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Aerobic oxidation of 8,11,13-abietatrienes catalyzed by *N*-hydroxyphthalimide combined with 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) and its application to synthesis of naturally occurring diterpenes

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ABSTRACT

Methyl 8,11,13-abietatriene-18-oate (**1b**) and 7-oxo-8,11,13-abietatrienes **10** and **15** were converted into 15-hydroperoxy-7-oxo-8,11,13-abietatrienes **13** and **16** by aerobic oxidation catalyzed by *N*-hydroxyphthalimide (NHPI) combined with 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) at room temperature, and several abietane and podocarpane terpenes were synthesized from **13** and **16**.

The oxidized derivatives[1] of 8,11,13-abietatrien-18-oic acid (**1a**) and 8,11,13-abietatriene (**2**) such as 15-hydroxy-7-oxo compounds **3a**[1c,d] and **4**[1b] and 7,14-dihydroxy compounds **5a**[1a,c,e] and **6a**[1d] have been isolated from the extracts of plants or from microorganism metabolites of **1a** and some of them have demonstrated promising antimicrobial and tumor-inhibitory properties (Fig. 1).[1c,f,g] Isolation and identification of **3a**, **5a**, and **6a** were carried out after converting into methyl esters **3b**, **5b**, and **6b**. Podocarpane phenols **7a**[2a] and **8**[2b] have been isolated, respectively, from *Pinus massoniana* and *Taiwania cryptomerioides*, and the antibacterial activity of **8** was reported.[2c] 13-Hydroxy-7-oxo compound **9** was also known as a potential antiviral agent.[3]

Since **1a** is readily and abundantly available from disproportionated rosin, **1a** has been utilized as a starting compound for naturally occurring abietane and podocarpane terpenes. A method for the preparation of **3a** and **9** from **1a** was already reported.[4] Oxidation of **1a** with chromic trioxide in acetic anhydride and acetic acid followed by hydrolysis with aqueous potassium hydroxide gave **3a** (26% from **1a**), and the corresponding methyl ester **3b** was oxidized with *t*-butyl hydroperoxide in acetic acid containing H_2SO_4 to afford **9** (19% from **1a**). However, the yields of **3a** and **9** were low in this method, and the use of noxious chromic trioxide for oxidation should be avoided if possible.

The aerobic oxidation of methyl 8,11,13-abietatrien-18-oate (**1b**) in the presence of benzoyl peroxide was reported to give 7-oxo compound **10** (25%) and 7-hydroperoxide **11** (29%) along with a small amount of 15-hydroperoxide **12**.[5] 15-hydroperoxy-7-oxo compound **13** was not found on oxidation. On the other hand, the 7-oxo compound **10**, prepared from **1b** by chromic oxidation in 52% yield, was oxidized under O_2 in the presence of 2.5 mol % benzoyl peroxide at 90 °C to give the reaction mixture containing hydroperoxide **13** (hydroperoxide content 40–50%); **13** was not isolated from the mixture.[6] The crude mixture was treated with acetic acid containing 1% $HClO_4$ to afford **9** in 30–35% yield. This method seems unsatisfactory for the preparation of **9**, because noxious chromic trioxide was used for oxidation of **1b** and the yield of **9** was low (ca. 15% from **1b**). A more efficient catalyst than benzoyl peroxide is necessary for the oxidation of **10**.

Novel aerobic oxidation of arylalkanes by *N*-hydroxyphthalimide (NHPI) as a catalyst at 100 °C was first reported by Ishii et al.[7,8] and the oxidation under milder conditions has been achieved by NHPI and co-catalyst systems such as NHPI and cobalt(II) acetate at room temperature,[9] NHPI and azobis(isobutyronitrile) (AIBN) at 75 °C,[10] and NHPI and 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) at 30 °C.[11] It is expected that the aerobic oxidation at around room temperature by the NHPI-cobalt(II) system or the NHPI-V-70 system can be applied to the conversion of abietatrienes **1b**, **2**, **10**, and **15** into the corresponding hydroperoxides **13** and **16**, which are important intermediates for the synthesis of naturally occurring diterpenes **3–6** and trinorditerpenes **7–9**. We report herein the optimal reaction conditions for the NHPI-catalyzed aerobic oxidation of 8,11,13-abietatrienes and its application to the synthesis of naturally occurring abietane and podocarpane terpenes.

The reaction of **1b**, prepared from **1a** by the treatment with CH_2N_2 in quantitative yield, under oxygen (1 atm) in acetonitrile in the presence of 0.1 equiv of NHPI and 0.04 equiv of cobalt(II) acetate was first examined (Table 1). When the reaction was performed at 30 °C for 48 h, **10**, **13**, **3b**, and **14** were obtained in 6%, 24%, 44%, and 14% yields, respectively (entry 1). The reaction at 50 °C chiefly afforded **3b** and **14** (entry 2). Although the production of **3b** and **14** was predicted because redox decomposition of the hydroperoxide with cobalt ion was already reported to give alcohol

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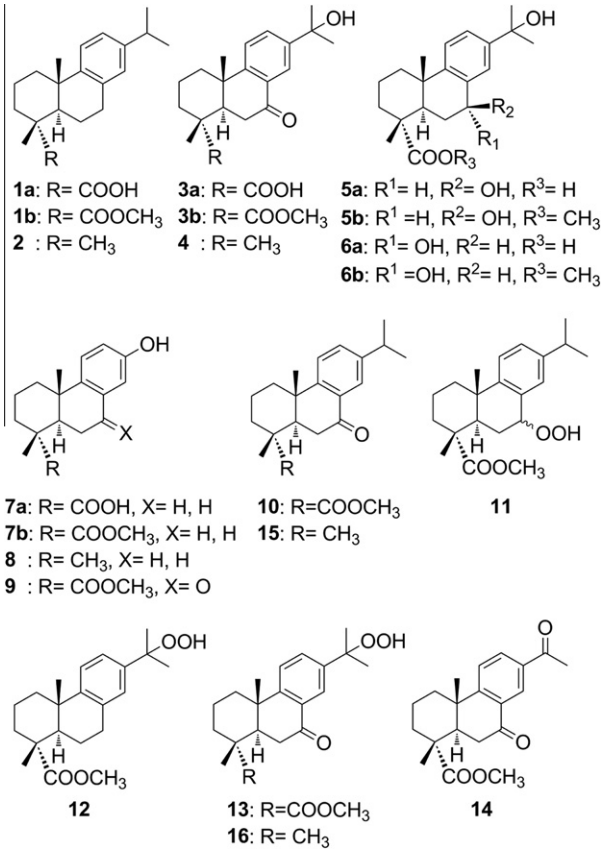
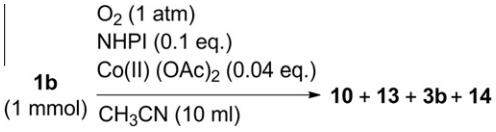


Figure 1. Abietane and podocarpane derivatives.

Table 1
Aerobic oxidation of **1b** catalyzed by NHPI combined with cobalt(II) acetate

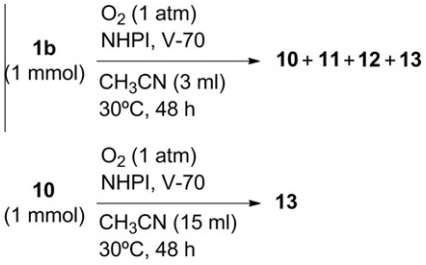


Entry	Temp (°C)	Time (h)	Isolated yield (%)				Recov. (%)
			10	**13**	**3b**	**14**	
1	30	48	6	24	44	14	0
2	50	48	0	0	55	20	0
3	30	24	40	38	13	Trace	0
4	23	48	41	34	7	Trace	0

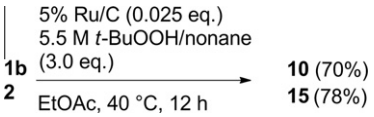
and ketone,[9] it is noteworthy that the hydroperoxide **13** was obtained under the conditions using NHPI and cobalt(II) acetate. To our knowledge this is the first isolation of the hydroperoxide on the oxidation of arylalkanes by the NHPI and cobalt(II) system When the reaction was carried out at 30 °C for 24 h or 23 °C for 48 h, **10** and **13** were the major products (entries 3 and 4).[12] Oxidation at a low temperature appreciably prevents the redox decomposition of the hydroperoxide **13** (entry 4). The 15-hydroperoxide **12** was not isolated in all cases. It seems likely that the production of **12** occurs first, followed by a more rapid conversion into **13** under the present oxidation conditions. One of the shortcomings of this reaction is that chromatographic separation of the hydroperoxide **13** and the alcohol **3b** is somewhat difficult.

The aerobic oxidation of **1b** and **10** catalyzed by NHPI combined with V-70 was investigated next (Table 2). The oxidation of **1b** in

Table 2
Aerobic oxidation of **1b** and **10** catalyzed by NHPI combined with 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70)



Entry	Substrate	NHPI (equiv)	V-70 (equiv)	Isolated yield (%)				Recov. (%)
				10	**11**	**12**	**13**	
1	**1b**	0.1	0.02	10	31	17	4	24
2	**1b**	1.0	0.20	16	8	10	41	0
3	**10**	0.1	0.02	—	—	—	23	74
4	**10**	1.0	0.20	—	—	—	90	Trace

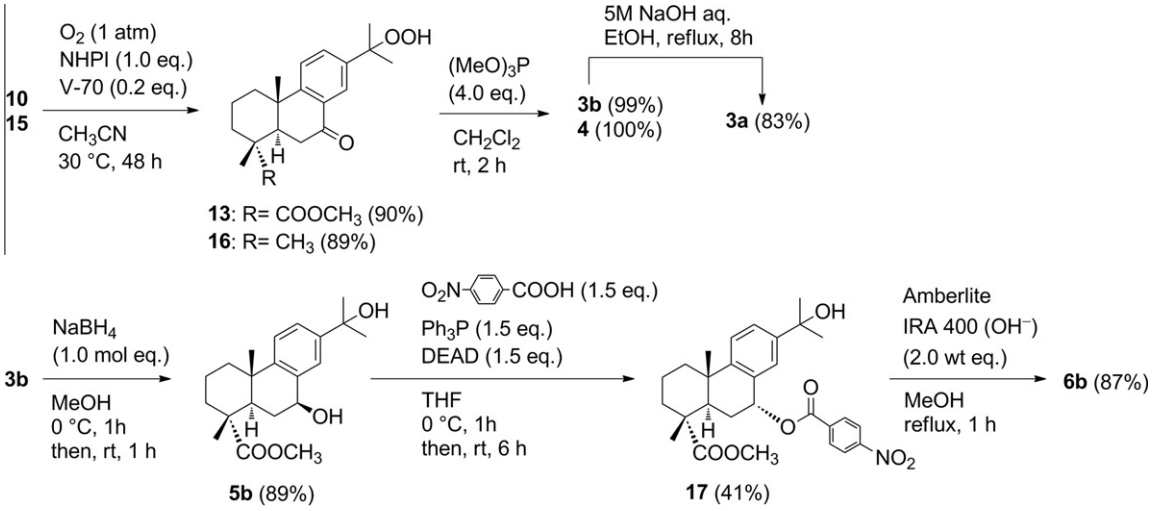


Scheme 1.

the presence of NHPI (0.1 equiv) and V-70 (0.02 equiv) under O_2 (1 atm) in acetonitrile for 48 h afforded 7-hydroperoxy and 7-oxo compounds **10** and **11** (41%), 15-hydroperoxide **12** (17%), and 15-hydroperoxy-7-oxo compound **13** (4%) (entry 1). Increasing NHPI and V-70 afforded **13** in 41% yield (entry 2). On the other hand, the oxidation of 7-oxo compound **10** predominantly gave **13**, and its yield was 90% when using 1.0 equiv of NHPI and 0.2 equiv of V-70 (entries 3 and 4).[13] When **10** obtained in 16% yield from the reactions shown in entry 2 is oxidized under the same conditions as described in entry 4, the total yield of **13** can reach up to 55% through twice oxidation processes.

Thus, oxidations of **1b** by the catalytic systems of both NHPI-cobalt(II) acetate (0.1 equiv and 0.04 equiv) and NHPI-V-70 (1.0 equiv and 0.2 equiv) gave the 15-hydroperoxy-7-oxo compound **13** in moderate yields, however, the oxidations of **1b** always accompanied minor products such as **10**, **11**, and **12**. The selective conversion of **10** into **13** by the NHPI-V-70-catalyzed oxidation is probably used as it is advantageous for the synthesis of naturally occurring diterpenes, if **10** is selectively prepared from **1b** by other methods. Chromic oxidation of 8,11,13-abietatrienes **1b** and **2** with chromic trioxide in aqueous acetic acid has been usually used for preparation of the corresponding 7-oxo compounds **10** and **15** in 52% and 67% yields, respectively.[6,14] In order to avoid chromic oxidation process, we first examined a new method for the oxidation of **1b** and **2**.[15] Murahashi and et al. have reported that a catalytic oxidation system with *t*-BuOOH in the presence of $RuCl_2(PPh_3)_2$ in benzene was suitable for the synthesis of aryl ketones from arylalkanes.[16] We applied this oxidation system to **1b** and **2** and optimized the reaction conditions. When 5% Ru/C in ethyl acetate was used in place of $RuCl_2(PPh_3)_2$ in benzene on oxidation with *t*-BuOOH, **1b** and **2** were oxidized to **10** and **15** in best yields of 70% and 78% as shown in Scheme 1. Details of optimization on the oxidation will be reported elsewhere.

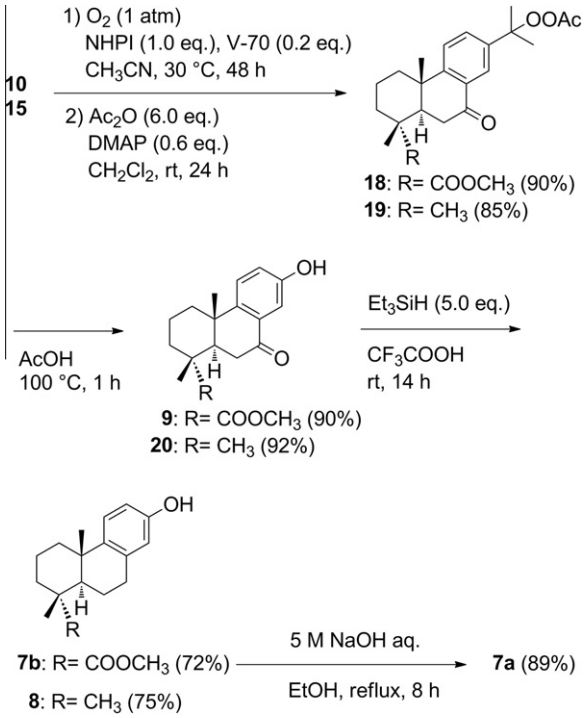
Scheme 2 summarizes the synthesis of the oxidized abietane terpenes from **10** and **15**. The aerobic oxidation of **10** and **15** catalyzed by NHPI and V-70 afforded 15-hydroperoxides **13** and **16** in



Scheme 2.

high yields, which were converted into alcohols **3b** and **4** by reduction with trimethyl phosphite. Hydrolysis of **3b** afforded the desired acid **3a**. On the other hand, the keto alcohol **3b** was reduced with sodium borohydride in methanol to give 7β,15-dihydroxy compound **5b**. The reaction of **5b** with *p*-nitrobenzoic acid using the Mitsunobu method[17] afforded 7α-*p*-nitrobenzoyloxy compound **17**. Methanolysis of **17** with refluxing methanol in the presence of the anion exchange resin Amberlite IRA 400 yielded methyl 7α,15-dihydroxy compound **6b** in 20% yield from **1a**. Although **6b** has been reported to be isolated from the microorganism metabolites of **1a**,[1e] its chemical conversion into **6b** was first reported in the present work.

Scheme 3 shows the synthesis of the naturally occurring podocarpane terpenes. The aerobic oxidation of **10** and **15** catalyzed by NHPI and V-70 followed by acetylation with acetic anhydride gave 15-acetylperoxy-7-oxo compounds **18** and **19** in good yields, which readily underwent rearrangement in acetic acid at 100 °C to afford 13-hydroxy-7-oxopodocarpatriene derivatives **9** and **20** in high yields. Reduction of **9** and **20** with triethylsilane in trifluoroacetic acid gave **7b** and **8**. Hydrolysis of **7b** gave the desired acid **7a**.



Scheme 3.

In conclusion, the aerobic oxidation of abietatrienes **1b**, **10**, and **15** catalyzed by NHPI and V-70 gave 15-hydroperoxy-7-oxo-8,11,13-abietatriene derivatives **13** and **16**. Naturally occurring abietane diterpenes **3a**, **4**, **5b**, and **6b** were synthesized from **13** and **16** as key intermediates. Furthermore, a facile synthesis of 13-hydroxy-8,11,13-podocarpatrienes **7a**, **8**, and **9** was accomplished via the present hydroperoxygenation of **10** and **15** followed by acetylation and rearrangement reaction.

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12. *General procedure*: To an acetonitrile (10 ml) solution of **1b** (314 mg, 1 mmol) and NHPI (16.3 mg, 0.1 mmol) in a 50-ml kjeldahl flask equipped with three-

way stopcock was added cobalt(II) acetate tetrahydrate (10.0 mg, 0.04 mmol). The atmosphere in the flask was replaced with oxygen by bubbling for 5 min, and then an oxygen balloon was attached to the flask through the three-way stopcock. The reaction mixture was stirred at 23, 30, or 50 °C for 48 or 24 h. The solvent was removed under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel with hexane–ethyl acetate (4:1 and then 2:1) to give the corresponding products.

13. *Typical procedure*: An acetonitrile (15 ml) solution of **10** (329 mg, 1 mmol) and NHPI (163 mg, 1.0 mmol) in a 50-ml kjeldahl flask equipped with three-way stopcock was added V-70 (62 mg, 0.2 mmol). The atmosphere in the flask was replaced with oxygen by bubbling for 5 min, and then an oxygen balloon was attached to the flask through the three-way stopcock. The reaction mixture was stirred at 30 °C for 48 h. The solvent was removed under reduced pressure to afford the residual solid. The residue was dissolved in hexane–ethyl acetate (1:1) and insoluble NHPI was filtered off and washed with hexane–ethyl acetate (1:1). After the filtrate has been evaporated under reduced pressure, the crude product was purified by flash column chromatography on silica gel with hexane–ethyl acetate (4:1 and then 2:1) to give **13** (324 mg) in 90% yield: mp 128.8–130.0 °C (hexane–diethyl ether). $[\alpha]_D^{20}$ +9.38 ($CHCl_3$, *c* 0.95). IR ($CHCl_3$) ν 3570, 3400, 3025, 2980, 2900, 1740, 1695, 1620, 1470, 1270, and 1130 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.27 (3H, s, H-20), 1.35 (3H, s, H-19), 1.59 and 1.60 (each 3H, s, H-16 and H-17), 1.60–1.64 (5H, m, H-1a, H-2, H-3), 2.33–2.45 (2H, m, H-1b, H-6), 2.68–2.83 (2H, m, H-5, H-6), 3.66 (3H, s, $COOCH_3$), 7.39 (1H, d, J = 8.4 Hz, H-11), 7.53 (1H, dd, J = 8.4 Hz, 2.4 Hz, H-12), 7.74 (1H, s, OOH), 8.04 ppm (1H, d, J = 2.4 Hz, H-14). ^{13}C NMR ($CDCl_3$) δ 16.31 (C-19), 18.05 (C-2), 23.55 (C-20), 25.91 and 26.11 (C-16 and C-17), 36.47 (C-3), 36.96 (C-1), 37.34 (C-10), 37.71 (C-6), 43.58 (C-5), 46.60 (C-4), 52.17 (C–OCH_3), 83.38 (C-15), 123.73 (C-14), 124.30 (C-11), 130.60 (C-8), 131.40 (C-12), 143.35 (C-13), 154.30 (C-9), 177.78 (C-18), 198.58 (C-7); Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.20; H, 8.02.
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