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Synthesis and structural characterization of two epimers driven from 20(*S*)-protopanaxadiol

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HIGHLIGHTS

- Two epimers, 20*S*, *24R*-epoxy dammarane-3β, 12β, 25-triol (**3**) and 20*S*, 24*S*-epoxy dammarane-3β, 12β, 25-triol (**4**) are prepared.
- The configuration of C-24 of **3** and **4** are *R*-form and *S*-form, respectively.
- **3** Generate a H-bonded tube with left-handed chiral channel.
- **4** Extend into 2D H-bonded network with right-handed and left-handed chiral channels.
- This study provides a facile way to synthesize and separate new types of chiral medicinal derivatives.

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ABSTRACT

Two epimers, 20*S*,*24R*-epoxy dammarane-3β,12β,25-triol (**3**) and 20*S*,24*S*-epoxy dammarane-3β,12β,25-triol (**4**) were prepared from 20(*S*)-protopanaxadiol, which were confirmed by ESI-MS, NMR, and X-ray single-crystal diffraction. The results indicate the configuration of C-24 of **3** and **4** are *R*-form and *S*-form, respectively. **3** and **4** crystallize in a orthorhombic space group *P2(1)2(1)2(1)*. Compound **3** have more complicated intramolecular hydrogen bonds than that of **4**, which results in the weaker molecular polarity in **3**. Crystal stacking displays that **3** generates a H-bonded tube with left-handed chiral channel, while **4** extends into two-dimensional network with right-handed and left-handed chiral channels in the solid state.

1. Introduction

Both *Panax ginseng* and *Panax quinquefolium*, belonging to the Araliaceae, are well-known traditional medicinal herbs. They are used as tonics and the treatment for diseases. *Panax ginseng* contains numbers of saponins, called ginsenoside, including an oleanolic acid-type saponin in addition to the major protopanaxadiol and protopanaxatriol-type saponins [1]. However, *Panax quinquefolium* contains an ocotillol-type (20*S*,24*R*-epoxyside) saponin with high activity [2], as well as oleanolic acid-type saponin, protopanaxadiol and protopanaxatriol-type saponins. Yu et al. have found that ocotillol, *20S*,24*R*-epoxy-dammarane-3β,6α,12β,25-tetraol which is degraded and isolated from *Panax quinquefolium* in poor yield, possesses cardioprotective effect on myocardial injury induced by isoproterenol in rats [3]. In our previous study, it was shown that ocotillol-type derivatives derived from 20(*S*)-protopanaxadiol and 20(*S*)-protopanaxatriol with *R*-form configuration of C-24 can result in a reduction in creatine kinase activity, superoxide dismutase and glutathione peroxidase activities and inhibit the elevation of malondialdehyde content [4,5]. Based on this, herein, we report the synthesis and X-ray single-crystal diffraction of the two epimers derived from 20(*S*)-protopanaxadiol. The synthetic route is illustrated in Fig. 1.

2. Results and discussion

20(*S*)-Protopanaxadiol was degraded from 20(*S*)-panaxadiol saponins with sodium methoxide in DMSO, purified over silica gel and crystallized from ethyl acetate. Epimeric 20*S*,24-epoxy-dammarane-3β,12β,25-triol acetate (2) was synthesized by reaction of 20(*S*)-protopanaxatriol and acetic anhydride in pyridine at room temperature and oxidation of the resulting 1 using *m*-CPBA. 20*S*,24*R*-epoxy dammarane-3β,12β,25-triol (3) [6] and

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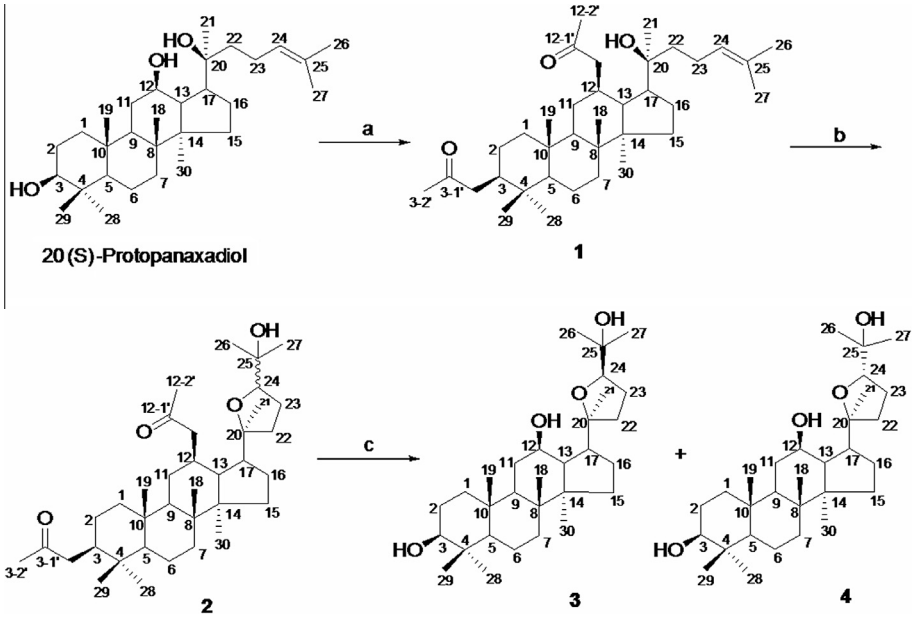

Fig. 1. Synthetic route of **3** and **4**. Reagents: (a) $(CH_3CO)_2O$, DMAP. Pyridine; (b) *m*-CPBA, CH_2Cl_2; (c) NaOH, DMSO, H_2O.

20*S*,24*S*-epoxy dammarane-3β,12β,25-triol (4) are prepared by reaction of 2 and sodium hydroxide in DMSO and water in 1:1 M ratio (Fig. 1). The structures of the epimers were confirmed by ESI-MS, ^{1}H NMR, ^{13}C NMR and X-ray single-crystal diffraction. According to the literature, the difference of 20(*S*)- and 20(*R*)-isomer in ocotillol-type saponin may be observed from the carbon signal of C-21 (*S*-form: δ28 ± 1; *R*-form: δ20 ± 1) in ^{13}C NMR spec-

Table 1
^{13}C NMR data of **1–4** ($CDCl_3$, δ, ppm).

No.	1	No.	2	No.	3	No.	4
1	38.5	1	38.5	1	50.2	1	38.9
2	23.5[a]	2	23.6	2	32.1	2	28.5
3	80.5	3	80.6	3	78.8	3	78.8
4	37.8	4	37.9	4	48.9	4	38.8
5	55.9	5	55.9	5	76.6	5	55.9
6	18.1	6	18.1	6	24.9	6	18.2
7	34.5	7	34.4	7	39.7	7	34.8
8	39.7	8	39.6	8	52.1	8	39.7
9	49.9	9	49.6	9	69.9	9	50.0
10	37.0	10	37.0	10	48.7	10	37.1
11	28.3	11	28.4	11	34.7	11	31.1
12	79.5	12	75.5	12	77.2	12	70.9
13	44.9	13	46.4	13	60.3	13	49.3
14	52.6[d]	14	52.4	14	70.6	14	51.9
15	31.4	15	30.9	15	38.8	15	32.5
16	27.1	16	27.6	16	28.0	16	27.4
17	52.9[d]	17	50.2	17	55.9	17	47.9
18	15.6	18	15.5[a]	18	18.2	18	15.3
19	16.2[e]	19	17.4[a]	19	20.9	19	16.2
20	73.6	20	85.5	20	87.4	20	86.4
21	26.2	21	26.9	21	28.4	21	27.5
22	36.1	22	39.8	22	37.1	22	31.2
23	22.2[a]	23	24.0	23	27.4	23	24.9
24	125.2	24	84.5	24	87.4	24	85.4
25	131.2	25	70.5	25	76.9	25	70.0
26	25.7	26	25.7	26	31.5	26	27.9
27	17.6[e]	27	22. 8	27	26.1	27	26.0
28	27.9	27	27.9	28	28.8	28	27.8
29	16.4[e]	29	16.0[a]	29	17.7	29	15.2
30	16.4[e]	30	16.5[a]	30	24.2	30	18.0
3-1′	170.7[c]	3-1′	170.8[a]				
3-2′	21.5[b]	3-2′	21.8[b]				
12-1′	169.5[c]	12-1′	170.5[a]				
12-2′	21.2[b]	12-2′	21.2[b]				

Table 2
Selected **c**rystal data for compound **3** and **4.**

Parameter	3	4
Empirical formula	$C_{30}H_{52}O_4$	$C_{30}H_{52}O_4$
Formula weight	476.72	476.72
CCDC	841280	911853
Crystal size (mm^3)	0.20 × 0.20 × 0.16	0.30 × 0.25 × 0.25
Crystal system	Orthorhombic	Orthorhombic
Space group	*P*2 (1) 2 (1) 2 (1)	*P*2 (1) 2 (1) 2 (1)
a (nm)	0.76793 (14)	0.73882 (14)
b (nm)	1.3067 (3)	1.3919 (3)
c (nm)	2.8084 (5)	2.7256 (5)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
V/nm^3	2.8181 (9)	2.8029 (9)
D_x (g cm^{-1})	1.124	1.130
F (000)	1056	1056
Absorportion coefficiention (mm^{-1})	0.072	0.072
Θ for data collection (°)	1.72–25.50	1.64–25.50
Final *R* indices	0.0416	0.0509
wR_2	0.1107	0.1009
S	1.055	1.074

$$R_1 = \sum ||F_o| - |F_c|| / \sum |F_o| \cdot wR_2 = \{\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]\}^{1/2}.$$

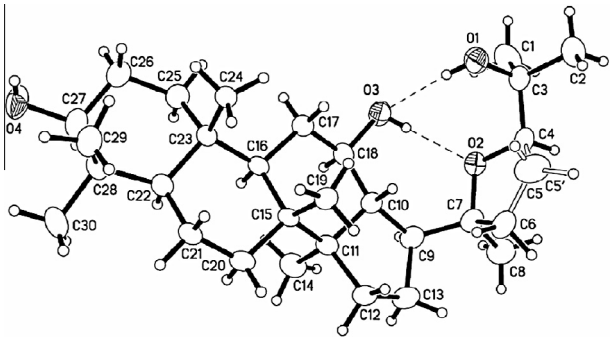

Fig. 2. The ORTEP figure of **3** with thermal ellipsoids shown at 30% probability.