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INFLEXARABDONINS A AND B, DITERPENOIDS FROM *RABDOSIA INFLEXA*

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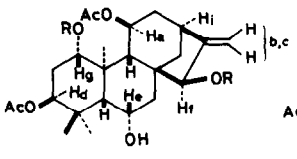
Key Word Index—*Rabdosia inflexia*; Labiatae; *ent*-kaurenoid; inflexarabdonins A and B.

Abstract—From the aerial parts of *Rabdosia inflexa*, two new *ent*-kaurenoid diterpenoids, inflexarabdonins A and B, were isolated and the structures determined on the basis of spectroscopic and chemical evidence.

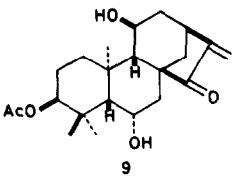
INTRODUCTION

From *Rabdosia inflexa* (Thunb.) Hara [1], four 15-oxo-*ent*-kaurenoids, inflexin (**3**), inflexinol (**4**), and inflexanins A (**9**) and B (**5**), have been isolated and characterized [2–5]. In a continuation of our studies on the biologically active constituents of the plants belonging to the genus *Rabdosia*, we examined the constituents of *R. inflexa* collected in Hiroshima Pref., Japan and isolated two new diterpenoids which we have named inflexarabdonins A (**1**) and B (**10**). This report deals with the structure elucidation of the new compounds.



1 R=H
2 R=COMe

	R^1	R^2	R^3	R^4
3	H	O	COMe	CH_2
4	H	αOH,βH	COMe	CH_2
5	H	αOH,βH	H	CH_2
6	H	αOH,βH	COMe	αH,βMe
7	H	O	COMe	αH,βMe
8	COMe	O	COMe	αH,βMe



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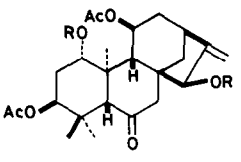

10 R=H
11 R=COMe

RESULTS AND DISCUSSION

Inflexarabdonin A (**1**) was found to have the molecular formula, $C_{24}H_{36}O_7$ (HRMS). It contained hydroxyl groups (ν_{max} 3600–3400 cm^{-1}), three protons on carbons having a secondary hydroxyl group [δ_H 3.71 (1H, *m*, changed to *dd*, $J=12$ and 4.5 Hz on addition of D_2O, H_g), 3.83 (1H, *dt*, $J=11$ and 3 Hz, changed to *t*, $J=3$ Hz on addition of D_2O, H_f), and 4.39 (1H, *m*, $W_{1/2}=6.5$ Hz, H_e)], two protons on carbons having an acetoxy group {δ_H 4.69 (1H, *t*, $J=3$ Hz, H_d) and 6.23 [1H, *br d*, $J=5$ Hz, H_a]}, an *exo*-methylene group {δ_H 5.04 [1H, *br d*, $J=3$ Hz, H_c] and 5.16 [1H, *br s*, H_b], δ_C 104.6 (*t*) and 158.2 (*s*)}, three tertiary methyl groups [δ_H 0.91, 1.29 and 1.46 (each 3H, *s*)] and two acetyl groups [δ_H 2.02 and 2.08 (each 3H, *s*)]. The ^{13}CNMR spectrum of **1** (Table 1) showed signals due to five methine carbons having an acetoxy or a hydroxyl group, two ester carbonyl groups, five methyl groups, four methylene groups, three methine groups and three quaternary carbon atoms, as well as the signals due to an *exo*-methylene group. Thus, inflexarabdonin A (**1**) had a tetracyclic ring system. Considering the structures of the diterpenoids isolated so far from the genus *Rabdosia* [6], inflexarabdonin A (**1**) was presumed to have a *ent*-kaur-16-ene structure as a basic skeleton. The location of two acetoxy and three hydroxyl groups was elucidated on the basis of the results of spin-spin decoupling and NOE experiments. On irradiation of H_b and H_c respectively, the signal of H_f collapsed to a singlet and that of H_i [δ2.66 (1H, *m*), H-13] became sharp. The signal of H_b changed to a sharp singlet and that of H_c collapsed to a singlet when H_f was irradiated. On irradiation of H_i, both signals due to H_b and H_c changed to a sharp doublet ($J=3$ Hz). Thus, a hydroxyl group was located at C-15, the stereochemistry of which is discussed later. The protons, H_a and H_d, are the equatorial protons and were presumed to be located on C-11 and C-3 in view of the co-occurrence of inflexin (**3**) and inflexinol (**4**). This was verified by the fact that a NOE (11.2%) for H_a was observed on irradiation at δ_H 1.46 (H_3-20) and NOE's (8.8 and 11.5%, respectively) were observed for H_d on irradiation at δ_H 0.91 (H_3-18) and 1.29 (H_3-19), respectively. The second secondary hydroxyl group is axial and was assigned to C-6α on the basis of the fact that NOE's (17.5 and 14.4%, respectively) were observed for H_e on irradiation at δ_H 0.91 and 1.29 respectively, and the hydroxyl group was not acetylated in the diacetate **2**. The third secondary

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Table 1. ^{13}C NMR data of inflexarabdonins A (**1**) and B (**10**)

Carbon	1	10
1	77.6	75.2
2	34.3	33.8
3	80.0	78.8
4	38.0	36.2
5	49.4	58.8
6	67.1	210.6
7	47.9	54.6
8	44.0[a]	49.3[b]
9	53.7	53.6
10	43.9[a]	50.2[b]
11	73.1	71.3
12	39.6	39.0
13	39.7	38.7
14	38.3	36.6
15	83.9	82.5
16	158.2	156.7
17	104.6	105.6
18	28.5	26.5
19	24.0	22.1
20	14.5	15.0
MeCO	21.0	20.7
	21.7	21.6
MeCO	169.4	169.4
	170.2	170.0

[a, b]The assignments may be interchanged.

hydroxyl group was assigned to C-1α by comparison of the ^{13}C NMR signal δ_C 77.6 and those of the ^1H-chemical shift and coupling pattern with those of **4** [δ_C 76.9, C-1; δ_H 3.69 (1H, *dd*, $J = 12$ and 5 Hz, H-1)]. Thus, the structure of inflexarabdonin A is represented as *ent*-1β,3α,6β,11α,15α-pentahydroxy-kaur-16-ene 1,3-diacetate (**1**) or its 15-epimer. Sodium borohydride reduction of inflexinol (**4**) gave **1**. From inspection of a Dreiding model, it appeared that hydride might attack from the less hindered α-side. Consequently, the hydroxyl group at C-15 would take the β-configuration. In order to establish the stereochemistry at C-15 and the absolute stereochemistry, inflexarabdonin A (**1**) was subjected to conditions suitable for a garryfoline-cuauchichicine rearrangement [7–9] to give dihydroinflexinol (**6**) [3, 5]. On the basis of the findings, the structure of inflexarabdonin A was determined to be **1**.

Inflexarabdonin B (**10**) was found to have the molecular formula, $C_{24}H_{34}O_7$ (HRMS). Its ^{13}C NMR spectrum (Table 1) showed signals due to an isolated ketone group, two ester carbonyl groups, an *exo*-methylene group and four secondary carbinyl carbon atoms in addition to the signals due to five methyl groups, four methylene groups, three methine groups and three quaternary carbon atoms. Besides the signals due to three tertiary methyl groups (δ_H 0.87, 1.09 and 1.33) and two acetyl groups (δ_H 2.06 and 2.12), the ^1H NMR spectrum showed signals due to an *exo*-methylene group {δ_H 5.08 [1H, *br d*, $J = 3$ Hz] and 5.20 [1H, *br d*, $J = 2$ Hz]}, two protons on the carbon having an acetoxy group {δ_H 4.60 (1H, *t*, $J = 3$ Hz) and 6.29 [1H, *br d*, $J = 5$ Hz]}, and two protons on the carbons having a hydroxyl group [δ_H 3.87 (1H, *dt*, $J = 11$ and 2.5 Hz, changed to *t*, $J = 2.5$ Hz on addition of D_2O) and 3.96 (1H, *m*, changed to *dd*, $J = 11.5$ and 5 Hz on addition of D_2O]. The ^1H NMR spectrum is very similar to that of inflexarabdonin A (**1**), except for the absence of the signal due to H-6β observed in that of **1**. Considering the molecular formula, inflexarabdonin B appeared to have a structure in which the 6α-hydroxyl group is oxidized to a ketone. This was supported by the fact that a NOE (8.1%) for the signal at δ_H 2.66 (1H, *s*, H-5), assigned to a methine proton adjacent to ketone group, was observed on irradiation at δ_H 0.87. Acetylation of **10** gave the diacetate **11** and selective sodium borohydride reduction of inflexin (**3**) gave **10**. Treatment of **10** under conditions suitable for a garryfoline-cuauchichicine rearrangement [7–9], followed by acetylation with acetic anhydride and pyridine gave dihydroinflexin monoacetate (**8**). On the basis of these findings, the structure of inflexarabdonin B was determined as *ent*-1β,3α,11α,15α-tetrahydroxy-kaur-16-en-6-one 1,3-diacetate (**10**).

EXPERIMENTAL

General. Mps: uncorr. ^1H NMR: 200 MHz; ^{13}C NMR: 50.1 MHz, TMS as int. standard. EIMS: 70 eV. CC: silica gel 60 (0.05–0.2 mm). TLC and prep TLC: silica gel 60 F_{254} (0.25 and 0.5 mm in thickness), respectively.

Plant material. Plant material was collected in the suburbs of Hiroshima City, Hiroshima Prefecture, Japan in early Oct., 1986 and identified as *Rabdosia inflexa* (Thunb.) Hara by Professor T. Seki (Miyajima Natural Botanical Garden, Faculty of Sciences, Hiroshima University). A voucher specimen (Y. Takeda No. 5) is deposited in the herbarium of the Faculty of Pharmaceutical Sciences, The University of Tokushima, Tokushima 770, Japan.

Isolation. Dried aerial parts of *R. inflexa* (1.37 kg) were extracted (× 2) with MeOH (36 l) for 2 weeks at room temp. The combined extracts were concd *in vacuo* to give a residue (266 g) which was dissolved in 90% MeOH (1.9 l) and the soln partitioned with *n*-hexane (800 ml × 3). The 90% MeOH layer was concd *in vacuo*. The residue was suspended in H_2O (1.4 l) and the suspension was extracted with EtOAc (1.4 l × 3). After being washed with H_2O, the EtOAc extract was dried and evapd *in vacuo* to give a residue (36 g) which was chromatographed on a silica gel (1 kg) column (Column I) developed with $CHCl_3$ (6 l), $CHCl_3$–Me_2CO (19:1) (6 l), $CHCl_3$–Me_2CO (9:1) (6 l) $CHCl_3$–Me_2CO (17:3) (6 l), $CHCl_3$–Me_2CO (4:1) (6 l), $CHCl_3$–Me_2CO (7:3) (6 l), $CHCl_3$–Me_2CO (1:1) (5.3 l) and Me_2CO (3 l). The eluates were collected as 500 ml fractions.

The residue (2.98 g) from fr. nos 16–18 was separated on a silica gel (100 g) column with $CHCl_3$ as eluant and recrystallized from a mixture of Et_2O and *n*-hexane to give inflexin (**3**) (0.81 g) as needles. Purification of the residue (5.6 g) from fr. nos 19–22 by silica gel CC (200 g, Et_2O) gave a mixture of inflexin (**3**) and inflexinol (**4**) (*ca* 1:1) (2.97 g). Purification of the residue (3.92 g) from fr. nos 23–29 by repeated silica gel chromatography ($CHCl_3$–MeOH 99:1; Et_2O) gave inflexinol (**4**) (1.51 g). The residue (2.60 g) from fr. nos 64–75 gave inflexanin B (**5**) (773 mg) by further purification.

The residue (2.07 g) from fr. nos 30–35 was separated by silica gel CC (100 g) (Column II) with Et_2O as eluant, collecting 7 ml fractions. Fr. nos 31–58 were combined and evapd *in vacuo* to give a residue (0.88 g) which was further separated by repeated silica gel CC (EtOAc–*n*-hexane; $CHCl_3$–Me_2CO) and prep. TLC ($CHCl_3$–MeOH and $CHCl_3$–Me_2CO) to give inflexanin A (**9**) (207 mg), inflexarabdonin A (**1**) (262 mg) and inflexarabdonin B (**10**) (16.7 mg).

Inflexin (**3**), inflexinol (**4**) and inflexanins A (**9**) and B (**5**) were identified by direct comparison with authentic samples.

Inflexarabdonin A (**1**). Mp 118–120° (from $CHCl_3$–*n*-hexane) $[\alpha]_D^{27.5}$ −5.5° (MeOH; *c* 1.95). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600–3400, 1725, 1370, 1260–1190, 1120, 1065, 1035 and 1025; ^1H NMR ($CDCl_3$): δ0.91, 1.29 and 1.46 (each 3H, *s*, tert. Me × 3), 2.02 and 2.08 (each 3H, *s*, OAc × 2), 2.42 (1H, *d*, *J* = 12.5 Hz, H-14α), 2.60 (1H, *d*, *J* = 11 Hz, OH), 2.66 (1H, *m*, $W_{1/2}$ = 9 Hz, H-13), 3.41 (1H, *d*, *J* = 6.5 Hz, OH), 3.71 (1H, *m*, changed to *dd*, *J* = 12 and 4.5 Hz on addition of D_2O, H-1), 3.83 (1H, *dt*, *J* = 11 and 3 Hz changed to *t*, *J* = 3 Hz on addition of D_2O, H-15), 4.39 (1H, *m*, $W_{1/2}$ = 6.5 Hz, H-6), 4.69 (1H, *t*, *J* = 3 Hz, H-3), 5.04 [1H, *br d*, *J* = 3 Hz, H-17], 5.16 [1H, *br s*, H-17] and 6.23 [1H, *br d*, *J* = 5 Hz, H-11]; ^{13}C NMR (see Table 1); MS *m/z*: 436.2468 $[M]^+$. $C_{24}H_{36}O_7$ requires: 436.2462.

Inflexarabdonin B (**10**). Amorphous powder, $[\alpha]_D^{24}$ −16.9° (MeOH; *c* 0.83). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1720, 1375, 1260–1200, 1120, 1025 and 950; ^1H NMR ($CDCl_3$): δ0.87, 1.09, 1.33 (each 3H, *s*, tert. Me × 3), 2.06 and 2.12 (each 3H, *s*, OAc × 2), 2.26 [1H, *br s*, H-9], 2.66 (1H, *s*, H-5), 2.68 (1H, *m*, H-13), 2.71 (1H, *d*, *J* = 11 Hz, OH), 2.96 (1H, *d*, *J* = 12 Hz, H-7), 3.42 (1H, *m*, OH), 3.87 (1H, *dt*, *J* = 11 and 2.5 Hz, changed to *t*, *J* = 2.5 Hz on addition of D_2O, H-15), 3.96 (1H, *m*, changed to *dd*, *J* = 11.5 and 5 Hz on addition of D_2O, H-1), 4.60 (1H, *t*, *J* = 3 Hz, H-3), 5.08 [1H, *br d*, *J* = 3 Hz, H-17], 5.20 [1H, *br d*, *J* = 2 Hz, H-17] and 6.29 [1H, *br d*, *J* = 5 Hz, H-11]; ^{13}C NMR (see Table 1); MS *m/z*: 434.2305 $[M]^+$. $C_{24}H_{34}O_7$ requires: 434.2305.

Inflexarabdonin A diacetate (**2**). Inflexarabdonin A (**1**) (7.8 mg) was dissolved in a mixture of Ac_2O (0.3 ml) and Py (0.3 ml) and the soln was warmed at 50° for 2 days. After addition of excess MeOH, the mixture was concd *in vacuo* to give a residue (9.6 mg) which was purified by prep. TLC ($CHCl_3$–Me_2CO 19:1; developed twice) to give the diacetate **2** (4.3 mg) as an amorphous powder. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1370, 1270–1190, 1060 and 1030; ^1H NMR ($CDCl_3$): δ0.94, 1.32 and 1.55 (each 3H, *s*, tert. Me × 3), 1.85, 2.02, 2.11 and 2.22 (each 3H, *s*, OAc × 4), 2.41 (1H, *d*, *J* = 12.5 Hz, H-14α), 2.66 (1H, *m*, H-13), 4.40 (1H, *m*, H-6), 4.70 (1H, *t*, *J* = 3 Hz, H-3), 4.80 [1H, *br s*, H-17], 4.92 [1H, *br s*, H-17], 4.95 (1H, *dd*, *J* = 11 and 4.5 Hz, H-1), 5.23 (1H, *t*, *J* = 2.5 Hz, H-15), and 5.58 (1H, *dd*, *J* = 4.5 and 2 Hz, H-11); MS *m/z*: 520.2713 $[M]^+$. Calc for $C_{28}H_{40}O_9$: 520.2673.

Reduction of inflexinol (**4**). To a soln of inflexinol (**4**) (21.1 mg) in MeOH (5 ml), a solution of $NaBH_4$ (10 mg) in MeOH (1 ml) was added dropwise with stirring and ice cooling. The mixture was stirred for 1 hr at 0°. The reaction mixture was diluted with H_2O (30 ml) and extracted with EtOAc (30 ml × 3). The extract was washed with satd NaCl aq. soln, dried and evapd *in vacuo* to give a residue (20.8 mg) which was purified by prep. TLC ($CHCl_3$–Me_2CO 9:1, developed twice) to give inflexarabdonin A (**1**) (14.8 mg) as colourless needles, mp 112–115°. MS *m/z*: 436.2425 $[M]^+$. Calc for $C_{24}H_{36}O_7$: 436.2462. This compound was identical to inflexarabdonin A of natural origin (mmp, IR and ^1H NMR).

Garryfoline–cuauchichicine rearrangement of inflexarabdonin A (**1**). To a soln of inflexarabdonin A (10 mg) in $CHCl_3$ (10 ml), 2 M HCl (2 drops) was added and the mixture was warmed at 50° for 24 hr with stirring. The reaction mixture was washed with H_2O (20 ml), dried and evapd *in vacuo* to give dihydroinflexinol (**6**) (9.1 mg) as an amorphous powder. MS *m/z*: 436.2457 $[M]^+$. Calc for $C_{24}H_{36}O_7$: 436.2462. This compound was identical to an authentic sample of dihydroinflexinol (**6**) [3, 5] (IR and ^1H NMR).

Inflexarabdonin B diacetate (**11**). Inflexarabdonin B (**10**) (4.7 mg) was dissolved in a mixture of Ac_2O (0.2 ml) and pyridine (0.2 ml) and the soln was kept at room temp. for 24 hr. After addition of excess MeOH, the mixture was concd *in vacuo* to give a residue (5.7 mg) which was purified by prep. TLC ($CHCl_3$–Me_2CO 19:1, developed twice) to give the diacetate **11** (3.2 mg) as an amorphous powder. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1370, 1260–1200 and 1035; ^1H NMR ($CDCl_3$): δ0.90, 1.18 and 1.36 (each 3H, *s*, tert. Me × 3), 1.90, 2.05, 2.14 and 2.27 (each 3H, *s*, OAc × 4), 2.43 [1H, *br s*, H-9], 2.66 (1H, *s*, H-5), 2.68 (1H, *m*, H-13), 2.78 (1H, *d*, *J* = 12 Hz, H-7), 4.62 (1H, *t*, *J* = 3 Hz, H-3), 4.87 [1H, *br s*, H-17], 4.96 (1H, *dd*, *J* = 3 and 1 Hz, H-17), 5.19 (1H, *dd*, *J* = 10 and 6 Hz, H-1), 5.24 (1H, *t*, *J* = 2.5 Hz, H-15), 5.56 (1H, *t*, *J* = 3 Hz, H-11); MS *m/z*: 518.2521 $[M]^+$. Calc for $C_{28}H_{38}O_9$: 518.2516.

Reduction of inflexin (**3**). To a soln of inflexin (**3**) (22 mg) in MeOH (5 ml), a soln of $NaBH_4$ (6 mg) in MeOH (1 ml) was added dropwise with stirring and ice cooling. The mixture was stirred for 30 min at 0°. The reaction mixture was diluted with H_2O (30 ml) and extracted with EtOAc (30 ml × 3). The extract was washed with satd NaCl aq. soln, dried and evapd *in vacuo* to give a residue (22.6 mg) which was purified by prep. TLC ($CHCl_3$–Me_2CO 19:1, developed three times) to give inflexarabdonin B (**10**) (11.6 mg) as an amorphous powder. MS *m/z*: 434.2288 $[M]^+$. Calc for $C_{24}H_{34}O_7$: 434.2305. This compound was identical to inflexarabdonin B of natural origin (IR and ^1H NMR).

Dihydroinflexin monoacetate (**8**). Dihydroinflexin (**7**) (7.3 mg) was dissolved in a mixture of Ac_2O (0.2 ml) and pyridine (0.2 ml) and the soln was left for 2 days at room temp. After usual work-up, the product was purified by prep. TLC ($CHCl_3$–Me_2CO 9:1) to give dihydroinflexin monoacetate (**8**) (7.0 mg) which was crystallized on addition of MeOH. Mp 186–188°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1720, 1375, 1245–1200, 1100, 1020, and 970; ^1H NMR ($CDCl_3$): δ0.88 (3H, *s*, tert. Me), 1.18 (3H, *d*, *J* = 7 Hz, Me-16), 1.24 and 1.34 (each 3H, *s*, tert. Me × 2), 1.88 (1H, *d*, *J* = 12.5 Hz, H-7), 1.96, 2.02 and 2.15 (each 3H, *s*, OAc × 3), 2.32 (1H, *d*, *J* = 13 Hz, H-14α), 2.32 (1H, *m*, H-16), 2.49 (1H, *m*, H-13), 2.85 (1H, *s*, H-5), 3.14 (1H, *d*, *J* = 12.5 Hz, H-7), 4.60 (1H, *t*, *J* = 3 Hz, H-3), 5.10 (1H, *dd*, *J* = 11.5 and 5 Hz, H-1), 5.55 (1H, *t*, *J* = 3.5 Hz, H-11); MS *m/z*: 476.2374 $[M]^+$, Calc for $C_{26}H_{36}O_8$: 476.2411.

Conversion of inflexarabdonin B (**10**) *into dihydroinflexin monoacetate* (**8**). Inflexarabdonin B (**10**) (6.1 mg) was dissolved in MeOH (2 ml). Conc. HCl (5 drops) was added to the soln and the mixture was stirred for 5 days at room temp. After addition of H_2O (20 ml), the reaction mixture was neutralized with small amount of $NaHCO_3$ and extracted with EtOAc (20 ml × 3). After being washed with satd NaCl aq. soln, the EtOAc extract was dried and evapd *in vacuo* to give a residue (5.3 mg) which was dissolved in a mixture of Ac_2O (0.2 ml) and Py (0.2 ml) and the mixture was kept at room temp. for 8 days, then, warmed at 50° for 2 days. After addition of excess MeOH, the reaction mixture was concd *in vacuo* to give a residue (7.2 mg) which was purified by prep. TLC ($CHCl_3$–Me_2CO 19:1, developed twice) to give dihydroinflexin monoacetate (**8**) (1.7 mg). MS *m/z*: 476.2406 $[M]^+$ Calc. for $C_{26}H_{36}O_8$: 476.2411. This compound was identical to the compound derived from inflexin (**3**) (IR and ^1H NMR).

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