REGIOSELECTIVE OXIDATION OF THE HYDROXYL GROUP IN POLYHYDROXYLATED TRITERPENES BY THE INDIRECT ANODIC OXIDATION METHOD

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Indirect anodic oxidation of soyasapogenol B (3β,22β,24-trihydroxyolean-12-ene) was carried out using KI as a mediator in *t*-BuOH-H_2O solution, so that the 3-ketone derivative was obtained as the only oxidation product in a favorable yield. As a result of application to various polyhydroxylated triterpenes, selective electrochemical oxidation was shown to occur in the C-3 hydroxyl group of the polyhydroxyl triterpenes with the C-24 hydroxyl group. The reaction pathway is discussed.

KEY WORDS indirect anodic oxidation; selective hydroxyl oxidation; polyhydroxylated triterpene; soyasapogenol B; electrochemical reaction; olean-12-en-3-one synthesis

Several electrochemical methods for the oxidation of the hydroxyl group have been developed, and in particular, indirect anodic oxidation using a suitable mediator was reported to be practical because of its low oxidative potential.1) However, electrochemical oxidation methods including indirect methods have been applied only to simple mono-hydroxyl compounds and further application to complex skeletal and highly functionalalized alcohols is needed to clarify the selectivity and specificity of the electrochemical reaction. During the course of our studies to develop electrochemical reactions of natural products,2) we have examined the indirect anodic oxidation of triterpene alcohols and saponins. In this communication, we describe a new regioselective anodic oxidation of a hydroxyl group in polyhydroxylated triterpenes and an oligoglycoside. Additionally, the reaction pathway is discussed on the basis of application of anodic oxidation for various triterpenes and their derivatives.3)

First, we examined the anodic oxidation of soyasapogenol B (3β,22β,24-trihydroxyolean-12-ene, **1**),4) using halide as a mediator in the solvent system with the ability to dissolve both triterpene and electrolytes. As is apparent from Table 1, indirect anodic oxidation of **1** under almost all conditions (Run 1—5) yielded the 3-ketone derivative (**2**)5) as the only oxidation product and, by exhaustive oxidation for 5 h (Run 6), the 3,22-diketone derivative (**4**)6) was obtained as a minor product. The electrolysis conditions (Run 1) using KI in *t*-BuOH-H_2O (1 : 1) was found to be most effective, and **2** was produced from **1** in 85.9% yield by electrolysis for 10 min. On the other hand, chemical oxidation with following oxidants [i) NBS/dioxane-H_2O (9 : 1); ii) Br_2/aq. $NaHCO_3$, HMPA-CH_2Cl_2; iii) CrO_3/pyridine] were found to give the 22-ketone derivative (soyasapogenol E, **3**) [i) **3** (70.0%), ii) **3** (53.2%), **4** (34.0%), iii) **1** (11.0%, recovered), **3** (51.0%), **4** (20.0%)]. This evidence showed that indirect anodic oxidation selectively proceeded oxidation of the 3-equatorial hydroxyl group in preference to the 22-axial hydroxyl group, which was easily oxidized by other oxidants.

Table 1. Indirect Anodic Oxidation[a)] of Soyasapogenol B (**1**)[b)] with Different Electrolytes and Solvent Systems

Run	Solvent (ml)	Electrolyte (mmol)	Time	Electricity (F/mol)	Product
1	*t*-BuOH-H_2O (1 : 1, 5.4)[c)]	KI (0.48)	10min	1.3	**2** (85.9%)
2	*t*-BuOH-H_2O (1 : 1, 5.4)[c)]	KBr (0.48)	10min	1.3	**2** (80.0%)
3	Et_2O-*t*-BuOH-H_2O (3 : 2 : 4, 5.4)[d)]	KI (0.48)	1h	7.8	**2** (76.9%)
4	*n*-hexane-*t*-BuOH-H_2O (2 : 3 : 4, 27)[d)]	KI (2.41)	2h	3.1	**2** (80.1%)
5	*n*-hexane-*t*-BuOH-H_2O (2 : 3 : 4, 5.4)[d)]	NaI (0.48)	2h	15.5	**2** (78.8%)
6	*n*-hexane-*t*-BuOH-H_2O (2 : 3 : 4, 27)[d)]	KI (2.41)	5h	7.7	**2** (54.2%), **3** (28.4%)
7	*n*-hexane-*t*-BuOH-H_2O (2 : 3 : 4, 5.4)[d)]	*n*-Bu_4NI (0.48)	1h	7.8	complex mixture

a) Constant-current electrolysis (Pt anode and cathode, 13 mA/cm^2) in an undivided beaker with vigorous stirring.
b) 0.022 mmol of **1** for Runs 1, 2, 3, 5, and 7; 0.262 mmol for Runs 4 and 6.
c) One-phase solution. d) Two-phase solution.

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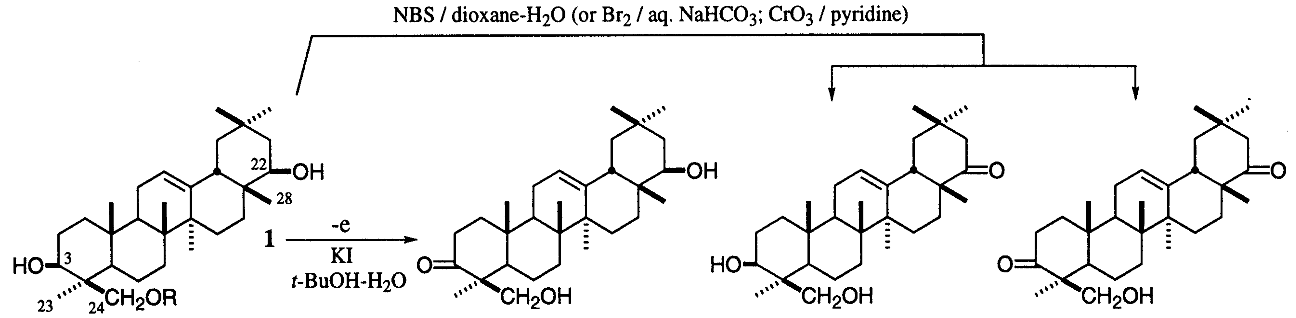
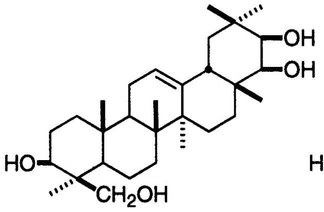


soyasapogenol B (**1**) : R=H
1a : R=pivaloyl
1b : R=TBDMS

2

3

4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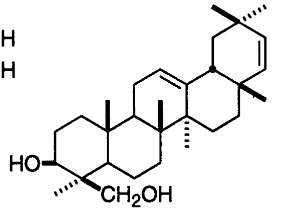
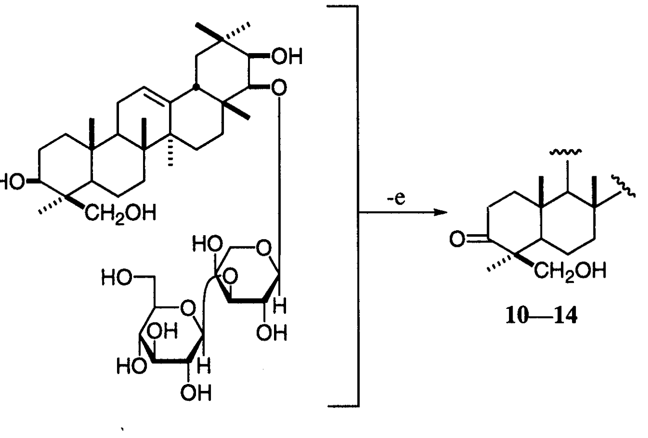

soyasapogenol C (**6**)



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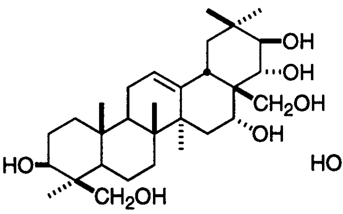
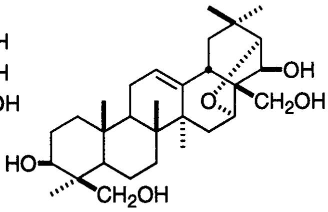
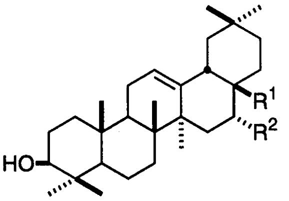
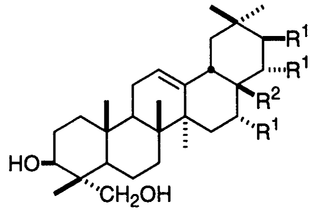
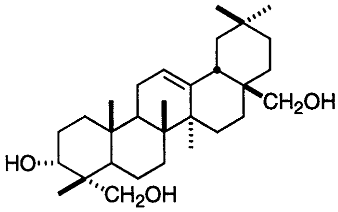
10—**14**


protoaescigenin (**7**)


aescigenin (**8**)


β-amyrin (**15**) : R^1=CH_3, R^2=H
erythradiol (**16**) : R^1=CH_2OH, R^2=H
primulagenin (**17**) : R^1=CH_2OH, R^2=OH


hederatriol (**18**) : R^1=H, R^2=CH_2OH
hederagenin methyl ester (**19**) : R^1=H, R^2=$COOCH_3$
theasapogenol A (**20**) : R^1=OH, R^2=CH_2OH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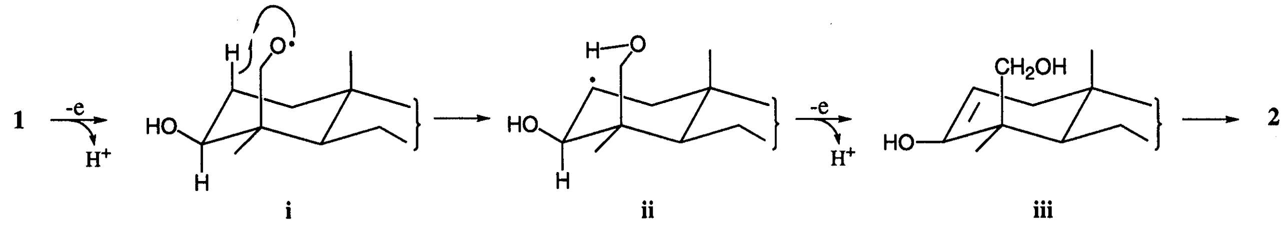

We next examined the extension of this oxidation method to other polyhydroxyl triterpenes (**5**—**8**, **15**—**20**)[4,7] and soyasapogenol A oligoglycoside (**9**).[8] Among them, triterpene alcohols (**5**—**8**) with the 3,24-dihydroxyl moiety were found to provide the corresponding 3-ketone derivative, respectively [**10** (72.7%),[9] **11** (92.0%),[10] **12** (82.3%),[11] and **13** (67.0%)[12]] by indirect anodic oxidation using KI in *t*-BuOH-H_2O. Furthermore, soyasapogenol A oligoglycoside (**9**) was also converted to the 3-ketone derivative (**14**)[13] in 80.2% yield without previous protection of the hydroxyl groups in the glycosidic moiety. On the other hand, other triterpene alcohols (**15**—**20**), which lacked the 24-hydroxyl group, yielded no product under the same anodic oxidation conditions as that for **5**—**8** and were recovered almost completely. These findings led us to assume that the selective anodic oxidation of the 3-hydroxyl group was specific to the triterpene alcohol with the 3,24-dihydroxyl moiety.

To shed light on the reaction pathway for selective anodic oxidation, we examined the electrolysis of the 24-protected derivatives (**1a, 1b**) and the 3-epimer (**21**) of **18**. In the case of the 24-protected derivatives (**1a, 1b**), no corresponding 3-ketone derivatives were obtained and the starting compounds were recovered. Here again, it was confirmed that the 24-hydroxyl group was indispensable to this selective anodic oxidation. The 3α,23-dihydroxyl derivative (**21**) was also found to give no product by anodic oxidation. On the basis of the above-mentioned evidence, although some other pathways could be considered, an electrochemical process would be proposed for the present anodic oxidation. Namely, electrochemically generated active iodine species may initially abstract a hydrogen atom from the less-hindered 24-primary hydroxyl group in **1** to form a radical intermediate (**i**), which would abstract the 2β-proton in the vicinity[14] to yield a radical (**ii**). One-electron oxidation at **ii** and successive deprotonation would provide the 3-ketone (**2**) *via* an enol (**iii**).

Recently, it was reported that dihydrosoyasaponin I and sandosaponins, which possess a ketone group in the triterpene moiety, showed more potent bioactivities than their alcoholic compounds, soyasaponins I and V.[15] Since the present anodic oxidation method requires no previous protection of hydroxyl groups, it may be significant in the synthesis of partially oxidized derivatives from triterpene saponins.

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4) Kitagawa I., Wang H. K., Taniyama T., Yoshikawa M., *Chem. Pharm. Bull.*, **36**, 153-161 (1988).
5) **2** : colorless fine crystals, mp 195-198°C, $[\alpha]_D$ +90.6° ($CHCl_3$), $C_{30}H_{48}O_3$. IR (KBr, cm^{-1}) : 3486, 1701. ^1H-NMR ($CDCl_3$, δ) : 0.88, 0.92, 1.00, 1.01, 1.04, 1.13, 1.27 (3 H each, all s, *tert*-CH_3x7), 3.43 (1 H, t-like, 22-H), 3.49, 3.98 (1 H each, both d, *J*=11.2 Hz, 24-H_2), 5.28 (1 H, dd, *J*=3.6, 3.6 Hz, 12-H). EI-MS (%) : *m/z* 456 (M^+, 6.5), 234 (100).
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9) 21β,22β,24-trihydroxyolean-12-en-3-one (**10**) : colorless fine crystals, mp 208-212°C, $[\alpha]_D$ +138.6° ($CHCl_3$), $C_{30}H_{48}O_4$, IR (KBr, cm^{-1}) : 3483, 1701, ^1H-NMR ($CDCl_3$) δ : 0.96 (6 H), 1.01 (9 H), 1.17, 1.27 (3 H each) (all s, *tert*-CH_3x7), 3.41, 3.51 (1 H each, both d, *J*=3.3 Hz, 21, 22-H), 3.49, 3.98 (1 H each, both d, *J*=11.0 Hz, 24-H_2), 5.28 (1 H, dd, *J*=3.6, 3.6 Hz, 12-H), EI-MS (%) : *m/z* 472 (M^+, 2.1), 250 (100).
10) 24-hydroxyolean-12,21-dien-3-one (**11**) : colorless fine crystals, mp 148-151°C, $[\alpha]_D$ +73.0° ($CHCl_3$), $C_{30}H_{46}O_2$, IR (KBr, cm^{-1}) : 3511, 1701, ^1H-NMR ($CDCl_3$) δ : 0.86, 0.96, 0.98, 1.00, 1.01, 1.13, 1.28 (3 H each, all s, *tert*-CH_3x7), 3.48, 3.99 (1 H each, both d, *J*=11.2 Hz, 24-H_2), 5.22, 5.29 (1 H each, both d, *J*=9.9 Hz, 21, 22-H), 5.33 (1 H, dd, *J*=3.3, 3.6 Hz, 12-H), EI-MS (%) : *m/z* 438 (M^+, 1), 216 (100).
11) 16α,21β,22α,24,28-pentahydroxyolean-12-en-3-one (**12**) : colorless fine crystals, mp 212-215°C, $[\alpha]_D$ +61.5° ($CHCl_3$), $C_{30}H_{48}O_6$, IR (KBr, cm^{-1}) : 3453, 1701, ^1H-NMR ($CDCl_3$) δ : 0.92, 0.99 (6 H each), 1.28, 1.43 (3 H each) (all s, *tert*-CH_3x6), 3.34, 3.55 (2 H, ABq, *J*=10.6 Hz, 28-H_2), 3.48, 3.97 (1 H each, both d, *J*=11.2 Hz, 24-H_2), 3.76, 3.87 (1 H each, both d, *J*=9.6 Hz, 21, 22-H), 4.58 (1 H, br s, 16-H), 5.32 (1 H, dd, *J*=3.0, 3.6 Hz, 12-H), Negative-mode FAB-MS : *m/z* 503 $[(M-H)^-]$.
12) 22α,24,28-trihydroxyolean-12-en-3-on-16α,21α-oxide (**13**) : a white powder, $[\alpha]_D$ +59.8° ($CHCl_3$), $C_{30}H_{46}O_5$, IR (KBr, cm^{-1}) : 3350, 1701, ^1H-NMR ($CDCl_3$) δ : 0.89 (3 H), 0.99 (6 H), 1.04, 1.27, 1.50 (3 H each) (all s, *tert*-CH_3x6), 3.48 (1 H, br s, 22-H), 3.50, 3.96 (1 H each, both d, *J*=11.2 Hz, 24-H_2), 3.62, 3.67 (2 H, ABq, *J*=11.0 Hz, 28-H_2), 4.22 (1 H, br s, 21-H), 4.49 (1 H, br s, 16-H), 5.25 (1 H, t-like, 12-H).
13) **14** : colorless fine crystals, mp 209-212°C, $[\alpha]_D$ +80.0° (MeOH), $C_{41}H_{66}O_{13}$, IR (KBr, cm^{-1}) : 3431, 1701, ^1H-NMR (pyridine-d_5, δ) : 1.01, 1.17, 1.23 (3 H each), 1.37 (6 H), 1.51 (3 H) (all s, *tert*-CH_3x7), 3.78 (1 H, br s, 22-H), 3.88, 4.38 (1 H each, both d, *J*=11.6 Hz, 24-H_2), 4.65 (1 H, t-like, 21-H), 4.89 (1 H, d, *J*=8.3 Hz, 1'-H), 5.26 (1 H, d, *J*=7.9 Hz, 1''-H), 5.36 (1 H, br s, 12-H), positive-mode FAB-MS : *m/z* 789 $[(M+Na)^+]$.
14) It is presumed that the 2β-H may be favorably abstracted through a six-membered transition state.
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