Revision of the Structures of Isodonal, Rabdolasional and Related Diterpenoids

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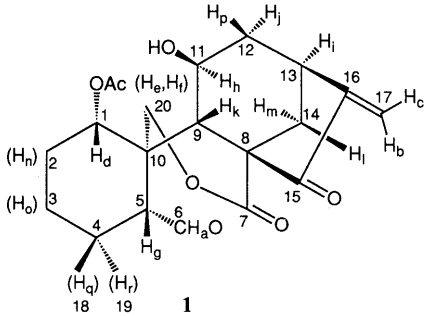
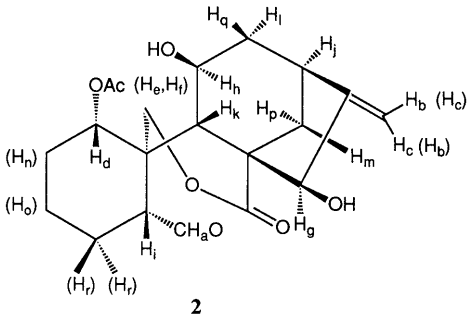
The structures of isodonal and rabdolasional were re-examined by means of two-dimensional nuclear magnetic resonance spectroscopy (2D-NMR) and were revised to 1 and 2 from the previously reported structures, 3 and 4. The structures of the chemically correlated diterpenoids, isodonoic acid and trichodonin were also revised to 7 and 8, respectively.

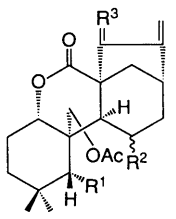
Keywords isodonal; rabdolasional; isodonoic acid; trichodonin; 6,7-seco-*ent*-kaurenoid; 2D-NMR; structure revision

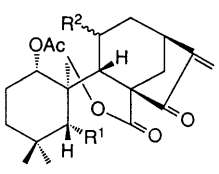
Isodonal[1,2] has been isolated from *Rabdosia japonica* HARA and *R. ternifolia* (D. DON) HARA and reported to have the structure (**3**) on the basis of interpretation of the spectroscopic data and the results of chemical reactions.[1] On the other hand, rabdolasional has been isolated from *Rabdosia lasiocarpa* (HAYATA) HARA and reported to have the structure (**4**)[3] by comparisons of its spectral data with those of isodonal. In the structure elucidation of both compounds, the locations of two acyl groups, acetyl and lactone groups, were not determined unambiguously according to present knowledge, because the acetyl group was hydrolyzed during the chemical transformation. It is possible that the mode of lactone linkage might have been changed. Thus, we re-examined the structures of isodonal and rabdolasional by two-dimensional nuclear magnetic resonance spectroscopy (2D-NMR) including proton two-dimensional correlated spectroscopy (^{1}H-COSY), proton two-dimensional nuclear Overhauser enhancement spectroscopy (^{1}H-NOESY), proton–carbon-13 two-dimensional correlation spectroscopy (^{1}H–^{13}C COSY) and proton–carbon-13 long range correlation spectroscopy (^{1}H–^{13}C LRCOSY). We reached the conclusion that the structures of these compounds should be revised to **1** and **2**, respectively. This paper deals with the structure revision of isodonal, rabdolasional, and the related compounds, trichodonin[1b] and isodonoic acid.[2]

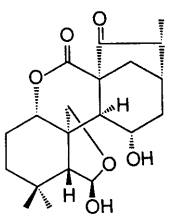
Isodonal[1] has an *ent*-6,7-seco-kaur-16-en-15-one structure as the basic skeleton as judged from the reported spectroscopic data and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum (Table I). In addition to the basic skeleton, isodonal contained a secondary hydroxyl group [δ_H 3.94 (1H, ddd, J=11.5, 9.5 and 7.4 Hz), H_h; δ_C 65.12], a secondary acyloxy group [δ_H 5.07 (1H, dd, J=11.3 and 4.1 Hz), H_d; δ_C 76.07], a primary acyloxy group [δ_H 4.99 and 5.04 (each 1H, d, J=12.6 Hz), H_f and H_e; δ_C 67.23], an acetyl group [δ_H 2.02 (3H, s); δ_C 21.40 and 170.86], a lactone group [δ_C 171.32], and an aldehyde group [δ_H 9.82 (1H, d, J=2.2 Hz, H_a; δ_C 204.91] as judged from its proton-nuclear magnetic resonance (^{1}H-NMR) (Table II) and ^{13}C-NMR spectra (Table I). The locations of these functional groups were examined first by ^{1}H-COSY; the spectrum is shown in Fig. 1. The connectivities for H_a (6-H)→H_g (5-H) and those for H_b (17-H_1)→H_c (17-H_1)→H_i (13-H)→H_l (14β-H)→H_m (14α-H) were observed by











3: R^1=CHO, R^2=α-OH, R^3=O
4: R^1=CHO, R^2=α-OH, R^3=α-OH, β-H
5: R^1=COOH, R^2=α-OH, R^3=O
6: R^1=CHO, R^2=β-OH, R^3=O

7: R^1=COOH, R^2=β-OH
8: R^1=CHO, R^2=α-OH

9

following the cross peaks through the lines A and B. The connectivities for H_i (13-H)→H_j (12α-H)→H_p (12β-H)→H_h (11-H)→H_k (9-H) and those for H_d (1-H)→H_n (2-H_2)→H_o (3-H_2) were also observed by following the cross peaks through the lines C and D. Thus, a hydroxyl group and an aldehyde group should be located at C-11 and C-6, respectively. The configuration of the hydroxyl group was

Table I. ^{13}C-NMR Data for Isodonal (**1**) and Rabdolasional (**2**)[a]

Carbon	1	2	Carbon	1	2
1	76.07 (d)	75.67 (d)	12	40.64 (t)	44.32 (t)
2	24.34 (t)	23.91 (t)	13	34.36 (d)	35.16 (d)
3	40.19 (t)	39.95 (t)	14	29.69 (t)	30.04 (t)
4	34.80 (s)	34.09 (s)	15	200.38 (s)	83.41 (d)
5	61.00 (d)	61.40 (d)	16	149.76 (s)	157.78 (s)
6	204.91 (d)	205.78 (d)	17	120.26 (t)	110.29 (t)
7	171.32 (s)	174.99 (s)	18	33.37 (q)	33.45 (q)
8	58.18 (s)	52.26 (s)	19	24.81 (q)	24.73 (q)
9	46.37 (d)	41.47 (d)	20	67.23 (t)	66.36 (t)
10	44.23 (s)	43.17 (s)	$\underline{C}H_3CO$	21.40 (q)	21.38 (q)
11	65.12 (d)	65.75 (d)	$CH_3\underline{C}O$	170.86 (s)	170.59 (s)

a) The spectra were measured at 25 °C in a mixture of $CDCl_3$–CD_3OD (2 : 1, v/v) for **1** and in $CDCl_3$ for **2**, and the chemical shifts are given in ppm (δ) relative to internal tetramethylsilane. Multiplicity detected by distortionless enhancement by polarization transfer (DEPT) experiments is given in parentheses.

Table II. ^{1}H-NMR Data[a] for Isodonal (**1**) and Rabdolasional (**2**)

Proton	1	2
1-H	5.07 (dd, 11.3, 4.1)	5.11 (dd, 10.2, 5.3)
2-H_2	1.92 (m)	1.91 (m)
3-H_2	1.62 (m)	1.62 (m)
5-H	3.95 (d, 2.2)	3.80 (d, 2.8)
6-H	9.82 (d, 2.2)	9.90 (d, 2.8)
9-H	2.36 (d, 11.5)	2.56 (d, 11.0)
11-H	3.94 (ddd, 11.5, 9.5, 7.4)	3.88 (ddd, 11.0, 9.6, 8.5)
12α-H	2.60 (ddd, 13.6, 9.4, 7.4)	*ca.* 2.50
12β-H	1.35 (dd, 13.6, 9.5)	1.26 (dd, 12.6, 9.5)
13-H	3.09 (dd, 9.4, 4.4)	2.70 (dd, 8.2, 5.4)
14α-H	1.94 (d, 12.6)	1.49 (d, 12.8)
14β-H	2.35 (dd, 12.6, 4.4)	2.02 (dd, 12.8, 5.4)
15-H	—	4.48 (t, 2.6)
17-H_1	5.60 (br s)	5.20 (m)
17-H_1	6.08 (br s)	5.21 (br s)
18-H_3	1.19 (s)	1.13 (s)
19-H_3	1.10 (s)	1.13 (s)
20-H_1	4.99 (d, 12.6)	4.91 (d, 12.2)
20-H_1	5.04 (d, 12.6)	4.95 (d, 12.2)
CH_3CO	2.02 (s)	2.02 (s)

a) The spectra were determined in $CDCl_3$–CD_3OD (2 : 1, v/v) for **1** and in $CDCl_3$ for **2**. The chemical shifts are given in ppm (δ) relative to internal tetramethylsilane. Multiplicity and *J* value (in Hz) are given in parentheses.

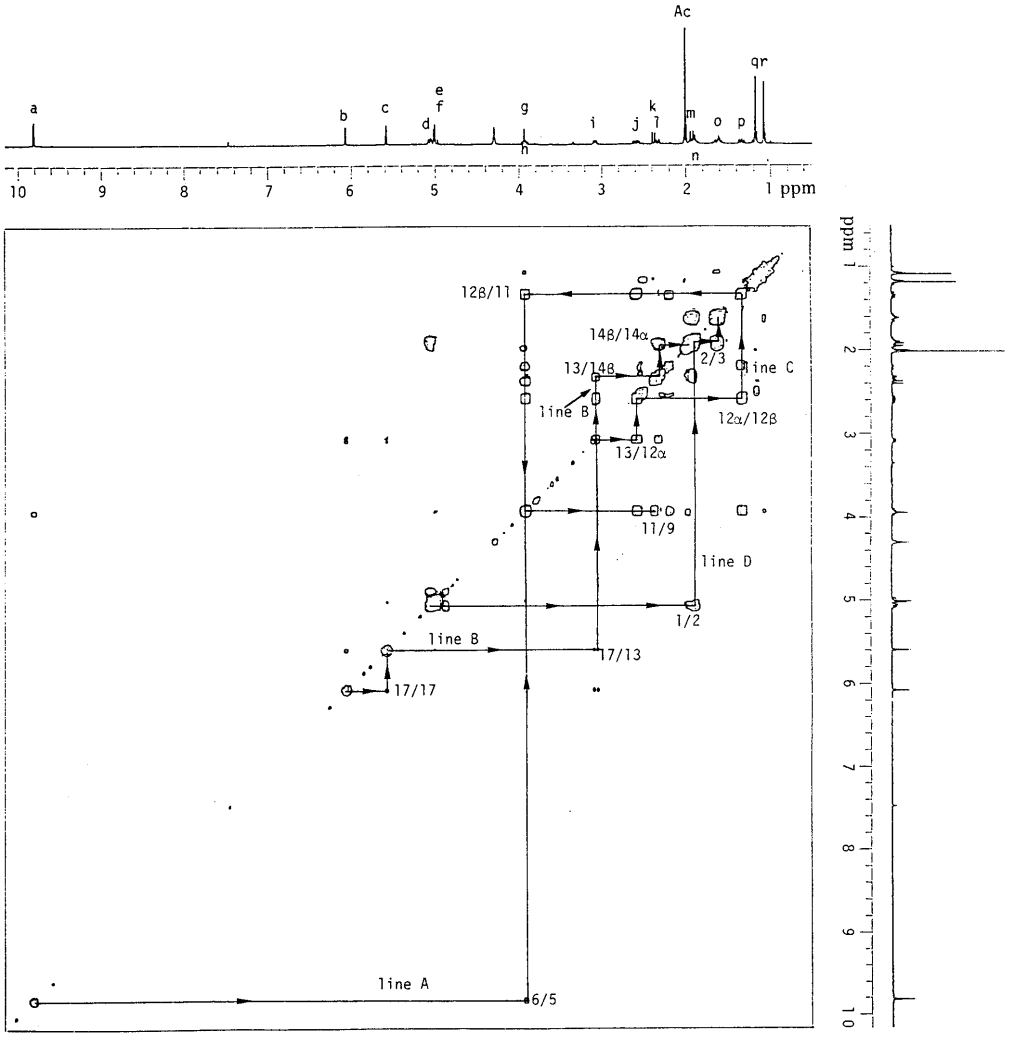


Fig. 1. ^{1}H-COSY Spectrum of Isodonal (**1**)

deduced to be β from the coupling pattern of H_h and the results of ^{1}H-NOESY (Fig. 2). The signal was coupled with H_k (9-H) ($J=11.5$ Hz), H_j (12α-H) ($J=7.4$ Hz) and H_p (12β-H) ($J=9.5$ Hz). As shown in Fig. 2, H_h showed cross peaks with H_m (14α-H) and H_p (12β-H) showed cross peaks with H_k (9-H). The results showed not only the β-configuration of the secondary hydroxyl group, but also a boat conformation of ring C. The aldehyde group was determined to be α-equatorial, since H_a showed cross peaks with H_q (18-H_3) and H_r (19-H_3), and H_g (5-H) showed cross peaks with H_q and H_k (9-H) in the ^{1}H-NOESY spectrum.

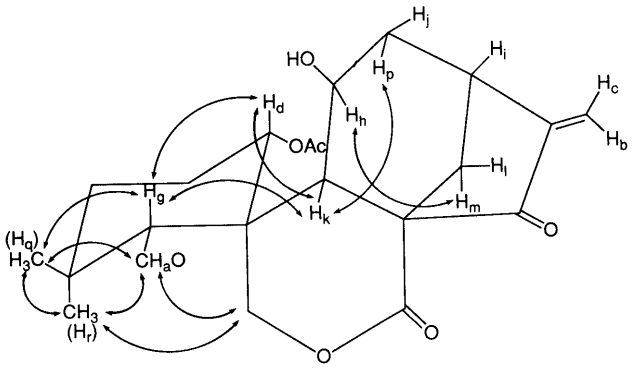


Fig. 2. Summary of NOESY Experiment for Isodonal (**1**)

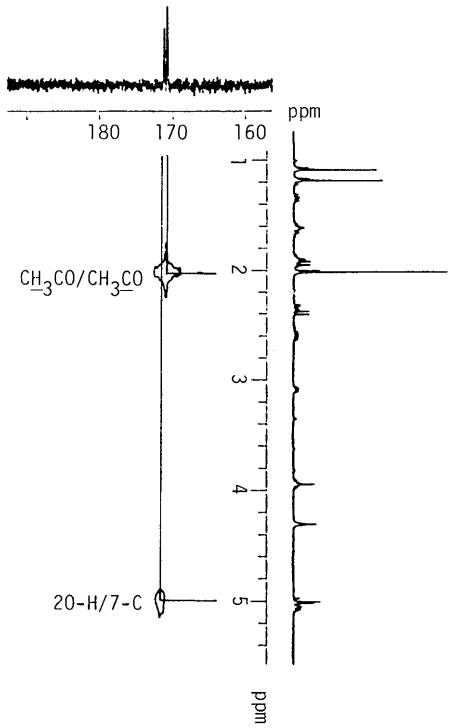


Fig. 3. ^{1}H–^{13}C-LRCOSY ($J=10$ Hz) Spectrum of Isodonal (**1**)

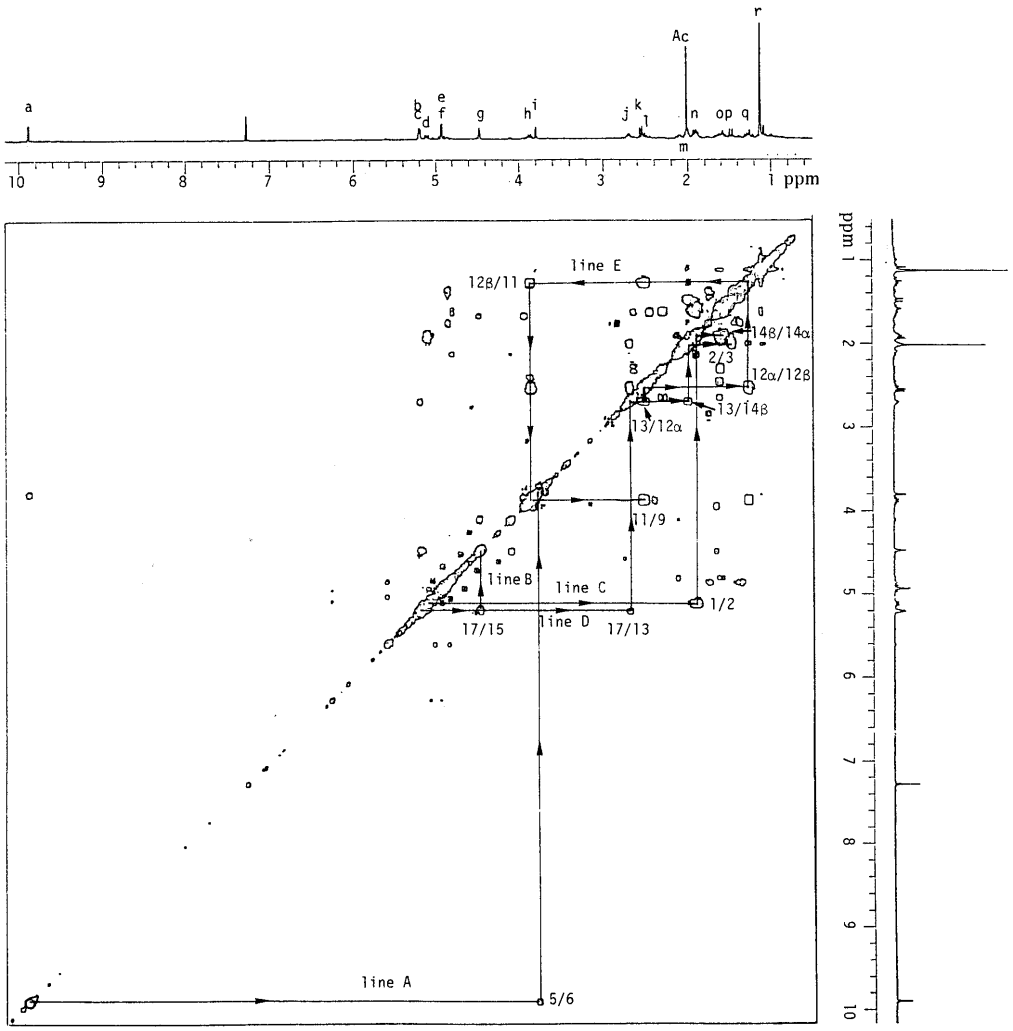


Fig. 4. ^{1}H-COSY Spectrum of Rabdolasional (**2**)

A primary acyloxy group and a secondary acyloxy group were determined to be located at C-20 and C-1, respectively, since H_a (6-H) and H_r (19-H_3) showed cross peaks with 20-H and H_d (1-H) showed cross peaks with H_g (5-H) and H_k (9-H) in the ^{1}H-NOESY spectrum. The remaining problem is the location of the two acyl groups, *i.e.* the acetyl and lactone groups. In order to solve this, we examined ^{1}H–^{13}C-LRCOSY (J=10 Hz) (Fig. 3) in the ester carbonyl region after assigning the ^{13}C-signals by ^{1}H–^{13}C-COSY. The signal at δ_C 170.86 showed cross peaks with the acetyl methyl protons. Thus, the signal was assigned to the carbonyl group in the acetyl group. Another signal at δ 171.32 was assigned to the carbonyl group in the lactone group and showed cross peaks with 20-H. Based on these results, the lactone is formed between C-7 and C-20 and the acetyl group is located at C-1. Thus, the structure of isodonal was revised to **1** from the previously reported structure, **3**.[1)]

Isodonoic acid,[2)] a minor constituent of *R. ternifolia* and trichodonin,[1b)] a minor constituent of *R. japonica* and *R. trichocarpa*, have been elucidated to have structures **5** and **6**, respectively by comparison of their spectral data and by chemical correlation with isodonal. Based on the revised structure of isodonal (**1**), the structures of isodonoic acid, a carboxylic acid congener at C-6, and trichodonin, an epimer at C-11, should also be revised to **7** and **8**, respectively. The revised structure of trichodonin is the same as that reported for trichorabdal H.[4,5)]

Rabdolasional was previously reported to have the structure (**4**)[3)] in which the ketone group at C-15 in isodonal is reduced to an allylic alcohol by comparison of the spectral data with those of isodonal and conversion to dihydroepinodosin (**9**) under the conditions of the garryfoline–cuauchichicine rearrangement.[6,7)] Since the structure of isodonal was revised, we also re-examined the structure of rabdolasional. Rabdolasional showed almost the same ^{1}H-NMR spectrum as that of isodonal (**1**) except for the appearance of a new signal at δ 4.48 (1H, t, J=2.6 Hz) assigned to 15α-H and an upfield shift of the signals due to 17-H_2. The ^{1}H-COSY spectrum is shown in Fig. 4. The connectivities for H_a (6-H)→H_i (5-H), those for H_b and H_c (17-H_2)→H_g (15-H), those for H_d (1-H)→H_n (2-H_2)→H_o (3-H_2), those for H_b and H_c (17-H_2)→H_j (13-H)→H_m (14β-H)→H_p (14α-H) and those for H_j (13-H)→H_l (12α-H)→H_q (12β-H)→H_h (11-H)→H_k (9-H) were observed by following the lines A, B, C, D and E, respectively. The results obtained from the ^{1}H-NOESY experiment were almost the same as in the case of isodonal (Fig. 2) except for the appearance of cross peaks between H_g (15α-H) and H_m (14β-H). Finally, ^{1}H–^{13}C-LRCOSY (J=10 Hz) (Fig. 5) was examined. One (δ_C 170.59) of the two carbonyl groups of the acyloxy group showed a cross peak with an acetyl group, confirming that the signal is due to the carbonyl group of the acetyl group. The remaining carbonyl group was thus assigned as the carbonyl group of the lactone moiety and the signal showed cross peaks with the protons at C-15 and C-20. Based on these results, the lactone is formed between C-7 and C-20. Thus, the structure of rabdolasional should be revised to **2**.

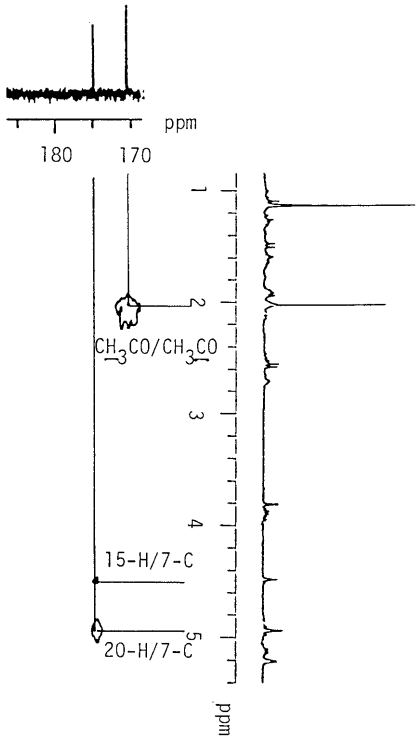


Fig. 5. ^{1}H–^{13}C-LRCOSY (J=10 Hz) Spectrum of Rabdolasional (**2**)

Although the discrimination of the structural types, **1** and **3**, is difficult, the use of 2D-NMR, especially ^{1}H–^{13}C-LRCOSY, to solve this problem is very effective.

Experimental

NMR Spectra NMR spectra were taken on a JEOL JNM GSX-400 spectrometer (^{1}H, 400 MHz and ^{13}C 100 MHz). The 2D-NMR spectra were measured by the use of the JEOL standard pulse sequences and the collected data were processed with the standard JEOL software. Samples (30 mg) were dissolved in 0.5 ml of the solvent.

Isodonal (1) and Rabdolasional (2) Isodonal and rabdolasional used in this report were previously isolated.[2,3)]

References and Notes

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5) Based on the present results, the name of trichodonin should be changed to trichorabdal H.
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