Four New Eremophilane Derivatives from *Ligularia sagitta*

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Four new compounds (**1a** and **2–4**), a series of uncommon eremophilane derivatives with C19-carbon skeleton, were isolated from the roots of *Ligularia sagitta* Maxim. Their structures were respectively determined by extensive spectroscopic analysis (IR, MS, NMR, and X-ray).

The roots of *Ligularia sagitta* possess efficacies of relieving phlegm and cough, invigorating circulation of blood, soothing pain, and particularly curing rheumatoid arthritis.[1] As a part of our ongoing study of this species, four new eremophilane derivatives were isolated from the roots of *L. sagitta* collected from Gannan Tibet Autonomous Region (S. A. 2000–3800 m), Gansu province of P. R. China. These compounds have an uncommon C19-carbon skeleton possibly formed via a Diels–Alder reaction in the biosynthetic process.[2,3] Herein, we report isolation and structure elucidation of the four new compounds **1a** and **2–4** (Figure 1).

The extract was purified by repeatedly chromatographed over a silica gel column with petroleum ether/acetone to afford compounds **2–4** and mixture containing **1**.

Compound **1a**, $[\alpha]_D^{20} + 4$ (*c* 0.3, $CHCl_3$), was obtained as colorless needles by acetylation of mixture containing **1**, it showed a molecular formular of $C_{22}H_{30}O_7$ as determined by HRESI-MS ($[M + NH_4]^+$ at *m/z* 424.2334, calcd. 424.2330). The IR spectrum showed absorption bands for hydroxy (3458 cm^{-1}), ester (1742 and 1729 cm^{-1}). ^1H NMR, ^{13}C NMR, and DEPT spectra showed the presence of an acetyl at δ_H 2.07 (3H, s), δ_C 21.1 q, 170.9 s, an ester carbonyl at δ_C 171.8 s, a double bond at δ_C 146.3 s, 135.0 s, as well as a methoxy group at δ_H 3.53 (3H, s), δ_C 62.5 q. The remaining five degrees of unsaturation suggested a pentacyclic structure for **1a**. The ^1H NMR spectrum of **1a** showed three methyl group signals at δ_H 1.86 (3H, d, $J = 2.0$ Hz), 1.19 (3H, d, $J = 7.2$ Hz), and 1.03 (3H, s), ^{13}C NMR (DEPT) displayed 19-carbon signals ($3 \times CH_3$, $5 \times CH_2$, $4 \times CH$, $7 \times C$) for the skeleton of **1a** except for a methoxy and an acetyl, suggesting that **1a** was an eremophilane derivative with C19-carbon skeleton.[2,3]

^1H–^1H COSY spectrum showed two spin coupling systems **a** (C-1, C-2, C-3, and C-4) and **b** (C-12 and C-16) as drawn with bold bonds (Figure 2). In particularly, with the aid of HMBC experiments, structure of **1a** possessed the C15-carbon skeleton of a series of normal eremophilane sesquiterpenes isolated from *L. sagitta* previously,[4] which could be supported by HMBC correlations of H_3-13 with C-7, C-11, C-12; H_3-14 with C-4, C-5, C-6, C-10; H_3-15 with C-3, C-4, C-5; H-6 with C-5, C-7, C-8, C-10, C-11; and H_2-9 with C-1, C-7, C-8, C-10. Most interestingly, the HMBC correlations of H_2-16 with C-8, C-11, C-17, C-18, C-19; H_2-9 with C-17; and H_2-19 with C-8, C-16, C-18 suggested that an additional carbon chain with an ester carbonyl connected to C-8 and C-12, and the presence of an oxygen bridge between C-8 and C-12 could also be revealed by HMBC correlations of H-12 with C-7, C-8, and C-17. Furthermore, the downfield shift of C-1 indicated that the ester moiety connected to C-1.[4,5] Thus, a planar structure with a C19-skeleton was deduced.

Stereochemically, in the biogenetic consideration of eremophilane derivatives isolated from Compositae species, the methyls at C-4 and C-5 were both assigned the β-orientation.[6] H-6 must have the α-orientation to allow the homoallylic coupling with Me-13 at δ 1.86 (3H, d, $J = 2.0$ Hz).[2] Thus, the absolute configurations at C-4, C-5, and C-6 were assigned to S, S, and R, respectively.

A single crystal X-ray diffraction analysis (Figure 3) was then carried out in order to determine the structure of **1a**. The X-ray demonstrated the linkage, α-orientation of the olide ring, A/B ring cis form, and it also showed that CH_2-19, OH-10, and H-12 were all β-orientated, and the absolute configurations at C-1, C-8, C-10, C-12, and C-17 were fixed to be S, R, S, R, and S, respectively. Based on the above findings, the structure, including the relative stereochemistry of **1a**, was unambiguously elucidated as an eremophilane derivative with 19-carbon skele-

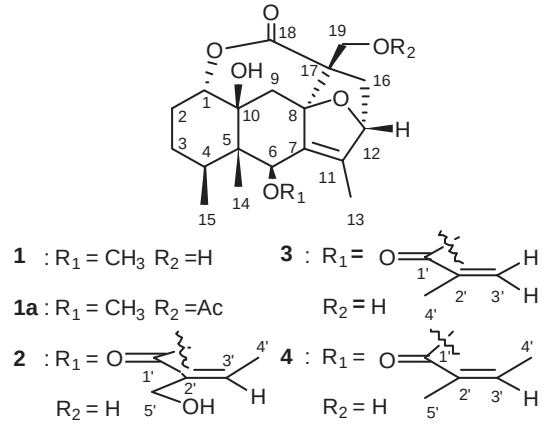

Figure 1. Structures of **1a** and **2–4**.

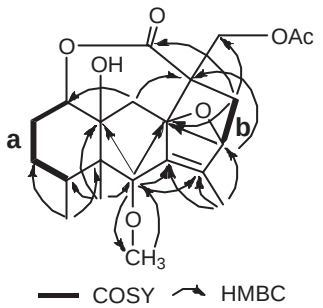

Figure 2. Key correlations of HMBC and ^1H–^1H COSY of compound **1a**.

Table 1. NMR spectra for compounds **1a** and **2–4**

Pos.	**1a**		**2**		**3**		**4**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1β	84.0 d	4.74 br s	83.5 d	4.97 br s	83.8 d	4.98 br s	83.6 d	4.97 br s
2a		2.40 m,		1.64 m,		2.38 m,		2.38 m,
2b	23.9 t	1.72 m	23.6 t	1.06 m	23.6 t	1.64 m	23.6 t	1.68 m
3a		2.39 m,		2.39 m,		2.39 m,		2.39 m,
3b	23.0 t	1.35 m	22.9 t	1.28 m	22.9 t	1.20 m	22.9 t	1.29 m
4α	32.6 d	2.00 m	33.0 d	1.60 m	33.0 d	1.54 m	33.0 d	1.57 m
5	46.7 s		44.8 s		44.8 s		44.9 s	
6α	80.4 t	4.27 d (2.0)	70.3 t	6.36 br s	70.6 t	6.23 d (2.0)	69.7 t	6.28 d (2.0)
7	135.0 s		133.7 s		133.8 s		133.8 s	
8	85.3 s		85.9 s		85.9 s		85.9 s	
9a		2.44 d 12.8		2.52 d 12.4,		2.52 d 12.4,		2.53 d 12.4,
9b	36.0 t	1.92 d 12.4	35.3 t	2.37 d 12.4	35.2 t	2.37 m	35.5 t	2.36 m
10	74.6 s		74.5 s		74.4 s		74.7 s	
11	146.3 s		146.1 s		146.2 s		146.0 s	
12β	82.9 d	4.55 d (4.0)	82.4 d	4.48 d (4.4)	82.3 d	4.47 d (3.2)	82.7 d	4.48 d (4.4)
13	10.9 q	1.86 d (2.0)	10.7 q	1.65 d (2.0)	10.6 q	1.59 d (2.0)	10.5 q	1.68 d (2.0)
14	15.9 q	1.03 s	16.1 q	1.15 s	16.9 q	1.18 s	16.1 q	1.13 s
15	17.3 q	1.19 d (7.2)	17.0 q	1.13 d (8.8)	17.0 q	1.18 br s	17.0 q	1.14 d (7.2)
16a		2.20 d (12.0)		2.10 m		2.03 d (12.8),		2.09 d (12.4),
16b	40.3 t	2.09 dd (12.0, 4.4)	40.7 t	1.94 m	40.7 t	1.88 dd (11.6)	40.7 t	1.95 dd (12.0, 4.8)
17	57.2 s		60.2 s		60.1 s		60.1 s	
18	171.8 s		175.3 s		175.7 s		175.1 s	
19a		4.77 (10.8)		4.00 d (11.6)		3.97 d (10.8)		3.97 s
19b	66.4 t	4.00 (11.6)	66.4 t	3.96 d (10.8)	66.3 t	3.94 m	66.4 t	3.97 s
OMe	62.5 q	3.53 s	—	—	—	—	—	—
OAc	170.9 s		—	—	—	—	—	—
	21.1 q	2.07 s	—	—	—	—	—	—
1′	—	—	166.9 s		167.4 s		167.5 s	
2′	—	—	131.2 s		135.9 s		127.3 s	
						a 5.61 s,		
3′	—	—	143.1 d	6.47 q (7.2)	126.9 s	b 6.15 s	140.4 d	6.16 qq (7.2, 1.2)
4′	—	—	17.0 q	2.09 d (7.6)	18.5 q	1.99 s	20.9 q	2.01 dq (7.6, 1.6)
5′	—	—	65.4 s	4.23 s	—	—	16.81 q	1.89 d (1.2)

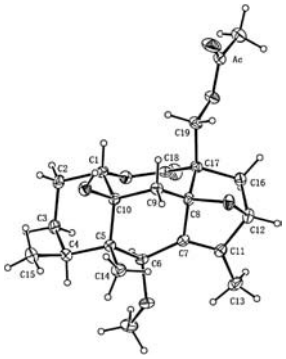

Figure 3. X-ray structre of compound **1a**.

ton. Crystallographic data for **1a** have been deposited in the Cambridge Crystallographic Data Centre.[7]

The ^{1}H NMR, ^{13}C NMR, and DEPT spectral data (Table 1) and IR spectra of compounds **2–4** closely resembled those of compound **1a**,[8] ^{1}H–^{1}H COSY spectra of **2–4** all showed a crosspeak between H-6 and Me-13, indicating that these four compounds had the same carbon skeleton except for the difference of substitutes at C-6, ^{1}H NMR of **2–4** all showed the same small coupling constant of 2 Hz, which also reavealed the α-orientation of H-6.

Compound **2**, $[\alpha]_D^{20}$ + 2.0 (*c* 1.8, $CHCl_3$), white amorphous powder, the HRESI-MS gave an ion peak of $[M + NH_4]^+$ at *m*/*z* 466.2436 (calcd 466.2435) consistent with the molecular formula of $C_{24}H_{32}O_8$. The presence of a 5-hydroxylangeloyl group could be distinguished by ^{1}H NMR spectral signals at δ_H 6.47 (1H, q, J = 7.2 Hz), 2.09 (3H, d, J = 7.6 Hz), 4.23 (2H, s).

Compound **3**, $[\alpha]_D^{20}$ + 2.4 (*c* 3.1, $CHCl_3$), white amorphous powder, the HRESI-MS showed the molecular formula as $C_{23}H_{30}O_7$ at *m*/*z* $[M + NH_4]^+$ 436.2329 (calcd 436.2330). ^{1}H NMR at δ_H 5.61, 6.15 (1H each, s), 1.99 (3H, s) revealed the presence of a methylacryloyl moiety.

Compound **4**, $[\alpha]_D^{20}$ + 1.0 (*c* 1.0, $CHCl_3$), white amorphous powder, the molecular formula was deduced as $C_{24}H_{32}O_7$ at *m*/*z* $[M + NH_4]^+$ 450.2482 (calcd 450.2486) from HRESI-MS. An angeloyl mioety could be distinguished by ^{1}H NMR at δ_H 6.16 (1H, qq, J = 7.2, 1.2 Hz), 2.01 (3H, dq, J = 7.6, 1.2 Hz), 1.89 (3H, d, J = 1.2 Hz).

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7 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as Supplementary publication No. CCDC-654457.
8 Supporting Information is available electronically on the CSJ-Journal website, http://www.csj.jp/journals/chem-lett/.

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