ELECTROCHEMICAL TRANSFORMATION OF PROTOSTANE TYPE TRITERPENES

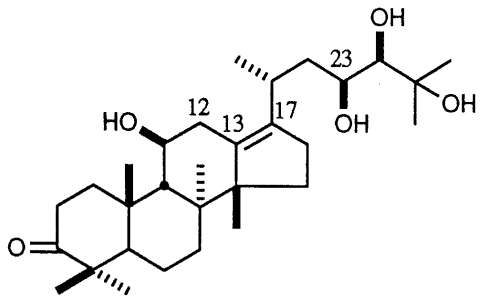
Nobutoshi MURAKAMI, Nobuhiro YAGI, Toshiyuki MURAKAMI, and Masayuki YOSHIKAWA*

Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607, Japan

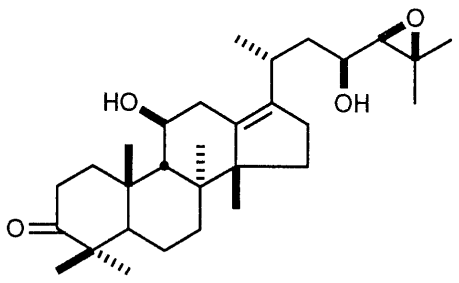
Anodic oxidation of 23-hydroxyprotost-13(17)-ene furnished an unprecedented triterpenoidal skeleton, 17,23-epoxyprotost-12-ene, while 23-acetoxyprotost-13(17)-ene was converted into 23-acetoxyprotost-13(17)-en-16-one.

KEY WORDS anodic oxidation; protostane type triterpene; 17,23-epoxyprotost-12-ene; 23-acetoxyprotost-13(17)-en-16-one; Alismatis Rhizoma

Protostane type triterpenes such as alisol A (**1**), B (**2**), A monoacetate, and B monoacetate (**6**) are present in Alismatis Rhizoma (Takushya in Japanese) in high yields[1], and some of them show various biological activities related to diuretic action.[2] In addition, protostane triterpenes with higher oxygen function than the above-mentioned four constituents have recently been isolated from various Alismatis Rhizoma of different origin.[3] However, neither chemical modification nor structure-activity relationship for the protostane triterpenes have been much examined in spite of their frequent use in natural medicine. Thus, we have investigated their chemical transformation by use of anodic oxidation as part of our investigation on chemical modification of naturally abundant principles.[4] This paper

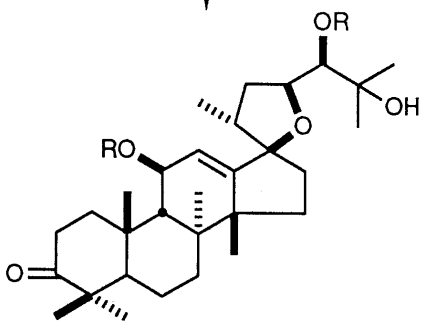


alisol A (**1**)



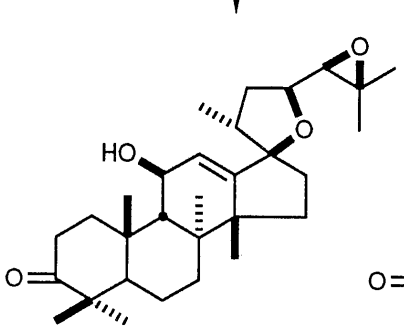
alisol B (**2**)

anode | -e⁻



3 : R=H
3a : R=Ac

anode | -e⁻



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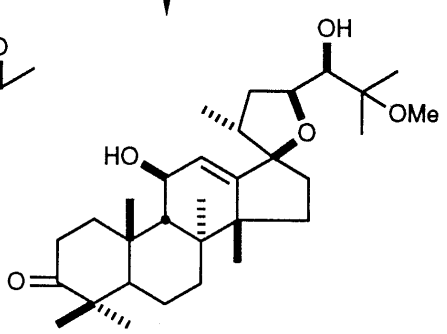

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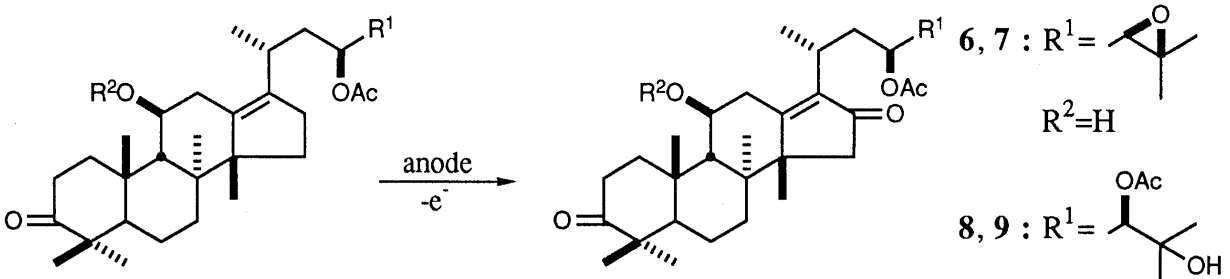
* To whom correspondence should be addressed.



alisol B monoacetate (**6**) alisol C monoacetate (**7**)
alisol A triacetate (**8**) **9**

describes two electrochemical transformations of protostane type triterpenes utilizing anodic oxidation.

When alisol A (**1**) was subjected to constant current electrolysis in MeOH (Pt-Pt electrode, current density 12.5 mA/cm^2) using an undivided cell at 0 °C for 40 min, an oxidized product (**3**) was obtained in 71.3 % (conversion yield) together with recovered **1** (15.5 %). The EI-MS spectrum of **3** exhibited a molecular ion peak at m/z 488, and the molecular formula was determined to be $C_{30}H_{48}O_5$ (Found : 488.3487, Calcd for M^+ : 488.3502) by the high-resolution EI-MS measurement. The ^{1}H-NMR spectrum of **3** showed the signals from an olefinic proton [δ 5.29 (1H, d, J=3.0), 12-H], an allylic oxymethine proton [δ 4.34 (1H, dd, J=3.0, 9.2), 11-H], and two adjacent oxymethine protons [δ 4.26 (1H, ddd, J=2.3, 2.6, 8.6), 23-H; 3.18 (1H, br s), 24-H].[5] Detailed comparisons of the ^{13}C-NMR data (Table 1) for **3** with those for **1** have shown that the A and B ring structures of both compounds are in accord with each other, but the structures of the C and D rings and the side chain moiety differ. The ^{13}C-NMR spectrum of **3** indicated the presence of a trisubstituted olefin [δ 121.8 (d, 12-C), 150.4 (s, 13-C)] and a quaternary carbon [δ 91.5 (s, 17-C)] bearing oxygen. Some significant C-H long-range correlations shown by arrows in the formula in Fig. 1 disclosed that the oxidized product (**3**) contained either 17,23-epoxyprotost-12-ene or 17,24-epoxyprotost-12-ene moiety.[6] Thus, **3** was acetylated with Ac_2O and pyridine in order to verify a framework. The ^{1}H-NMR spectrum of its acetate (**3a**) showed that the signal due to 24-H [δ 4.78 (1H, d, J=2.0)] shifted downfield in comparison with that of **3**, but the 23-H signals of **3** and **3a** [δ 4.49 (1H, ddd, J=2.0, 2.4, 7.8)] appeared at nearly similar chemical shifts. The stereostructure at 17-C in **3** was determined by the results obtained from difference NOE experiments. Irradiation of 12-H, 21-H$_3$, and 23-H caused 11.8 % for 20-H, 1.1 % for 16α-H, and 9.2 % for 16β-H. Consequently, 17-*R* configuration of **3** was established.

Table 1. ^{13}C-NMR Data for **3**, **4**, and **5** (68MHz, $CDCl_3$)

C	3	4	5	C	3	4	5
1	32.2	32.2	32.3	16	31.4	31.5	31.8
2	34.0	33.9	33.9	17	91.5	91.1	91.7
3	219.5	219.6	219.6	18	23.6	24.9	25.3
4	46.9	46.8	46.9	19	25.2	25.2	25.2
5	49.1	49.0	49.0	20	40.3	40.7	39.1
6	20.4	20.3	20.4	21	13.8	13.9	14.3
7	34.6	34.4	34.5	22	36.4	36.3	38.7
8	41.3	41.2	41.5	23	76.3	76.0	73.7
9	49.4	49.5	49.3	24	77.1	66.9	78.2
10	36.6	36.5	36.6	25	73.1	57.1	77.1
11	69.3	69.7	69.4	26	26.5	19.3	19.6
12	121.8	121.4	121.1	27	26.7	24.6	22.2
13	150.4	150.6	150.8	28	29.2	29.2	29.2
14	50.6	50.6	50.5	29	20.3	20.3	20.3
15	30.3	30.2	30.4	30	25.1	23.6	23.6
				OCH_3			49.2

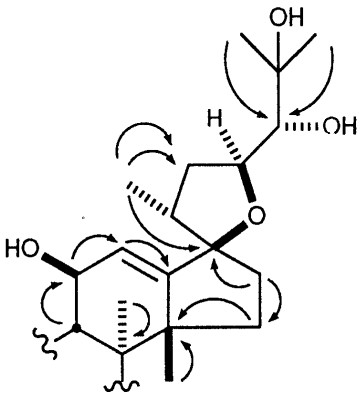


Fig.1. HMBC Correlations of **3**

Anodic oxidation of another triterpene having 23-hydroxyprotost-13(17)-ene framework, alisol B (**2**), proceeded under the same reaction condition as **1** to afford two 17,23-epoxyprotost-12-enes (**4** and **5**) in 51.9 % and 19.4 % conversion yields with recovery of **2** (43.3 %). Their chemical structures were confirmed by physicochemical properties including ^{1}H- and ^{13}C-NMR spectra (Table 1).[7] Of the two products, **5** would be considered to be secondarily generated from **4** by methanolysis in the acidified reaction medium.

Since the above-mentioned electrochemical transformation was concerned with the 23-hydroxyl group in the side chain moiety, anodic oxidation of the protostane triterpene possessing an acetoxyl group on 23-C, alisol B monoacetate (**6**), was next examined. Constant current electrolysis of **6** in MeOH with Pt-Pt electrode using $NaClO_4$ as supporting electrolyte in an undivided cell (current density : 20 mA/cm^2) at 0 °C for 3h gave alisol C monoacetate (**7**)[1b] in 58.2 % (conversion yield) with recovered **6** (20.0 %). Similarly, alisol A triacetate (**8**) containing 23-acetoxyprotost-13(17)-ene moiety afforded 16-oxoalisol A triacetate (**9**) in 51.0 % conversion yield along with recovery of **8** (20.7 %).

In conclusion, we found the two electrochemical transformation of protostane type triterpenes initiated by allylic oxidation[8] that 23-hydroxyprotost-13(17)-enes and 23-acetoxyprotost-13(17)-enes were converted into 17,23-epoxyprotost-12-enes and 23-acetoxyprotost-13(17)-en-16-ones, respectively. Because the 17,23-epoxyprotost-12-enes are unprecedented, their biological activities are of interest. Additionally, it is worthwhile that alisol C monoacetate (**7**), whose content is lower than that of alisol B monoacetate (**6**), was prepared from **6** in one step without previous protection of the hydroxyl group.

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5) **3** : a white powder, $[\alpha]_D^{21}$ +24.8° (MeOH), IR (KBr) : 3414, 1701 cm^{-1}, ^{1}H-NMR (270MHz, $CDCl_3$, δ) : 0.88 (3H, d, J=6.6, 21-H_3), 0.98, 1.08, 1.08, 1.12, 1.23, 1.26, 1.28 (3H each, all s, tert.-CH_3x7).

6) In the HMBC spectrum of **3**, no apparent correlation was observed between 17-C and 23-H.

7) **4** : colorless oil, $[\alpha]_D^{20}$ +72.8°, $C_{30}H_{46}O_4$, IR (KBr) : 3418, 1701 cm^{-1}, ^{1}H-NMR (270MHz, $CDCl_3$, δ) : 0.92 (3H, d, J=6.6, 21-H_3), 0.99, 1.08, 1.08, 1.12, 1.18, 1.31, 1.33 (3H each, all s, tert.-CH_3x7), 2.79 (1H, d, J=8.6, 24-H), 3.76 (1H, ddd, J=4.6, 8.6, 12.9, 23-H), 4.34 (1H, dd, J=3.0, 9.6, 11-H), 5.59 (1H, d, J=3.0, 12-H), EI-MS m/z (%) : 470 (M^+); **5** : colorless oil, $[\alpha]_D^{20}$ +74.9° ($CHCl_3$), $C_{31}H_{50}O_5$, IR (KBr) : 3439, 1701 cm^{-1}, ^{1}H-NMR (270MHz, $CDCl_3$, δ) : 0.89 (3H, d, J=6.9, 21-H_3), 0.97, 1.08, 1.08, 1.10, 1.12, 1.20, 1.30 (3H each, all s, tert.-CH_3x7), 3.23 (3H, s, OCH_3), 3.27 (1H, d, J=3.0, 24-H), 4.21 (1H, ddd, J=3.0, 4.3, 8.9, 23-H), 4.35 (1H, dd, J=3.3, 9.6, 11-H), 5.56 (1H, d, J=3.3, 12-H), EI-MS m/z (%) : 502 (M^+), The location of the methoxyl group was confirmed by the HMBC spectrum in which a correlation peak was observed between 25-C and the methoxyl proton.

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