Diterpenoid Acids from *Grindelia nana*

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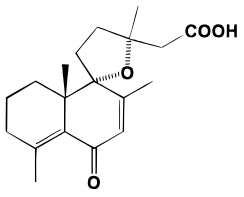
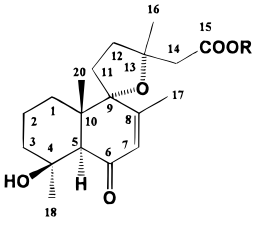
Two new norditerpenoid acids of the labdane-type (norgrindelic acids), 4,5-dehydro-6-oxo-18-norgrindelic acid (**1**) and 4*β*-hydroxy-6-oxo-19-norgrindelic acid (**2**), as well as a new grindelic acid derivative, 18-hydroxy-6-oxogrindelic acid (**3**), were isolated from the aerial parts of *Grindelia nana*. In addition, the known compounds, 6-oxogrindelic acid, grindelic acid, methyl grindeloate, 7α,8α-epoxygrindelic acid, and 4α-carboxygrindelic acid were also isolated. The structures of the new compounds were characterized on the basis of spectroscopic analysis.

Many species of the New World genus *Grindelia* (family Asteraceae, tribe Astereae, subtribe Soladiginae) are characterized by the abundant production of resinous exudates that cover the surfaces of the leaves, stems, and involucres of the flower heads.[1] Previous phytochemical investigations on members of this genus have shown that diterpenoid acids of the labdane type (grindelic acids,[2−9] harvadic acids,[10] discoidic acids,[11] cordobic acids[12]) and some manoyl oxide derivatives[13] are widespread. *Grindelia nana* Nutt. has not been previously investigated chemically, but the ethanol extract demonstrated in vitro more than a 20% inhibitory effect on HIV-1 reverse transcriptase at 0.5 *μ*g/mL.[14] In the present study, we report the isolation and structure characterization of three new diterpenoid acids of the labdane type (grindelic acids): 4,5-dehydro-6-oxo-18-norgrindelic acid (**1**), 4*β*-hydroxy-6-oxo-19-norgrindelic acid (**2**), and 18-hydroxy-6-oxogrindelic acid (**3**). The known compounds, 6-oxogrindelic acid,[9,15,16] grindelic acid and its methyl ester,[2,17,18] 7α,8α-epoxygrindelic acid,[15,17] and 4α-carboxygrindelic acid[8,19] were also isolated and identified.

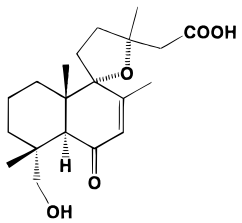


1



2 R = H

2a R = Me



3 R = OH

Compound **1** was isolated as a colorless oil with $[\alpha]^{25}_{D}$ −13.9° (*c* 0.18, $CHCl_3$). Its molecular formula $C_{19}H_{26}O_4$ was deduced from the HREIMS. The IR spectrum of **1** displayed absorption bands at 3350 and 1712 cm^{-1} and were attributable to a carboxyl group. A further band at 1665 cm^{-1} suggested the presence of a dienone moiety, which was also supported by a UV absorption maximum at 241 nm. The ^1H NMR spectrum of **1** displayed signals for four tertiary methyl groups, including two overlapping olefinic methyls appearing at *δ* 2.04 (6H, s, H-17 and H-19), which showed in the $^1H-^{13}C$ COSY spectrum correlations with two methyl carbon signals at *δ* 21.2 and 23.2, a methyl attached to an oxygen-bearing carbon (*δ* 1.39, s, H-16), and a methyl resonating at *δ* 1.05 (s, H-20). A pair of doublets appeared at *δ* 2.50 and 2.64 (J = 14.0 Hz), indicating the presence of an isolated methylene group (H-14a and H-14b). These methylene proton signals showed in the $^1H-^{13}C$ COSY spectrum correlations with a carbon signal at *δ* 48.4 (t), consistent with the presence of the isolated C-14, which was adjacent to a carbonyl function and a fully substituted carbon.[5,9,19] An olefinic proton signal at *δ* 5.90 (br s, H-7) displayed in the $^1H-^1H$ COSY spectrum an allylic coupling with the methyl signal at *δ* 2.04, indicating the presence of a vinyl methyl (H-17). The ^{13}C NMR spectrum of **1**, in agreement with the molecular formula, revealed signals corresponding to 19 carbon atoms in the molecule. Analysis of the ^{13}C NMR and DEPT (90 and 135) spectral data with the aid of the $^1H-^{13}C$ COSY spectrum led to the deduction of the multiplicities of the carbon atoms and established the presence of four methyls (*δ* 27.2, 24.8, 23.2, 21.2), one tetrasubstituted and one trisubstituted olefinic carbon (*δ* 156.5, 149.9, 132.9, 130.4), six aliphatic methylenes (*δ* 48.4, 38.4, 34.7, 30.3, 28.6, 18.1), two oxygenated quaternary carbons (*δ* 89.3, 82.6), two carbonyl carbons (*δ* 190.3, 174.7), and one quaternary carbon (*δ* 44.3). All of the above spectral evidence suggested that this compound was a norditerpene acid. Furthermore, comparison of the ^1H and ^{13}C NMR spectral data of **1** with those of 6-oxogrindelic acid, which was isolated from this species and previously reported,[9,15,16] permitted the assignment of **1** as an 18-nor-4,5-dehydro analogue of **3**. This inference was confirmed by the absence of the proton and carbon signals of Me-18 in **1**. In addition, the absence of the characteristic signal of H-5 in **1** together with the replacement of C-4 and C-5 by tetrasubstituted olefinic signals resonating at *δ* 149.9 and 132.9, as well as the significant downfield shift (*δ* 2.04) of the methyl group at C-4 (Me-19), when compared with that at *δ* 1.11 for 6-oxogrindelic acid, confirmed the presence of a $\Delta^{4,5}$ double bond in **1**. Also, a carbonyl carbon (C-6) at *δ* 190.3, together

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Table 1. Observed NMR Long-Range Carbon−Proton Correlations (COLOC) of Compounds **1** and **2a**

carbon	1	2a
C-1	H-3a, CH_3-20	CH_3-20
C-2	H-3b	H-1a, H-3b
C-3	H-1a, CH_3-19	CH_3-18
C-4	H-2a, CH_3-19	H-2a, H-2b, H-5, CH_3-18
C-5	H-3a, H-3b, H-7, CH_3-19, CH_3-20	H-3a, H-3b, H-7, CH_3-18, CH_3-20
C-6		H-5
C-7	CH_3-17	H-5, CH_3-17
C-8	CH_3-17	CH_3-17
C-9	H-7, H-12a, CH_3-20	H-5, H-7, CH_3-17, CH_3-20
C-10	H-2b, H-11a, H-11b, CH_3-20	H-2a, H-5, H-20
C-11	H-12a	H-12a, H-12b
C-12	H-14a, H-14b, CH_3-16	H-14a, H-14b, CH_3-16
C-13	H-14a, H-14b, CH_3-16	H-14a, H-14b, CH_3-16
C-14	CH_3-16	CH_3-16
C-15	H-14a	H-14a, H-14b, 15-OCH_3
C-16	H-14a, H-14b	H-12a, H-14a, H-14b
C-17	H-7	H-7
C-18		H-3a, H-3b, H-5
C-19	H-3a, H-3b	
C-20	H-1a, H-1b	H-1b, H-5

with the presence of IR and UV absorptions at 1665 cm^{-1} and 241 nm, respectively, supported the dienone segment −C(4)═C(5)−CO(6)−C(7)═C(8)− in **1**. The final structure of **1** was supported by a 2D long-range coupling (COLOC) experiment (Table 1). The most important correlations were observed between the olefinic quaternary carbon at δ 132.9 (C-5) and the protons H-3, H-7, Me-19, and Me-20, as well as between the olefinic secondary carbon at δ 130.4 (C-7) and Me-17 protons. The relative configurations at C-9, C-10, and C-13 were established to be the same as those of the known 6-oxogrindelic acids[5,9] by comparison of ^1H and ^{13}C chemical shifts with published values. Therefore, **1** was identified as 4,5-dehydro-6-oxo-18-norgrindelic acid.

Compound **2** was purified and investigated as its methyl ester **2a** by treatment of **2** with ethereal diazomethane. Compound **2a**, a colorless oil, had $[\alpha]^{25}_D$ −51.1° (*c* 0.19, $CHCl_3$) and showed a molecular ion peak $[M]^+$at *m/z* 350 (100%) in the EIMS, while the molecular formula, $C_{20}H_{30}O_5$, was determined by HREIMS (*m/z* 350.4529). The IR spectrum showed characteristic bands for a hydroxyl group (3580 cm^{-1}), an ester carbonyl group (1740 cm^{-1}), and α,*β*-unsaturated carbonyl (1685 cm^{-1}). The characteristic features of the ^1H NMR spectrum included four tertiary methyl signals, including one vinyl methyl (δ 1.99, br s, H-17) exhibited allylic coupling with an olefinic proton signal at δ 5.73 (1H, br s, H-7) in the $^1H-^1H$ COSY spectrum, two methyl groups attached to an oxygen-bearing carbon [(δ 1.36, s, H-18) and (δ 1.41, s, H-16)], while the remaining methyl appeared at δ 1.10 (s, H-20). A pair of doublets appeared at δ 2.59 and 2.75 (J = 14.0 Hz), indicating the presence of an isolated methylene group (H-14a and H-14b). The singlet proton signal at δ 2.91, which correlated with a carbon resonance at δ 55.0 (d) in the $^1H-^{13}C$ COSY spectrum, showed the presence of this methine carbon adjacent to three fully substituted carbons. The ^{13}C NMR spectral data of **2a** displayed 19 carbon resonances in addition to the characteristic signal of the methoxyl group (δ 51.4, OMe-15). This indicated that **2a** was a nor-grindelic acid similar to **1**. However, several differences were apparent. The ^{13}C NMR resonances of the tetrasubstituted double bond ($\Delta^{4,5}$) of **1** were replaced by a quaternary oxygenated carbon (δ 70.2, C-4) and a methine carbon (δ 55.0, C-5), and the signal of the C-6 carbonyl carbon resonated more downfield at δ 203.4 in **2a** compared with δ 190.3 in **1**. Additionally, the proton signal of the methyl group at C-4 was significantly more upfield (δ 1.36) in **2a** than (δ 2.04) in **1**, which indicated attachment to an oxygen function. All these differences clearly indicated that **2a** was a 4-hydroxy derivative of **1**. The singlet proton signal at δ 2.91, which was assigned from the 2D COLOC experiments to H-5, confirmed the presence of a hydrogen proton at C-5. Finally, the long-range correlations in the COLOC spectra (Table 1) between C-4 (δ 70.2) and the protons H-5, and Me-18 and between C-5 (δ 55.0) and the protons H-7, Me-18, and Me-20 supported the hydroxyl group at C-4. Confirmation of the 19-nor structure was obtained from the absence of the characteristic carbon signal of Me-19, while the ^{13}C NMR chemical shift at δ 31.5, which was assigned from the 2D $^1H-^{13}C$ COSY and COLOC spectra to the methyl group at C-4, was in agreement with those reported for Me-18 in similar grindelic acid derivatives.[9,17] The relative stereochemistry at C-4 was determined by the downfield shift (δ 1.10) of the angular methyl at C-10 (Me-20), which was in agreement with a *β*-configuration (axial) of the hydroxyl group at C-4.[8] Furthermore, in the difference NOE spectrum the clear enhancement between H-5α and Me-18 and the absence of any effect between Me-18 and Me-20*β*, supported the configuration at C-4 and also corroborated a 19-norstructure. Therefore, **2a** was identified as methyl-4*β*-hydroxy-6-oxo-19-norgrindeloate.

Compound **3**, a colorless oil, had $[\alpha]^{25}_D$ −41.2° (*c* 0.16, $CHCl_3$). The HREIMS exhibited a $[M]^+$ peak at *m/z* 350.4513 in accordance with the molecular formula $C_{20}H_{30}O_5$ (calcd 350.4520). This molecular formula indicated that this compound might be a hydroxyl derivative of 6-oxogrindelic acid, especially as the ^1H and ^{13}C NMR spectra were, in parts, very similar. However, differences were observed as the signal of the methyl group (Me-18) was replaced by a pair of doublets at δ 3.31 and 3.55 (J = 12.0 Hz) in **3**. Therefore, a hydroxyl group was assumed at C-18. This result was supported by the ^{13}C NMR data, which showed that the signals of C-18 at δ 33.6 and C-19 at δ 21.6 in 6-oxogrindelic acid were replaced by a secondary oxygenated carbon at δ 74.2 and a methyl carbon (C-19) at δ 20.1, respectively, in **3**. The significant downfield shift of H-5α (δ 2.98), compared with that at δ 2.72 in 6-oxogrindelic acid, as well as the chemical shift (δ 0.97) of Me-20, which was very similar to that (δ 0.95) of 6-oxogrindelic acid, were in good agreement with the α-orientation (equatorial) of this −CH_2OH group at C-4.[8,19] Further support for the relative stereochemistry at C-4 was given by the difference NOE spectroscopy which showed effects between H-5α and H-18b, as well as between the methyl group signal of Me-19 and Me-20*β*. The assignments of all protons and carbons in **3** could be substantiated by the 2D $^1H-^1H$ and $^1H-^{13}C$ COSY spectra. Therefore, **3** was identified as 18-hydroxy-6-oxogrindelic acid. The 18-acetoxy derivative of **3** was previously isolated from *G. stricta*.[8]

Experimental Section

General Experimental Procedures. Optical rotations were deduced with a JASCO-20C automatic recording spectropolarimeter. The UV spectrum was recorded on a Perkin-Elmer Lambda 3B UV−vis spectrophotometer. The IR spectra (films, $CHCl_3$) were obtained on a Shimadzu IR 470 spectrometer. The ^1H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$), and 2D NMR spectra were measured with a JEOL JNM EX-400 spectrometer, with TMS as an internal standard. The signals of the deuterated solvent ($CDCl_3$) were obtained as the reference (the singlet at 7.25 ppm for the ^1H NMR data and the triplet centered at 77.0 ppm for the ^{13}C NMR data). ^1H and ^{13}C NMR assignments were supported by $^1H-^1H$

COSY, $^1H-^{13}C$ COSY, and COLOC experiments. Mass spectra (EIMS and HREIMS) were recorded on a JEOL JMS-D300 mass spectrometer using direct inlet electron-impact ionization (70 eV). For column chromatography, Si gel 60 (70−230 mesh, Merck) and Sephadex LH-20 were used. Components were detected on TLC plates using a UV lamp (254 and 365 nm). For preparative TLC, precoated Si gel plates (Merck 60 F_{254}) of 0.25 mm thickness were used.

Plant Material. Aerial parts of *G. nana* were collected in Siskiyou, Jackson County, OR, in July 1992. A voucher specimen (G-T-0062) has been deposited at the herbarium of Gifu Pharmaceutical University, Japan.

Extraction and Isolation. The air-dried plant material (800 g) was ground and extracted at room temperature with CH_2Cl_2−MeOH (1:1). The extract was concentrated in vacuo to obtain a residue of 78 g, which was fractionated by column chromatography (5 × 100 cm) on Si gel (700 g). Elution with petroleum ether−Et_2O gave three fractions: 1 (petroleum ether−Et_2O, 3:1, 2 L), 2 (petroleum ether−Et_2O 1:1, 2 L), and 3 (Et_2O, 2 L). Fraction 1 was further purified by column chromatography (Si gel 400 g, elution with CH_2Cl_2−*n*-hexane, 1:2) to yield two further fractions, 1A (800 mL) and 1B (800 mL). Fraction 1A was purified on a Sephadex LH-20 column (4 × 80 cm, 250 g), by elution with CH_2Cl_2−*n*-hexane−MeOH (4:7:0.5, 4 × 100 mL), to afford methyl grindeloate (800 mg) and grindelic acid (900 mg), the third subfraction was further purified by preparative TLC (petroleum ether−Et_2O, 1:2) to obtain 7α,8α-epoxygrindelic acid (30 mg). Fraction 2 was further fractionated by column chromatography (Si gel 300 g) by elution with (CH_2Cl_2−*n*-hexane, 1:2) to yield two fractions: 2A (500 mL) and 2B (500 mL). The first fraction, 2A, was further separated and purified on a Sephadex LH-20 column (4 × 80 cm, 250 g), elution with CH_2Cl_2−*n*-hexane−MeOH (4:7:0.5, 4 × 100 mL), to afford 6-oxogrindelic acid (100 mg), the second subfraction was further purified by preparative TLC (petroleum ether−Et_2O, 1:1) to obtain **1** (16 mg). The second fraction, 2B, was subjected to further separation and purification by preparative TLC (petroleum ether−Et_2O, 1:2) to give **3** (18 mg) and 4α-carboxygrindelic acid (18 mg). Fraction 3 was methylated by treatment with ethereal CH_2N_2, and first chromatographed on Si gel (*n*-hexane−CH_2Cl_2) and then subjected to further separation and purification by column chromatography (Sephadex LH-20; elution with CH_2Cl_2−*n*-hexane−MeOH, 4:7:0.5, 4 × 50 mL) to give **2a** (16 mg).

4,5-Dehydro-6-oxo-18-norgrindelic acid (1): colorless oil, $[\alpha]^{25}_D$ −13.9°(*c* 0.18, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 285 (sh, 3.64), 241 (3.89) nm; IR ($CHCl_3$) ν_{max} 3350, 1712 (COOH), 1665 (dienone C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.90 (1H, br s, H-7), 2.64 (1H, d, J = 14.0 Hz, H-14a), 2.50 (1H, d, J = 14.0 Hz, H-14b), 2.21 (2H, m, H-11b and H-12b), 2.13 (2H, m, H-3a and H-3b), 2.04 (6H, s, H-17 and H-19), 2.00 (1H, m, H-11a), 1.98 (1H, m, H-12a), 1.95 (1H, m, H-1b), 1.70 (1H, m, H-2b), 1.55 (2H, m, H-1a and H-2a), 1.39 (3H, s, H-16), 1.05 (3H, s, H-20); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.3 (s, C-6), 174.7 (s, C-15), 156.5 (s, C-8), 149.9 (s, C-4), 132.9 (s, C-5), 130.4 (d, C-7), 89.3 (s, C-9), 82.6 (s, C-13), 48.4 (t, C-14), 44.3 (s, C-10), 38.4 (t, C-12), 34.7 (t, C-3), 30.3 (t, C-1), 28.6 (t, C-11), 27.2 (q, C-16), 24.8 (q, C-20), 23.2 (q, C-19), 21.2 (q, C-17), 18.1 (t, C-2); EIMS (direct inlet) 70 eV, *m/z* 318 (M^+, 90) ($C_{19}H_{26}O_4$), 303 (M^+ − Me, 16), 279 (6), 218 (22), 175 (100), 148 (60), 147 (45), 109 (33), 91 (26), 69 (24), 55 (22); HREIMS *m/z* 318.4109 (calcd for $C_{19}H_{26}O_4$, 318.4104).

Methyl-4β-hydroxy-6-oxo-19-norgrindeloate (2a): colorless oil, $[\alpha]^{25}_D$ −51.1° (*c* 0.19, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 290 (4.01), 257 (3.96) nm; IR ($CHCl_3$) ν_{max} 3580 (OH), 1740 (COOR), 1685 (α,β-unsaturated C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.73 (1H, br s, H-7), 3.68 (3H, s, CH_3O-15), 2.91 (1H, s, H-5), 2.75 (1H, d, J = 14.0 Hz, H-14a), 2.59 (1H, d, J = 14.0 Hz, H-14b), 2.30 (1H, m, H-12b), 2.20 (1H, m, H-11b), 2.05 (1H, m, H-12a), 2.00 (1H, m, H-11a), 1.99 (3H, br s, H-17), 1.80 (1H, m, H-3b), 1.70 (2H, m, H-1b and H-2b), 1.55 (1H, m, H-1a), 1.41 (3H, s, H-16), 1.36 (3H, s, H-18), 1.28 (1H, m, H-3a), 1.10 (3H, s, H-20); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.4 (s, C-6), 171.1 (s, C-15), 156.5 (s, C-8), 128.2 (d, C-7), 89.8 (s, C-9), 82.8 (s, C-13), 70.2 (s, C-4), 55.0 (d, C-5), 51.4 (q, OCH_3), 47.5 (t, C-14), 45.4 (s, C-10), 39.7 (t, C-3), 38.4 (t, C-12), 32.7 (t, C-1), 31.5 (q, C-18), 28.5 (t, C-11), 27.6 (q, C-16), 20.9 (q, C-17), 18.2 (q, C-20), 17.1 (t, C-2); EIMS (direct inlet) 70 eV, *m/z* 350 (M^+, 100) ($C_{20}H_{30}O_5$), 332 (M^+ − H_2O, 30), 322 (M^+ −CO, 20), 277 (M^+ − CH_2COOMe, 9), 259 (M^+ −CH_2COOMe − H_2O, 25), 224 (40), 197 (20), 111 (25), 82 (15); HREIMS *m/z* 350.4529 (calcd for $C_{20}H_{30}O_5$, 350.4520).

18-Hydroxy-6-oxogrindelic acid (3): colorless oil, $[\alpha]^{25}_D$ −41.2° (*c* 0.16, $CHCl_3$). UV ($CHCl_3$) λ_{max} (log ϵ) 243 (3.95) nm; IR ($CHCl_3$) ν_{max} 3550, 3350 (OH), 1710 (COOH), 1680 (C=CCO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.76 (1H, br s, H-7), 3.55 (1H, d, J = 12.0 Hz, H-18a), 3.31 (1H, d, J = 12.0 Hz, H-18b), 2.98 (1H, s, H-5), 2.65 (1H, d, J = 14.0 Hz, H-14a), 2.52 (1H, d, J = 14.0 Hz, H-14b), 2.25 (1H, m, H-12b), 2.18 (1H, m, H-11a), 2.10 (1H, m, H-2b), 2.05 (2H, m, H-3a and H-11a), 2.02 (3H, s, H-17), 1.98 (1H, m, H-12a), 1.80 (1H, m, H-1b), 1.75 (1H, m, H-2b), 1.58 (1H, m, H-1a), 1.50 (1H, m, H-2a),1.44 (3H, s, H-16), 1.06 (3H, s, H-19), 0.97 (3H, s, H-20); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.4 (s, C-6), 174.5 (s, C-15), 157.5 (s, C-8), 129.1 (d, C-7), 89.7 (s, C-9), 82.8 (s, C-13), 74.2 (t, C-18), 54.6 (d, C-5), 48.8 (t, C-14), 45.4 (s, C-10), 38.7 (t, C-12), 37.5 (s, C-4), 36.8 (t, C-3), 32.2 (t, C-1), 31.5 (q, C-19), 28.3 (t, C-11), 27.3 (q, C-16), 21.2 (q, C-17), 17.5 (t, C-2), 17.4 (q, C-20); HREIMS *m/z* 350.4513 (calcd for $C_{20}H_{30}O_5$, 350.4520); EIMS (direct inlet) 70 eV, *m/z* 350 (M^+, 20) ($C_{20}H_{30}O_5$), 291 (M^+ − CH_2COOH, 6), 233 (8), 210 (100), 183 (35), 149 (15), 135 (18), 111 (40), 82 (19), 55 (13).

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