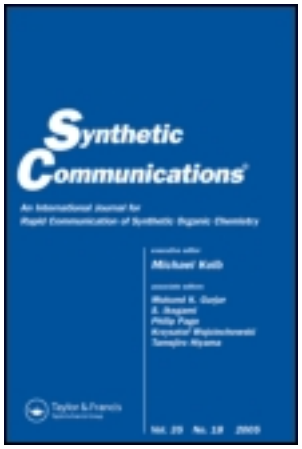

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Facile Access to 3-Alkyl-Substituted 3-Hydroperoxy-2,4-pyrrolidinediones Using Manganese(III)-Catalyzed Aerobic Oxidation

M. Aminul Haque [a] & Hiroshi Nishino [a]

[a] Department of Chemistry, Graduate School of Science and Technology, Kumamoto University, Kumamoto, Japan

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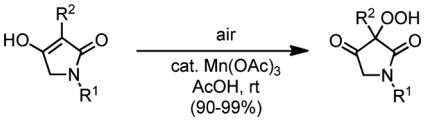
FACILE ACCESS TO 3-ALKYL-SUBSTITUTED 3-HYDROPEROXY-2,4-PYRROLIDINEDIONES USING MANGANESE(III)-CATALYZED AEROBIC OXIDATION

M. Aminul Haque and Hiroshi Nishino

Department of Chemistry, Graduate School of Science and Technology, Kumamoto University, Kumamoto, Japan

GRAPHICAL ABSTRACT



R^1 = Bn, Bu, *t*-Bu, *i*-Pr R^2 = Me, Et, Pr, Bu, *n*-C_6H_{13}

Abstract *3-Alkyl-substituted 2,4-pyrrolidinediones were directly oxidized under very mild manganese(III)-catalyzed aerobic oxidation conditions to give the corresponding 3-hydroperoxy-2,4-pyrrolidinediones in quantitative yields. The scope and limitations for the synthesis of the hydroperoxyprrolidinediones are described.*

Keywords Aerobic oxidation; catalytic oxidation; hydroperoxidation; hydroperoxypyrrolidinediones; manganese(III) acetate; 2,4-pyrrolidinediones

INTRODUCTION

Hydroperoxides are known as the first intermediate for the oxidative decomposition of unsaturated higher fatty acids in vivo, are normally unstable, and thus are successively oxidized into degradation products.[1] Some heterocyclic hydroperoxides function as antitumor,[2] antimalarial,[3] antibiotic,[4] antibacterial,[4] and anti-inflammatory agents.[5] Therefore, the synthesis of new heterocyclic hydroperoxides is important from the viewpoint of determining their activities, even though they may be unstable. We previously reported that the manganese(III)-catalyzed oxidation of 4-monosubstituted 1,2-diphenylpyrazolidine-3,5-diones gave the corresponding 4-hydroperoxypyrazolidinediones (Scheme 1).[6a] Because the reaction is quite simple and convenient for the synthesis of hydroperoxides, we attempted to apply the hydroperoxidation to 3-alkyl-substituted 2,4-pyrrolidinediones to synthesize new types of heterocyclic hydroperoxides.

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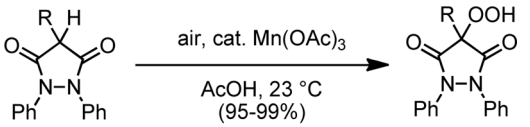
Address correspondence to H. Nishino, Department of Chemistry, Graduate School of Science and Technology, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan. E-mail: nishino@sci.kumamoto-u.ac.jp



R = Me, Et, Pr, *i*-Pr, Bu, *t*-Bu, Bn, Cp

Scheme 1. Manganese(III)-catalyzed direct hydroperoxidation of pyrazolidinediones.

RESULTS AND DISCUSSION

3-Alkyl-substituted 2,4-pyrrolidinediones were prepared by the Dieckmann condensation of *N*-alkanoyl-*N*-alkylglycinates, which were produced by the reaction of α-bromoacetate with alkylamines followed by alkanoylation with the corresponding alkanoyl chloride.[7] The 2,4-pyrrolidinediones exist as an enol form in an aprotic polar solvent, such as dimethylsulfoxide (DMSO-d_6).[8]

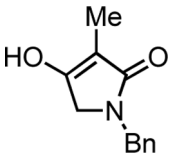
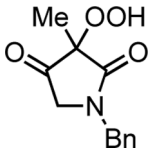
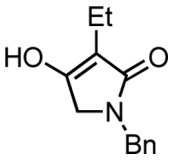
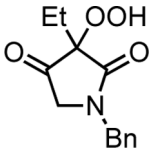
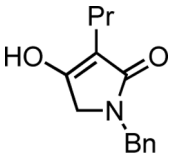
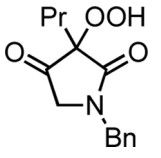
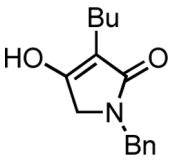
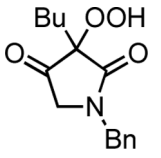
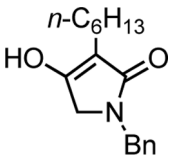
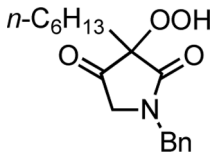
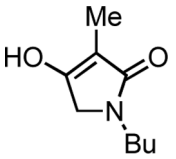
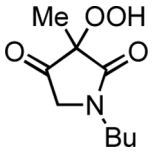
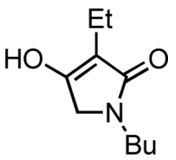
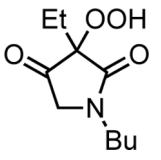
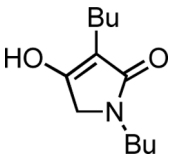
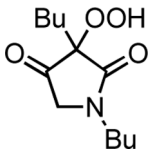
With the 3-substituted 2,4-pyrrolidinediones in hand, we explored the hydroperoxidation of 2,4-pyrrolidinedione ($R^1 = Bn$, $R^2 = Me$). The reaction was carried out in glacial acetic acid at room temperature using a stoichiometric amount of manganese(III) acetate. After 2 h, the oxidant was consumed and the desired hydroperoxide was obtained in 65% yield (Scheme 2 and Table 1, entry 1). Because the product seemed to be decomposed by the manganese(III) oxidant,[6] the reaction using a catalytic amount of manganese(III) acetate was next examined. The reaction was carried out under similar conditions and quenched by adding water after 14 h, giving the corresponding hydroperoxide in a modest yield (entry 2), probably as a result of the instability of the product in the solvent. The reaction under an oxygen atmosphere also gave a similar result (entry 3). Finally, we found the optimum reaction conditions; that is, the reaction was conducted at room temperature in air for 2 h using a catalytic amount of manganese(III) acetate and produced the hydroperoxide in 94% yield (entry 4).

A broad singlet signal (1H) in the ^{1}H NMR spectrum of the hydroperoxide ($R^1 = Bn$, $R^2 = Me$) appeared at δ 11.28 ppm and a broad absorption band appeared at 3400–3000 cm^{-1} in the infrared (IR) spectrum, which were assigned to a hydroperoxy group because the product in dichloromethane showed a positive potassium iodide–starch test. The ^{1}H NMR spectrum also showed two doublets at δ 4.79 and 4.64 ($J = 14.7$ Hz) due to the H-5 methylene protons of the pyrrolidinedione. The ^{13}C NMR spectrum revealed two carbonyl carbons at δ 204.1 and 171.3 ppm and in the IR spectrum at 1786 and 1666 cm^{-1} assigned to a keto group and amide

R^1 = Bn, Bu, *t*-Bu, *i*-Pr
R^2 = Me, Et, Pr, Bu, *n*-C_6H_{13}

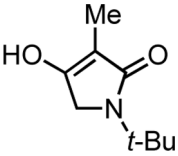
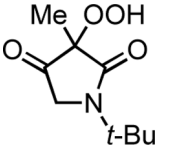
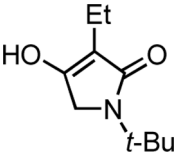
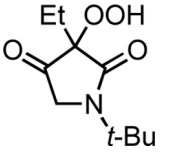
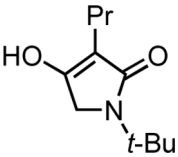
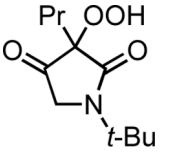
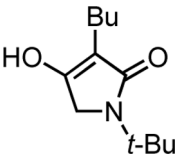
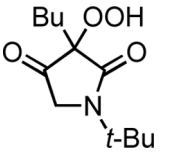
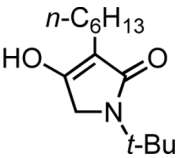
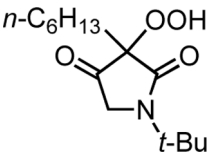
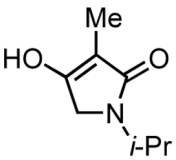
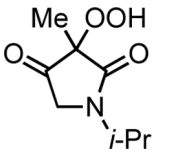
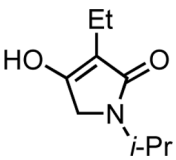
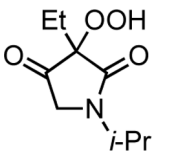
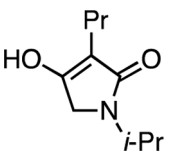
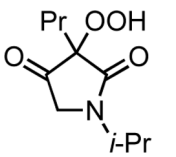
Scheme 2. Manganese(III)-catalyzed aerobic oxidation of 3-alkyl-substituted 2,4-pyrrolidinediones.

Table 1. Reaction of 3-substituted 2,4-pyrrolidinediones in the presence of manganese(III) acetate[a]

Entry	Pyrrolidinedione	Sub./$Mn(OAc)_3$[b]	T (h)	Product	(%)[c]
1		1:1	2		65
2		1:0.1	14		68
3		1:0.1	2		70[d]
4		1:0.1	2		94
5		1:0.1	2		95
6		1:0.1	2		98
7		1:0.1	2		93
8		1:0.1	2		96
9		1:0.1	1.5		91
10		1:0.1	1.5		90
11		1:0.1	1.5		95

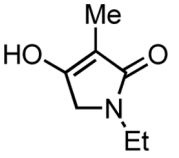
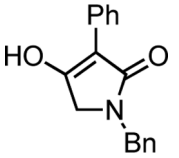
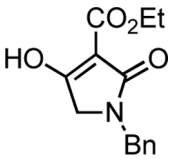
(*Continued*)

Table 1. Continued

Entry	Pyrrolidinedione	Sub./$Mn(OAc)_3$[b]	T (h)	Product	(%)[c]
12		1:0.1	1.5		90
13		1:0.1	1.5		96
14		1:0.1	1.5		99
15		1:0.1	1.5		99
16		1:0.1	1.5		98
17		1:0.1	1.5		95
18		1:0.1	1.5		97
19		1:0.1	1.5		98

(*Continued*)

Table 1. Continued

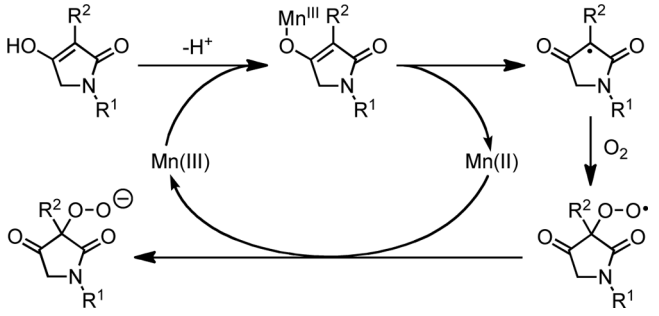
Entry	Pyrrolidinedione	Sub./$Mn(OAc)_3$[b]	T (h)	Product	(%)[c]
20		1:0.1	1.5	Comp. mix.[e]	
21		1:0.1	2	n.r.[f]	
22		1:0.1	2	Comp. mix.[e]	

[a]The reaction of 2,4-pyrrolidinediones (1 mmol) was carried out in acetic acid (25 mL) at ambient temperature in air.
[b]Molar ratio.
[c]The yield based on the amount of 2,4-pyrrolidinedione.
[d]The reaction was conducted under an oxygen atmosphere (1 atm).
[e]The reaction gave an intractable mixture.
[f]The reaction did not occur and the substrate was recovered.

carbonyl group, respectively. The high-resolution fast atom bombardment (FAB) mass spectrum also agreed with the exact mass. As a result, the structure of the product was determined to be 1-benzyl-3-hydroperoxy-3-methylpyrrolidine-2,4-dione. Although the product crystallized from diethyl ether/hexane provided single crystals, unfortunately, the crystals did not survive during the x-ray diffraction measurement.

To expand the scope of this reaction with respect to the 2,4-pyrrolidinediones, the reaction of various 3-alkylsubstituted 2,4-pyrrolidinediones ($R^1 = Bu$, *t*-Bu, or *i*-Pr, $R^2 = Et$, Pr, Bu, or hexyl) was conducted under the optimized reaction conditions mentioned previously, and similar hydroperoxides were obtained in comparable yields (entries 5–19). Although the hydroperoxides were obtained as colorless solids, except for the 1-butyl-3-hydroperoxypyrrolidine-2,4-dione as a liquid, the products gradually decomposed at ambient temperature in air within 2 or 3 days along with the evolution of gas and even when stored in a refrigerator at $-20\,^{\circ}C$ for a half year.

A similar reaction of 1-ethyl-2,4-pyrrolidinedione ($R^1 = Et$, $R^2 = Me$) gave an intractable mixture and the corresponding hydroperoxide was not isolated (entry 20). This is probably because of the instability of the product as well as the substrate, since 1-methyl-2,4-pyrrolidinedione ($R^1 = R^2 = Me$) was also prepared by a manner similar to that mentioned previously but in a poor yield because of its instability. The reaction



Scheme 3. Catalytic oxidation pathway.

of 2,4-pyrrolidinediones with 3-phenyl and 3-ethoxycarbonyl groups also failed. The 3-phenyl-substituted 2,4-pyrrolidinedione ($R^1 = Bn$, $R^2 = Ph$) has a solubility problem and it did not dissolve even in acetic acid, ethanol, and chloroform at room temperature. Therefore, the reaction did not occur and the pyrrolidinedione was recovered (entry 21). The 2,4-pyrrolidinedione-3-carboxylate ($R^1 = Bn$, $R^2 = CO_2Et$) gave an intractable mixture (entry 22). The pyrrolidinedione radical at C-3 might be labilized by the ethoxycarbonyl group such as an electron-withdrawing group (vide infra).

The mechanism for the formation of the hydroperoxides could be explained by the manganese(III)-catalyzed aerobic oxidation, similar to the production of the 4-hydroperoxypyrazolidinediones.[6a] The mechanism is outlined in Scheme 3. The alkyl group (R^2) substituted at C-3 must be essential for the formation of the pyrrolidinedione radical followed by capturing molecular oxygen.

In summary, we have demonstrated the facile hydroperoxidation of 3-alkyl-substituted 2,4-pyrrolidinediones under manganese(III)-catalyzed aerobic oxidation conditions, although the 3-hydroperoxypyrrolidine-2,4-diones were not stable at ambient temperature in air except for the *N*-benzyl-protected hydroperoxypyrrolidinedione ($R^1 = Bn$, $R^2 = Me$). The oxidation of the 2,4-pyrrolidinediones having a small *N*-protecting group, such as the methyl and ethyl group, and an electron-withdrawing group at the C-3 position, such as ethoxycarbonyl group, produced a complex mixture, and the attempted isolation of the hydroperoxide was unsuccessful. The reaction of 3-phenyl-substituted 2,4-pyrrolidinedione did not proceed because of poor solubility in acetic acid under the reaction conditions.

EXPERIMENTAL

Materials

The NMR spectra were measured at 300 MHz and 500 MHz for ^1H and at 75 Hz and 125 Hz for ^{13}C, respectively, with tetramethylsilane as the internal standard. The chemical shifts are reported in parts per million (ppm) and the coupling constants in hertz. The IR spectral data are expressed in centimeters^{-1}. The electron impact mass spectrometry (EIMS) spectra were recorded at the ionizing voltage of 70 eV. The high-resolution mass spectra (HRMS) were measured and the elemental analyses were performed at the Analytical Center of Kumamoto University, Kumamoto, Japan.

Preparation of 2,4-Pyrrolidinediones[7]

Propanoyl chloride (1.65 mL; 19.2 mmol) was added dropwise to a mixture of ethyl (benzylamino)acetate (3.22 mL, 17.4 mmol)[7a,b] and triethylamine (4.85 mL, 34.8 mmol) in $CHCl_3$ (25 mL) at 0 °C over 15 min. After stirring for another 1.5 h at room temperature, the mixture was diluted with $CHCl_3$ to 50 mL; washed with a 5% aqueous acetic acid solution (25 mL), water (50 mL), and brine (25 mL); dried over anhydrous $MgSO_4$; and then concentrated to dryness, affording the liquid propanoyl-protected (benzylamino)acetate with sufficient purity for use in the next step.

The prepared propanoyl-protected (benzylamino)acetate (2.5 g, 10.03 mmol) in tetrahydrofuran (50 mL) was added dropwise to a refluxing suspension of NaH (60% dispersion in mineral oil) (500 mg, 11.03 mmol) and tetrahydrofuran (50 mL) in a 300-mL, three-necked flask. After this addition, the mixture was continuously heated under reflux for 12 h. A pale yellow solid was formed during the heating and then filtered under suction. The obtained solid was dissolved in a minimum volume of water and very carefully acidified with 2 M H_2SO_4, giving 1-benzyl-3-methyl-2,4-pyrrolidinedione (keto form) as a crude precipitate. The precipitate was purified by silica-gel column chromatography, eluting with a mixture of ethyl acetate and hexane followed by recrystallization using the appropriate solvent. The other 2,4-pyrrolidinediones were prepared by a manner similar to that described previously.

1-Benzyl-4-hydroxy-3-methyl-3-pyrrolin-2-one (Enol Form)

$R_f = 0.57$ (EtOAc/hexane = 9:1 v/v); colorless needles (from ethanol/hexane); mp 146–150 °C; IR ($CHCl_3$) ν 1784 and 1697 (C=O); ^{1}H NMR (DMSO-d_6) δ 10.65 (1H, s, OH), 7.15–7.35 (5H, m, arom H), 4.46 (2H, s, CH_2-C=O), 3.63 (2H, s, $PhCH_2$), 1.58 (3H, s, Me); ^{13}C NMR (DMSO-d_6) δ 173.2 (C-2, C=O), 164.8 (C-4), 138.4, 128.6, 127.4, 127.1 (arom C), 100.2 (C-3), 49.0 (C-5, CH_2), 44.6 ($PhCH_2$), 6.4 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{12}H_{14}NO_2$ 204.1025 (M + H). Found 204.1002.

General Procedure

Manganese(III) acetate dehydrate (26.8 mg; 0.1 mmol) was added to a solution of the 2,4-pyrrolidinedione (1 mmol) in glacial acetic acid (25 mL). The mixture was stirred at room temperature in air for 1.5–2 h, and then the reaction was quenched by adding water (25 mL) to the mixture. The aqueous reaction mixture was extracted three times with CH_2Cl_2 (30 mL). The combined extract was washed with water and then a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous magnesium sulfate, and concentrated to dryness. Although the product was almost pure, it was further purified by silica-gel flash column chromatography, eluting with EtOAc/hexane (8:2 v/v) if needed.

1-Benzyl-3-hydroperoxy-3-methylpyrrolidine-2,4-dione

Yield (221.1 mg, 94%); $R_f = 0.67$ (EtOAc/hexane = 8:2 v/v); colorless blocks (from Et_2O/hexane); mp 78–79 °C; IR ($CHCl_3$) ν 3400–3000 (OOH), 1786, 1666

(C=O); ^{1}H NMR ($CDCl_3$) δ 11.28 (1H, s, OOH), 7.36–7.27 (5H, m, arom H), 4.79 (1H, d, $J = 14.7$ Hz, CH_2), 4.64 (1H, d, $J = 14.7$ Hz, CH_2), 3.75 (2H, s, CH_2), 1.39 (3H, s, Me); ^{13}C NMR ($CDCl_3$) δ 204.1 (C-4, C=O), 171.3 (C-2, C=O), 134.0, 129.1, 128.4, 128.3 (arom C), 82.5 (C-3), 53.4 (C-5, CH_2), 46.8 ($PhCH_2$), 16.7 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{12}H_{14}NO_4$ 236.0923 (M + H). Found 236.0935.

1-Benzyl-3-ethyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (236.8 mg, 95%); $R_f = 0.53$ (EtOAc/hexane = 6:4 v/v); colorless solid; mp 72–76 °C; IR ($CHCl_3$) ν 3500–3100 (OOH), 1782, 1693 (C=O); ^{1}H NMR ($CDCl_3$) 11.45 (1H, s, OOH), 7.38–7.26 (5H, m, arom H), 4.73 (2H, s, CH_2), 3.74 (1H, d, $J = 17.7$ Hz, CH_2), 3.64 (1H, d, $J = 17.7$ Hz, CH_2), 1.85 (2H, q, $J = 7.4$ Hz, CH_2), 0.89 (3H, t, $J = 7.4$ Hz, Me); ^{13}C NMR ($CDCl_3$) 204.7 (C-4, C=O), 171.0 (C-2, C=O), 134.2, 129.1, 128.4, (arom C), 86.1 (C-3), 54.1 (C-5, CH_2), 46.8 ($PhCH_2$), 25.1 (CH_2), 16.70 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{13}H_{15}NO_4Na$ 272.0899 (M + Na). Found 272.0906.

1-Benzyl-3-hydroperoxy-3-propylpyrrolidine-2,4-dione

Yield (258.0 mg, 98%); $R_f = 0.54$ (EtOAc/hexane = 5:5 v/v); colorless solid; mp 112 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1784, 1693 (C=O); ^{1}H NMR ($CDCl_3$) 11.62 (1H, s, OOH), 7.37–7.27 (5H, m, arom H), 4.76 (1H, d, $J = 14.7$, CH_2), 4.67 (1H, d, $J = 14.7$ Hz, CH_2), 3.74 (1H, d, $J = 17.7$, CH_2), 3.64 (1H, d, $J = 17.4$ Hz, CH_2), 1.75 (2H, t, $J = 8.4$ Hz, CH_2), 1.31 (2H, m, CH_2), 0.88 (3H, t, $J = 7.4$ Hz, Me); ^{13}C NMR ($CDCl_3$) 204.8 (C-4, C=O), 171.1 (C-2, C=O), 134.2, 129.1, 128.4, 128.3 (arom C), 85.7 (C-3), 54.1 (C-5, CH_2), 46.8 ($PhCH_2$), 33.5, 15.9 (CH_2), 14.1 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{14}H_{17}NO_4Na$ 286.1055 (M + Na). Found 286.1032.

1-Benzyl-3-butyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (257.9 mg, 93%); $R_f = 0.58$ (EtOAc/hexane = 5:5 v/v); colorless solid; mp 80–81 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1784, 1695 (C=O); ^{1}H NMR ($CDCl_3$) 11.37 (1H, s, OOH), 7.38–7.26 (5H, m, arom H), 4.72 (2H, s, CH_2), 3.74 (1H, d, $J = 17.6$ Hz, CH_2), 3.64 (1H, d, $J = 17.6$ Hz, CH_2), 1.79 (2H, t, $J = 8.1$ Hz, CH_2), 1.18 (4H, m, $2CH_2$), 0.84 (3H, t, $J = 6.9$ Hz, Me); ^{13}C NMR ($CDCl_3$) 204.8 (C-4, C=O), 171.0 (C-2, C=O), 134.2, 129.1, 128.4, 128.3 (arom C), 85.7 (C-3), 54.1 (C-5, CH_2), 46.8 ($PhCH_2$), 31.4, 24.4, 22.8 (CH_2), 13.6 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{15}H_{19}NO_4Na$ 300.1212 (M + Na). Found 300.1219.

1-Benzyl-3-hexyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (293.2 mg, 96%); $R_f = 0.60$ (EtOAc/hexane = 4:6 v/v); colorless solid; mp 78–80 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1784, 1691 (C=O); ^{1}H NMR ($CDCl_3$) 11.56 (1H, s, OOH), 7.38–7.27 (5H, m, arom H), 4.75 (1H, d, $J = 15.0$ Hz, CH_2), 4.69 (1H, d, $J = 15.0$ Hz, CH_2), 3.75 (1H, d, $J = 18.0$ Hz, CH_2), 3.64 (1H, d,

$J = 18.0$ Hz, CH_2), 1.78 (2H, t, $J = 7.8$ Hz, CH_2), 1.21 (8H, m, 4xCH_2), 0.85 (3H, t, $J = 6.5$ Hz, Me); ^{13}C NMR ($CDCl_3$) 204.8 (C-4, C=O), 171.1 (C-2, C=O), 134.2, 129.1, 128.4, 128.3 (arom C), 85.7 (C-3), 54.1 (C-5, CH_2), 46.8 ($PhCH_2$), 31.6, 31.3, 29.2, 22.4 (2C) (CH_2), 14.0 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{17}H_{23}NO_4Na$ 328.1525 (M + Na). Found 328.1493.

1-Butyl-3-hydroperoxy-3-methylpyrrolidine-2,4-dione

Yield (183.0 mg, 91%); $R_f = 0.52$ (EtOAc/hexane = 6:4 v/v); colorless liquid; IR ($CHCl_3$) ν 3400–3100 (OOH), 1784, 1693 (C=O); ^{1}H NMR ($CDCl_3$) 11.75 (1H, s, OOH), 3.90 (2H, s, CH_2), 3.53 (2H, t, $J = 6.9$ Hz, CH_2), 1.60 (2H, m, CH_2), 1.36 (2H, m, CH_2), 1.35 (3H, s, CH_3), 0.96 (3H, t, $J = 7.2$ Hz, Me); ^{13}C NMR ($CDCl_3$) 204.9 (C-4, C=O), 171.3 (C-2, C=O), 82.2 (C-3), 53.9 (C-5, CH_2), 42.6, 28.6, 19.9 (CH_2), 16.6, 13.7 (Me). FAB HRMS (acetone/NBA) calcd. for $C_9H_{15}NO_4Na$ 224.0899 (M + Na). Found 224.0897.

1-Butyl-3-ethyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (193.7 mg 90%); $R_f = 0.66$ (EtOAc/hexane = 6:4 v/v); colorless liquid; IR ($CHCl_3$) ν 3400–3100 (OOH), 1782, 1689 (C=O); ^{1}H NMR ($CDCl_3$) 11.85 (1H, s, OOH), 3.90 (1H, d, $J = 18.0$ Hz, CH_2), 3.83 (1H, d, $J = 18.0$ Hz, CH_2), 3.63 (1H, m, CH_2), 3.48 (1H, m, CH_2), 1.79 (2H, q, $J = 7.2$ Hz, CH_2), 1.61 (2H, m, CH_2), 1.39 (2H, m, CH_2), 0.96 (3H, t, $J = 7.2$ Hz, Me), 0.88 (3H, t, $J = 7.5$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.3 (C-4, C=O), 170.7 (C-2, C=O), 85.7 (C-3), 54.5 (C-5, CH_2), 42.6, 28.4, 24.6, 19.7 (CH_2), 13.4, 6.7 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{10}H_{17}NO_4Na$ 238.1055 (M + Na). Found 238.1036.

1,3-Dibutyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (231.1 mg, 95%); $R_f = 0.53$ (EtOAc/hexane = 5:5 v/v); colorless liquid; IR ($CHCl_3$) ν 3400–3100 (OOH), 1784, 1689 (C=O); ^{1}H NMR ($CDCl_3$) 11.85 (1H, s, OOH), 3.88 (1H, d, $J = 18.0$ Hz, CH_2), 3.83 (1H, d, $J = 18.0$ Hz, CH_2), 3.61 (1H, m, CH_2), 3.48 (1H, m, CH_2), 1.73 (2H, t, $J = 7.8$ Hz, CH_2), 1.59 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.25 (4H, m, 2CH_2), 0.96 (3H, t, $J = 7.2$ Hz, Me), 0.85 (3H, t, $J = 6.8$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.3 (C-4, C=O), 170.8 (C-2, C=O), 85.3 (C-3), 54.4 (C-5, CH_2), 42.3, 30.9, 28.3, 24.2, 22.5, 19.6 (CH_2), 13.4, 13.3 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{12}H_{21}NO_4Na$ 266.1368 (M + Na). Found 266.1375.

1-(*t*-Butyl)-3-hydroperoxy-3-methylpyrrolidine-2,4-dione

Yield (181.0 mg, 90%); $R_f = 0.55$ (EtOAc/hexane = 7:3 v/v); colorless solid; mp 99–100 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1782, 1697 (C=O); ^{1}H NMR ($CDCl_3$) 11.27 (1H, s, OOH), 3.94 (2H, s, CH_2-C=O), 1.49 (9H, s, *t*-Bu), 1.32 (3H, s, Me); ^{13}C NMR ($CDCl_3$) 205.3 (C-4, C=O), 171.5 (C-2, C=O), 83.2 (C-3), 55.8 (>C<), 52.8 (C-5, CH_2), 28.1 ($3CH_3$), 16.9 (Me). FAB HRMS (acetone/NBA) calcd. for $C_9H_{16}NO_4$ 202.1079 (M + H). Found 202.1069.

1-(*t*-Butyl)-3-ethyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (206.6 mg, 96%); $R_f = 0.64$ (EtOAc/hexane = 4:6 v/v); colorless solid; mp 130–131 °C; IR ($CHCl_3$) ν 3500–3200 (OOH), 1780, 1695 (C=O); ^{1}H NMR ($CDCl_3$) 12.34 (1H, s, OOH), 4.08 (1H, d, $J = 18.3$ Hz, CH_2), 3.97 (1H, d, $J = 18.3$ Hz, CH_2), 1.58 (2H, q, $J = 7.5$ Hz, CH_2), 1.41 (9H, s, *t*-Bu), 0.77 (3H, t, $J = 7.5$ Hz, Me); ^{13}C NMR ($CDCl_3$) 207.7 (C-4, C=O), 169.2 (C-2, C=O), 85.3 (C-3), 54.5 (>C<), 53.3 (C-5, CH_2), 27.1 (3Me), 24.6 (CH_2), 16.9 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{10}H_{17}NO_4Na$ 238.1055 (M + Na). Found 238.1045.

1-(*t*-Butyl)-3-hydroperoxy-3-propylpyrrolidine-2,4-dione

Yield (227.1 mg, 99%); $R_f = 0.44$ (EtOAc/hexane = 4:6 v/v); colorless solid; mp 112–113 °C; IR ($CHCl_3$) ν 3450–3050 (OOH), 1782, 1685 (C=O); ^{1}H NMR ($CDCl_3$) 11.59 (1H, s, OOH), 3.95 (1H, d, $J = 17.8$ Hz, CH_2), 3.84 (1H, d, $J = 17.8$ Hz, CH_2), 1.69 (2H, t, $J = 8.4$ Hz, CH_2), 1.49 (9H, s, *t*-Bu), 1.29 (2H, m, CH_2), 0.88 (3H, t, $J = 7.1$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.7 (C-4, C=O), 171.3 (C-2, C=O), 86.5 (C-3), 55.8 (>C<), 53.3 (C-5, CH_2), 33.7 (CH_2), 27.5 (3Me), 15.9 (CH_2), 14.1 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{11}H_{20}NO_4$ 230.1392 (M + H). Found 230.1042.

1-(*t*-Butyl)-3-butyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (240.9 mg, 99%); $R_f = 0.58$ (EtOAc/hexane = 4:6 v/v); colorless solid; mp 87–88 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1782, 1685 (C=O); ^{1}H NMR ($CDCl_3$) 11.47 (1H, s, OOH), 3.95 (H, d, $J = 18.0$ Hz, CH_2), 3.83 (1H, d, $J = 18.0$ Hz, CH_2), 1.72 (2H, t, $J = 7.2$ Hz, CH_2), 1.49 (9H, s, *t*-Bu), 1.25 (4H, m, $2CH_2$), 0.82 (3H, t, $J = 7.1$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.8 (C-4, C=O), 171.2 (C-2, C=O), 86.4 (C-3), 55.8 (>C<), 53.6 (C-5, CH_2), 31.4 (CH_2), 27.5 (3Me), 24.4, 22.7 (CH_2), 13.5 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{12}H_{22}NO_4$ 244.1549 (M + H). Found 244.1521.

1-(*t*-Butyl)-3-hexyl-3-hydroperoxypyrrolidine-2,4-dione

Yield (276.9 mg, 98%); $R_f = 0.45$ (EtOAc/hexane = 3:7 v/v); colorless solid; mp 94 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1780, 1685 (C=O); ^{1}H NMR ($CDCl_3$) 11.20 (1H, s, OOH), 3.94 (H, d, $J = 17.4$ Hz, CH_2), 3.83 (1H, d, $J = 17.4$ Hz, CH_2), 1.71 (2H, m, CH_2), 1.49 (9H, s, *t*-Bu), 1.27 (8H, m, $4CH_2$), 0.85 (3H, t, $J = 6.9$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.7 (C-4, C=O), 171.3 (C-2, C=O), 86.6 (C-3), 55.9 (>C<), 53.6 (C-5, CH_2), 31.8, 31.3, 29.2 (CH_2), 27.6 (3Me), 22.4, 22.3 (CH_2), 13.97 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{14}H_{26}NO_4$ 272.1862 (M + H). Found 272.1857.

3-Hydroperoxy-3-methyl-1-(*i*-propyl)pyrrolidine-2,4-dione

Yield (177.8 mg, 95%); $R_f = 0.41$ (EtOAc/hexane = 7:3 v/v); colorless solid; mp 82–84 °C; IR ($CHCl_3$) ν 3400–3100 (OOH), 1784, 1685 (C=O); ^{1}H NMR ($CDCl_3$) 11.65 (1H, s, OOH), 4.66 (1H, sept, $J = 6.6$ Hz, CH), 3.87 (1H, d, $J = 17.7$ Hz,

CH_2), 3.80 (1H, d, $J = 17.7$ Hz, CH_2), 1.32 (3H, s, Me), 1.25 (3H, d, $J = 6.6$ Hz, Me), 1.22 (3H, d, $J = 6.6$ Hz, Me); ^{13}C NMR ($CDCl_3$) 204.9 (C-4, C=O), 170.5 (C-2, C=O), 82.6 (C-3), 49.0 (C-5, CH_2), 43.1 (CH), 19.43, 18.88, 16.36 (Me). FAB HRMS (acetone/NBA) calcd. for $C_8H_{13}NO_4Na$ 210.0742 (M + Na). Found 210.0740.

3-Ethyl-3-hydroperoxy-1-(*i*-propyl)pyrrolidine-2,4-dione

Yield (195.2 mg, 97%); $R_f = 0.50$ (EtOAc/hexane = 7:3 v/v); colorless solid; mp 63–65 °C; IR ($CHCl_3$) ν 3600–3100 (OOH), 1782, 1685 (C=O); ^1H NMR ($CDCl_3$) 11.66 (1H, s, OOH), 4.69 (1H, sept, $J = 6.6$ Hz, CH), 3.85 (1H, d, $J = 17.4$ Hz, CH_2), 3.71 (1H, d, $J = 17.4$ Hz, CH_2), 1.79 (2H, q, $J = 7.3$ Hz, CH_2), 1.26 (3H, d, $J = 6.6$ Hz, Me), 1.23 (3H, d, $J = 6.6$ Hz, Me), 0.78 (3H, t, $J = 7.3$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.3 (C-4, C=O), 170.1 (C-2, C=O), 86.4 (C-3), 49.7 (C-5, CH_2), 43.1 (CH), 24.7 (CH_2), 19.7, 18.9, 6.8 (Me). FAB HRMS (acetone/NBA) calcd. for $C_9H_{15}NO_4Na$ 224.0899 (M + Na). Found 224.0895.

3-Hydroperoxy-1-(*i*-propyl)-3-propylpyrrolidine-2,4-dione

Yield (211.0 mg, 98%); $R_f = 0.59$ (EtOAc/hexane = 7:3 v/v); colorless solid; mp 78 °C; IR ($CHCl_3$) ν 3600–3100 (OOH), 1782, 1685 (C=O); ^1H NMR ($CDCl_3$) 11.71 (1H, s, OOH), 4.68 (1H, sept, $J = 6.6$ Hz, CH), 3.85 (1H, d, $J = 17.7$ Hz, CH_2), 3.72 (1H, d, $J = 17.7$ Hz, CH_2), 1.71 (2H, t, $J = 8.4$ Hz, CH_2), 1.30 (2H, m, CH_2), 1.26 (3H, d, $J = 6.6$ Hz, Me), 1.22 (3H, d, $J = 6.6$ Hz, Me), 0.88 (3H, t, $J = 7.2$ Hz, Me); ^{13}C NMR ($CDCl_3$) 205.3 (C-4, C=O), 170.2 (C-2, C=O), 86.0 (C-3), 49.7 (C-5, CH_2), 43.0 (CH), 33.3 (CH_2), 19.6, 18.9 (Me), 15.9 (CH_2), 14.0 (Me). FAB HRMS (acetone/NBA) calcd. for $C_{10}H_{17}NO_4Na$ 238.1055 (M + Na). Found 238.1044.

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REFERENCES

1. (a) Halliwell, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*; Oxford University Press: Oxford, 1989; pp. 1–81; (b) Tappel, A. L. *The Enzymes*; Academic Press: New York, 1963; vol. 8; (c) Porter, N. A. Mechanisms for the autoxidation of polyunsaturated lipids. *Acc. Chem. Res.* **1986**, *19*, 262–268; (d) Patai, S. (Ed.). *The Chemistry of Peroxides*; Wiley: New York, 1983; (e) Pryor, W. A. (Ed.). *Free Radicals in Biology*; Academic Press: New York, 1984.
2. (a) Dembitsky, V. M. Bioactive peroxides as potential therapeutic agents. *Eur. J. Med. Chem.* **2008**, *43*, 223–251; (b) Lage, H.; Duarte, N.; Coburger, C.; Hilgeroth, A.; Ferreira, M. J. U. Antitumor activity of terpenoids against classical and atypical multidrug resistant cancer cells. *Phytomed.* **2010**, *17*, 441–448; (c) Casteel, D. A. Peroxy natural products. *Nat. Prod. Rep.* **1999**, *16*, 55–73; (d) Camerman, A.; Smith, H. W.; Camerman, N. Activated cyclophosphamide anticancer drugs: Molecular structures of *cis*- and *trans*-4-hydroperoxyisophosphamides. *J. Med. Chem.* **1983**, *26*, 679–683; (e) Camerman, N.; Fawcett, J. K.;

Camerman, A. Structures of two isomeric bicyclic derivatives of 4-hydroperoxyisophosphamide. *J. Med. Chem.* **1983**, *26*, 683–686.

3. (a) White, N. J. Qinghaosu (artemisinin): The price of success. *Science* **2008**, *320*, 330–334; (b) Vennerstorm, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; Mclntosh, K.; Padmanilayam, M.; Tomas, J. S.; Cheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. Identification of an antimalarial synthetic trioxolane drug development candidate. *Nature* **2004**, *430*, 900–904; (c) Redlay, R. G. Medical need, scientific opportunity, and the drive for antimalarial drugs. *Nature* **2002**, *415*, 686–693; (d) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. From mechanistic studies on artemisinin derivatives to new modular antimalarial drugs. *Acc. Chem. Res.* **2002**, *35*, 167–174; (e) Kim, H.-S.; Begum, K.; Ogura, N.; Wataya, Y.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. Antimalarial activity of yingzhaosu a analogues. *J. Med. Chem.* **2002**, *45*, 4732–4736; (f) Xu, X. X.; Dong, H. Q. Enantioselective total synthesis of all four stereoisomers of yingzhaosu C. *Tetrahedron Lett.* **1994**, *35*, 9429–9432; (g) Boukouvalas, J.; Pouliot, R.; Fréchette, Y. Concise synthesis of yingzhaosu C and *epi*-yingzhaosu C by peroxyl radical cyclization: Assignment of relative configuration. *Tetrahedron Lett.* **1995**, *36*, 4167–4170; (h) Griesbeck, A. G.; Neudörfl, J.; Hörauf, A.; Specht, S.; Raabe, A. Antimalarial peroxide dyads from natural artemisinin and hydroxyalkylated 1,2,4-trioxanes. *J. Med. Chem.* **2009**, *52*, 3420–3423.
4. (a) Royels, B. J. L. Naturally occurring tetramic acids: Structure, isolation, and synthesis. *Chem. Rev.* **1995**, *95*, 1981–2001; (b) Reed, G. A.; Griffin, I. O.; Eling, T. E. Inactivation of prostaglandin H synthase and prostacyclin synthase by phenylbutazone: Requirement for peroxidative metabolism. *Mol. Pharmacol.* **1985** *27*, 109–114; (c) Vennerstorm, J. L.; Holmes Jr., T. J. Preparation and evaluation of electrophilic derivatives of phenylbutazone as inhibitors of prostaglandin-H-synthase. *J. Med. Chem.* **1987**, *30*, 563–567; (d) Mentz, V. P.; Schulz, M.; Kluge, R. Chemische Darstellung von Phenylbutazon-hydroperoxid und Prüfung der Substanz auf Herzwirksamkeit unter In-vitro- und In-vivo-Bedingungen. *Arzneim.-Frosch.* **1987**, *37*, 1229–1232.
5. (a) Weiner, M.; Piliero, S. J. Nonsteroid anti-inflammatory agents. *Annu. Rev. Pharmacol.* **1970**, *10*, 171–198; (b) Coyne, W. E. *Medicinal Chemistry*, 3rd ed.; A. Burger (Ed.); Wiley: New York, 1970; pp. 953–975.
6. (a) Rahman, M. T.; Nishino, H. Manganese(III)-catalyzed facile direct hydroperoxidation of some heterocyclic 1,3-dicarbonyl compounds. *Org. Lett.* **2003**, *5*, 2887–2890; (b) Rahman, M. T.; Nishino, H.; Qian, C.-Y. Synthesis of 4,4-bis(2-hydroperoxyalkyl) pyrazolidine-3,5-diones using manganese(III)-catalyzed autoxidation. *Tetrahedron Lett.* **2003**, *44*, 5225–5228; (c) Rahman, M. T.; Nishino, H. Manganese(III)-based oxidation of 1,2-disubstituted pyrazolidine-3,5-diones in the presence of alkenes. *Tetrahedron* **2003**, *59*, 8383–8392.
7. (a) Fugger, J.; Tien, J. M.; Hunsberger, I. M. The preparation of substituted hydrazines, I: Alkylhydrazines via alkylsydnone. *J. Am. Chem. Soc.* **1955**, *77*, 1843–1848; (b) King, J. A.; McMillan, F. H. The preparation of some ⟨-benzylamino-β,β-dialkoxypropionic acid derivatives. *J. Am. Chem. Soc.* **1950**, *72*, 1236–1240; (c) Koech, P. K.; Krische, M. J. Catalytic addition of metallo-aldehyde enolates to ketones: A new C−C bond-forming hydrogenation. *Org. Lett.* **2004**, *6*, 691–694; (d) Speziale, A. J.; Jaworski, E. G. N-Substituted glycinate and alaninate esters. *J. Org. Chem.* **1960**, *25*, 728–732; (e) Zhu, Y.; Zou, X.; Hu, F.; Yao, C.; Liu, B.; Yang, H. Synthesis and herbicidal evaluation of novel 3-[(⟨-hydroxy-substituted)benzylidene]pyrrolidine-2,4-diones. *J. Agri. Food Chem.* **2005**, *53*, 9566–9570.
8. Chowdhury, F. A.; Nishino, H.; Kurosawa, K. Simple route to azabicyclic peroxides from tetramic acid derivatives using manganese(III)-based molecular oxygen trapping reaction. *Heterocycles* **1999**, *51*, 575–591.