[M+H]^+$, $C_{16}H_{23}N_2O^+$; calc. 259.1810).

Lycoposerramine-T (=*(7*E*,9a*S*,11*S*,13*S*,13a*S*)-2,3,4,5,6,8,9,9a,10,11,12,13-Dodecahydro-11-methyl-8-oxo-1*H*-indeno[1,7a-*e*]azonine-11,13-diyl Diacetate*; **2**). Colorless amorphous solid. $[\alpha]_D^{25} = +44.0$ ($c = 0.15$, $CHCl_3$). IR ($CHCl_3$): 1732, 1717. ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 363 (4, M^+), 346 (10), 304 (100). HR-FAB-MS: 364.2107 ($[M+H]^+$, $C_{20}H_{30}NO_5^+$; calc. 364.2124).

N-*Methyllycoposerramine-T* (=*(7*E*,9a*S*,11*S*,13*S*,13a*S*)-2,3,4,5,6,8,9,9a,10,11,12,13-Dodecahydro-4,11-dimethyl-8-oxo-1*H*-indeno[1,7a-*e*]azonine-11,13-diyl Diacetate*; **3**). Colorless amorphous solid. $[\alpha]_D^{25} = +57.4$ ($c = 0.11$, $CHCl_3$). IR ($CHCl_3$): 1734, 1716. ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 377 (25, M^+), 362 (100), 334 (29), 321 (40), 318 (52), 290 (46), 262 (60), 205 (34), 204 (46). HR-EI-MS: 377.2203 ($[M^+$, $C_{21}H_{31}NO_5^+$; calc. 377.2202).

N-*Formyllycoposerramine-T* (=*(7*E*,9a*S*,11*S*,13*S*,13a*S*)-4-Formyl-2,3,4,5,6,8,9,9a,10,11,12,13-dodeca-hydro-11-methyl-8-oxo-1*H*-indeno[1,7a-*e*]azonine-11,13-diyl Diacetate*; **4**). Colorless amorphous solid. $[\alpha]_D^{24} = +66.9$ ($c = 0.19$, $CHCl_3$). IR ($CHCl_3$): 1732, 1719, 1667. ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 391 (18, M^+), 362 (41), 349 (21), 331 (40), 304 (20), 289 (45), 271 (38), 243 (36), 205 (100). HR-EI-MS: 391.1999 (M^+, $C_{21}H_{29}NO_6^+$; calc. 391.1995).

Table 2. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$, 400 and 100 MHz) *of Compounds* **2**–**4**[1]). δ in ppm, J in Hz.

Position	**2**		**3**		**4**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1a	3.03–3.05 (*m*)	46.6	2.66–2.72 (*m*)	55.0	3.57 (*ddd*, *J* = 14.1, 3.7, 3.7)	47.2
1b	2.78–2.85 (*m*)		2.20–2.29 (*m*)		3.19–3.34 (*m*)	
2a	2.70–2.77 (*m*)	30.8	2.80–2.86 (*m*)	30.3	2.79 (*dddd*, *J* = 12.8, 12.8, 12.8, 3.2)	29.5
2b	2.25–2.35 (*m*)		2.29–2.31 (*m*)		2.35–2.44 (*m*)	
3	6.72 (*dd*, *J* = 11.7, 6.7)	138.1	6.72 (*dd*, *J* = 12.2, 7.1)	138.8	6.64 (*dd*, *J* = 12.4, 6.4)	135.2
4		141.7		141.6		143.0
5		205.8		206.1		205.3
6a	3.08–3.11 (*m*)	41.4	3.08 (*dd*, *J* = 16.7, 12.1)	41.5	3.06–3.15 (*m*)	41.3
6b	2.33–2.36 (*m*)		2.32–2.38 (*m*)		2.33–2.40 (*m*)	
7	2.29–2.36 (*m*)	33.5	2.35–2.42 (*m*)	33.5	2.35–2.44 (*m*)	33.3
8a	2.25–2.38 (*m*)	33.7	2.25–2.31 (*m*)	33.5	2.24–2.28 (*m*)	33.4
8b	1.67–1.72 (*m*)		1.67–1.72 (*m*)		1.63–1.71 (*m*)	
9a	2.91–2.98 (*m*)	47.2	2.66–2.72 (*m*)	55.4	3.45 (br. *dd*, *J* = 10.8, 10.8)	45.3
9b	2.63–2.71 (*m*)		2.48–2.51 (*m*)		3.18–3.25 (*m*)	
10a	1.67–1.72 (*m*)	26.3	1.67–1.72 (*m*)	24.8	2.10–2.20 (*m*)	21.5
10b	1.36–1.44 (*m*)		1.38–1.42 (*m*)		1.42–1.48 (*m*)	
11a	2.29–2.33 (*m*)	30.0	2.45–2.48 (*m*)	29.2	1.92–1.96 (*m*)	30.8
11b	1.85–1.93 (*m*)		1.72–1.78 (*m*)		1.92–1.96 (*m*)	
12		47.2		46.9		47.0
13	5.40 (*dd*, *J* = 3.0, 3.0)	74.7	5.39 (*dd*, *J* = 3.0, 3.0)	74.8	5.36 (*dd*, *J* = 3.2, 3.2)	74.6
14a	2.97–3.05 (*m*)	32.7	3.00 (*ddd*, *J* = 16.2, 2.9, 2.9)	32.7	2.99–3.13 (*m*)	32.6
14b	1.67–1.72 (*m*)		1.67–1.72 (*m*)		1.63–1.71 (*m*)	
15		78.6		78.7		78.4
16	1.52 (*s*, 3 H)	27.4	1.51 (*s*, 3 H)	27.4	1.51 (*s*, 3 H)	27.3
13-OAc	1.81 (*s*, 3 H)	169.4, 21.0	1.81 (*s*, 3 H)	169.4, 21.0	1.81 (*s*, 3 H)	169.5, 20.9
15-OAc	1.95 (*s*, 3 H)	170.1, 23.0	1.94 (*s*, 3 H)	170.1, 23.0	1.95 (*s*, 3 H)	170.1, 23.0
N–R			2.35 (*s*, 3 H)	47.7	8.03 (*s*)	162.9

Formylation of **2**. 2,2,2-Trifluoroethyl formate (TFEF; 24 µl) was dissolved in methyl *tert*-butyl ether (MTBE; 976 µl). To a stirred soln. of **2** (0.9 mg) in MTBE (0.2 ml) was added 10 µl of the above described TFEF/MTBE soln. in an ice bath for 5 min. Then, the mixture was allowed to stand at r.t. for 2.5 h. The mixture was poured into chilled aq. $NaHCO_3$ and extracted with $CHCl_3$. The org. layer was dried ($MgSO_4$) and evaporated to dryness. The residue was purified over SiO_2 ($CHCl_3$/MeOH) to afford semi-synthetic **4**. The spectroscopic data of semi-synthetic **4** were completely identical with those of natural **4** including optical rotation.

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