Studies on the Constituents of *Viburnum* Species. XVIII.\(^1\)
Viburnols: Six New Triterpenoids from *Viburnum dilatatum* Thunb.\(^2\)

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Six new triterpenoids, viburnols F, G, H, I, J and K, were isolated from the leaves of *Viburnum dilatatum* Thunb. (Caprifoliaceae). The structures were determined by extensive spectroscopic studies. Viburnols F, G and I are the first example of a new class of modified dammarane-type triterpenes.

**Key words** *Viburnum dilatatum*; Caprifoliaceae; triterpene; dammarane; viburnol

We have recently reported the isolation of five new triterpenoids, viburnols A, B, C, D and E, from the CHCl\(_3\) extract of the leaves of *Viburnum dilatatum* Thunb.\(^3\) In a previous communication,\(^2\) we reported the isolation and structural elucidation of six new triterpenoids, viburnols F—K, obtained from the remaining fractions of the same extract. In this paper, we present a full account of the structure elucidation of viburnols F (1), G (2), H (3), I (4), J (5) and K (6).

Viburnol F (1) was obtained as its methyl ester 1a, \([\alpha]_D^{20}\)
\(+43.5^\circ\) (CHC\(_3\)). The molecular formula of 1a was assigned as \(C_{31}H_{46}O_7\) on the basis of the MS and \(^{13}\)C-NMR spectral data. Its \(^1\)H- and \(^{13}\)C-NMR spectra were similar to those of viburnol E.\(^1\) The \(^1\)H- and \(^{13}\)C-NMR spectra of 1a, however, lacked the signals due to a methylene (C-1) and a cyclic ketone (C-2) of viburnol E and instead showed signals characteristic of two oxygenated carbons [a methine (\(\delta_C 4.37, \delta_C 82.5\)) and a quaternary carbon (\(\delta_C 85.5\))], a methoxycarbonyl group (\(\delta_H 3.76, \delta_C 174.9, 51.9\) and two hydroxyl groups (\(\delta_H 4.68, 4.28\), each 1H, disappearing on D\(_2\)O exchange). These findings suggested that the two hydroxy groups are located at the C-1 and -2 positions, and the methoxycarbonyl group is located at the hydroxy-bearing quaternary carbon (\(\delta_C 85.5\)), in the five-membered A-ring. The location of the methoxycarbonyl on C-2 was deduced from the heteronuclear multiple bond coherence (HMBC) spectrum. The quaternary carbon at \(\delta_C 85.5\) showed HMBC correlations with the methyl protons at \(\delta 1.05\) (28-CH\(_3\)) and 0.84 (29-CH\(_3\)), which are also correlated to the quaternary carbon at \(\delta 46.7\) (C-4). On the other hand, the methine carbon at \(\delta 82.5\) showed a correlation with the methyl protons at \(\delta 1.09\) (19-CH\(_3\)), which are also correlated to the quaternary carbon at \(\delta 46.0\) (C-10). Thus, the structure of ring A of 1a was indicated.

The stereochemistry of 1a was deduced from the difference nuclear Overhauser effect (NOE) spectra. The observation of NOE enhancements between 1-H/19-CH\(_3\) (but not between 1-OH/19-CH\(_3\)), 19-CH\(_3\)/29-CH\(_3\), 29-CH\(_3\)/2-COOCH\(_3\) and 2-COOCH\(_3\)/1-H indicated that they were all on the same face (\(\beta\)) of the molecule, while the presence of interactions between 1-OH/9-H and 2-OH/28-CH\(_3\) revealed that these were on the same face (\(\alpha\)), opposite to the \(\beta\)-face. The signal of 9-H of 1a was shifted to a lower field (\(\Delta \delta =0.46\)) than that of viburnol E indicating the presence of steric compression between 1x-OH and 9-H. Moreover, the carbon signal of C-9 was shifted upfield from that of viburnol E by \(\Delta \delta =7.4\) due to the \(\gamma\)-gauche effect with 1x-OH (C-19 seems not to be affected by 1-OH). All other HMBC (Fig. 1) and NOE

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Fig. 1. HMBC Correlations of 1a

Fig. 2. NOE Enhancements of 1a

except that 3 had an oxygenated methine (δ 82.4) instead of the methylene group in viburnol D. Thus, 3 may be formulated as a hydroxy derivative of viburnol D at ring A. The 1H-NMR spectrum of 3, however, showed signals of a methine proton at δ 3.89 (1H, s) and a methylene proton at δ 2.25 and 3.48 (each 1H, d, J = 13.0 Hz). The multiplicities of these signals indicated that the keto group is located between a hydroxymethine and a methylene group, possibly on C-2. The location of the hydroxy group on C-3 was deduced from the HMBC spectrum, that is, cross peaks were observed between the methylene protons and C-9, -10 and -19, and between the hydroxymethine proton and C-4, -28 and -29. The stereochemistry of the hydroxyl group at C-3 was determined as β on the basis of the NOE difference spectra, in which NOE enhancements were observed at 3-H and 9-H when one of the methylene protons (δ 82.25) at C-1 was irradiated. All other HMBC and NOE correlations of 3 were the same as those of viburnol D. On the basis of the above data, the structure of viburnol H (3) is proposed to be as depicted in the formula.

Viburnol I (4) was obtained as its methyl ester 4a, [α]D + 20.0° (CHCl₃). The molecular formula of 4a was assigned as C₃₁H₄₈O₇, on the basis of the MS and ¹³C-NMR spectral data. From comparison of the NMR spectral data of 2a with those of viburnol E, it was deduced that 2a possesses an oxygenated quaternary carbon (δC 89.2), a methoxycarbonyl group (δH 3.76, δC 172.4, 52.9) and a hydroxyl group (δH 5.64, 1H, disappearing on D₂O exchange) instead of a methylene (C-1) group in viburnol E. These findings suggested that a tertiary alcohol and a methoxycarbonyl group are located at the C-1 position in the five-membered A-ring. This deduction was supported by the HMBC spectrum. The carbon at δ 89.2 showed a correlation with the methyl protons at δ 1.02 (19-CH₃), which are also correlated to the quaternary carbon at δ 49.0 (C-10). Furthermore, correlations were observed between the carbon at δ 217.3 (C-3) and the protons of 1-OH (δ 5.64), 28-CH₃ and 29-CH₃ (δ 1.07, 1.17). Thus, the structure 2a was indicated. The hydroxyl group at C-1 was determined to be on the same side as 19-CH₃ from the NOE difference spectrum. The C-19 signal of 2a was shifted upfield from that of viburnol E by Δ δ -3.3 due to the γ-gauche effect of 1β-OH. All other HMBC and NOE correlations of 2a were the same as those of viburnol E. On the basis of the above data, the structure of viburnol G (2) was established as depicted.

Viburnol H (3) was obtained as an amorphous powder, [α]D + 43.3° (CHCl₃). The molecular formula of 3 was assigned as C₃₀H₄₈O₇ on the basis of the MS and ¹³C-NMR spectral data. The ¹H- and ¹³C-NMR spectral data of 3 were closely related to those of viburnol D,¹³ except that 3 had an oxygenated methine (δ 82.4) instead of the methylene group in viburnol D. Thus, 3 may be formulated as a hydroxy derivative of viburnol D at ring A. The 1H-NMR spectrum of 3, however, showed signals of a methine proton at δ 3.89 (1H, s) and a methylene proton at δ 2.25 and 3.48 (each 1H, d, J = 13.0 Hz). The multiplicities of these signals indicated that the keto group is located between a hydroxymethine and a methylene group, possibly on C-2. The location of the hydroxy group on C-3 was deduced from the HMBC spectrum, that is, cross peaks were observed between the methylene protons and C-9, -10 and -19, and between the hydroxymethine proton and C-4, -28 and -29. The stereochemistry of the hydroxyl group at C-3 was determined as β on the basis of the NOE difference spectra, in which NOE enhancements were observed at 3-H and 9-H when one of the methylene protons (δ 82.25) at C-1 was irradiated. All other HMBC and NOE correlations of 3 were the same as those of viburnol D. On the basis of the above data, the structure of viburnol H (3) is proposed to be as depicted in the formula.

Viburnol I (4) was obtained as its methyl ester 4a, [α]D + 20.0° (CHCl₃). The molecular formula of 4a was assigned as C₃₁H₄₈O₇, on the basis of the MS and ¹³C-NMR spectral data. From comparison of the NMR spectral data of 4a with those of viburnol B methyl ester,¹³ it was deduced that 4a possesses a hemiacetal (δC 49.9, δC 105.2) and a carbonyl (1738 cm⁻¹, δC 202.8) instead of methylene (C-1) and λ-lactone carbonyl (C-2) groups in viburnol B. The planar structure of 4a was finally deduced from the HMBC spectrum. The cross peaks between the proton at δ 4.99 and C-11 (δ 75.8), and between the 19-CH₃ (δ 1.07) and the carbon at δ 105.2, suggested the presence of a five-membered hemiacetal ring between C-1 and -11. The cross peaks between the methyl protons at δ 1.25 and 1.37 (28-CH₃, 29-CH₃) and carbon signals at δ 202.8, 50.3 (C-3) and 45.5 (C-5), respectively, suggested that the carbon signal at δ 202.8 is assignable to C-3. The remaining methoxycarbonyl moiety should, therefore be connected with this carbonyl. The presence of the α-ketomethyl ester moiety was supported by the electron impact (EI) mass fragment at m/z 287 [M⁺ - H₂O - C₆H₁₀O (C-20/22 cleavage) - C₆H₁₀O₃ (C-4/5 cleavage)]. On the basis of the above data, 4a was suggested to be an α-seco dammarane-type triterpene having a five-membered hemiacetal ring and methoxyl group. The stereochemistry of the hemiacetal group at C-1 was determined by an NOE experiment; a significant NOE between 1-H and 19-CH₃ was observed. Moreover, the carbon signal of C-5 in 4a was shifted upfield from that of viburnol B methyl ester by Δ δ - 9.8 due to the γ-gauche effect of 1α-OH (C-19 seems to be unaffected by the 1-OH). All other HMBC and NOE correlations of 4a were the same as those of viburnol B methyl ester. On the basis of the above data, the structure of viburnol I (4) was established to be as depicted in the formula.

Viburnol J (5) was obtained as an amorphous powder, [α]D + 45.5° (CHCl₃). The molecular formula of 5 was assigned as C₂₉H₄₄O₄ on the basis of the MS and ¹³C-NMR spectral data. From a comparison of the NMR spectral data of 5 with those of viburnol C,¹³ it was
deduced that 5 possesses an isopropenyl group ($\delta_4$ 4.92, 4.68, 1.75, $\delta_5$ 144.4, 114.6, 22.9) instead of a hydroxyl and two methyl (C-28, -29) groups in viburnol C. The isopropenyl group was located at C-5 from the HMBC spectrum. The carbon signal at $\delta$ 56.1 (C-5) showed correlations with the methyl protons ($\delta$ 1.75) and with the olefin protons ($\delta$ 4.92, 4.68). All other HMBC and NOE correlations of 5 were the same as those of viburnol C. On the basis of the above data, the structure of viburnol J (5) was established to be as depicted in the formula.

Viburnol K (6) was obtained as an amorphous powder, [a]D +25.5° (c = 0.4, CHCl3). The molecular formula of 6 was assigned as C26H40O14 on the basis of the MS and 13C-NMR spectral data. From a comparison of the NMR spectral data of 6 with those of viburnol C, it was deduced that 6 possesses a methylene ($\delta_3$ 40.2) group instead of a hydroxyl-bearing carbon (C-4), two methyls (C-28, -29) and a methine (C-5) in viburnol C. The carbon signals of C-6 and -10 in 6 were shifted upward from those of viburnol C by $\delta$ 4.1 and $\delta$ 5.5, respectively, because of the loss of the $\beta$-substituent effect. These findings suggested that the methylene carbon at $\delta$ 40.2 could be assigned as C-5. All other HMBC and NOE correlations of 6 were the same as those of viburnol C. On the basis of the above data, the structure of viburnol K (6) was established to be as depicted in the formula. Viburnol K (6) is the first example of a ring A-tetramer (C-3, -4, -28 and -29) triterpene isolated from a natural source.

The methyl esters 1a, 2a and 4a may be artifacts formed from the corresponding acids 1, 2 and 4 during the extraction and isolation processes.

Viburnols F (1), G (2), H (3), I (4), J (5) and K (6) were presumably biosynthesized from viburnol D (Fig. 3), so all the chiral centers of 1 (except C-1 and -2), 2 (except C-1), 3 (except C-3), 4, 5 and 6 are expected to coincide with those of viburnol D, whose absolute configuration was elucidated from the circular dichroism (CD) spectrum.13 Based on this assumption, the full structures of viburnols F—K (1—6) are as shown in Chart I.

Compounds 1—6 are new dammarane-type triterpenes, and compounds 1, 2 and 4 are the first examples of a new class of modified dammarane-type triterpenes. Furthermore, the occurrence of compounds 1 and 2 gives important clues to the biosynthesis of the A-nor-triterpene-noid, viburnol E.

It is likely that all the viburnols (except viburnols D and H) are biosynthesized from the postulated intermediate (7; dammar-24-ene-2,3,23-trione-1z,11z,20z-triol). Bonds cleavages at ring A followed by recyclylation would afford viburnols F (route A), G (route B), A (route C) and I (route D) (Fig. 3).23

Experimental

The instruments, materials and experimental conditions were the same as in our previous paper.11

Extraction and Isolation

The extraction and isolation procedures were as described in our previous paper.11 Compounds 1a (10.0 mg), 2a (7.0 mg), 3 (30.0 mg), 4a (6.5 mg), 5 (10.0 mg) and 6 (9.5 mg) were isolated from frs 3-24—3-28 by preparative HPLC.

Viburnol F Methyl Ester (1a): An amorphous powder, [a]D +43.5° (c = 0.3, CHCl3), IR (CHCl3) cm⁻¹: 3421, 2954, 1727, 1672, 1613, UV $_{max}$ (MeOH) nm (logε): 241.0 (3.89), EI-MS m/z: 516 (M-HO-H). FAB-MS m/z: 535 (M+H)⁺, HR-MS m/z: 516.3459 (M+H-O, Caled for C26H41O14; 516.3451). H-NMR (270 MHz, CDCl3): δ 6.07 (IH, brt, J = 1.2, 12-H, 24-H), 6.48 (1H, brs, 1-OH), 4.40 (1H, s, 20-OH), 4.37 (1H, s, 1-H), 4.28 (1H, s, 2-OH), 3.99 (IH, dd, J = 11.2, 10.5, 5.0, 11-H), 3.76 (3H, s, COOH), 2.54, 2.61 (2H, d, J = 16.4 Hz, 22-CH2), 2.42 (1H, brs, 1-0H), 2.21 (1H, m, 12-H), 2.17 (3H, d, J = 1.2 Hz, 27-CH3), 2.18 (1H, d, J = 11.2 Hz, 26-CH3), 1.21 (3H, s, 18-CH3), 1.09 (3H, s, 19-CH3), 1.05 (3H, s, 28-CH3) 0.97 (6H s, 18-30-CH3), 0.84 (3H, s, 29-CH3). 13C-NMR (67.8 MHz, CDCl3): Table I. Viburnol F Methyl Ester (2a): An amorphous powder, [a]D +73.8° (c = 0.4, CHCl3), IR (CHCl3) cm⁻¹: 3451, 2957, 1755, 1719, 1672, 1613, UV$_{max}$ (MeOH) nm (logε): 240.0 (3.79), EI-MS m/z: 514 (M-HO-H). FAB-MS m/z: 533 (M+H)⁺, HR-MS m/z: 514.3306 (M+H-O, Caled for C26H40O14; 514.3295). H-NMR (270 MHz, CDCl3): δ 6.05 (1H, brt, J = 1.2, 12-H, 24-H), 5.64 (1H, s, 1-OH), 4.37 (1H, s, 20-OH), 3.82 (1H, m, 11-H), 3.76 (3H, s, COOH), 3.34 (3H, d, J = 8.9 Hz, 11-OH), 2.57 (2H, s, 22-CH2), 2.32 (1H, m, 12-H), 2.17 (3H, d, J = 1.2 Hz, 27-CH3), 2.06 (1H, d, J = 10.9 Hz, 9-H), 1.92 (3H, d, J = 1.2 Hz, 26-CH3), 1.20 (3H, s, 21-CH3), 1.17 (3H, s, 29-CH3), 1.07 (3H, s, 28-CH3), 1.02 (6H, s, 18-30-CH3), 0.94 (3H, s, 29-CH3). 13C-NMR (67.8 MHz, CDCl3): Table I.

Viburnol H (3): An amorphous powder, [a]D +43.5° (c = 0.7, CHCl3), IR (CHCl3) cm⁻¹: 3475, 3019, 2974, 1704, 1674, 1614, UV$_{max}$ (MeOH) nm (logε): 240.0 (3.79), EI-MS m/z: 470 (M+H-O). FAB-MS m/z: 489 (M+H⁺), HR-MS m/z: 470.3366 (M-H-O, Caled for C25H39O15; 470.3396). H-NMR (270 MHz, CDCl3): δ 6.06 (1H, brt, J = 1.3 Hz, 24-H), 4.36 (1H, brs, 20-OH), 4.36 (1H, brs, 12-H), 4.36 (1H, brs, 11-H), 3.89 (1H, s, 3-H), 3.43 (1H, s, J = 13.0 Hz, 1-H), 2.52 (2H, s, 22-CH2), 2.25 (1H, d, J = 13.0 Hz, 1-H), 2.22 (1H, m, 12-H), 2.17 (3H, d, J = 1.3 Hz, 27-CH3), 1.92 (3H, d, J = 1.3 Hz, 26-CH3), 1.70 (1H, d, J = 10.6 Hz, 9-H), 1.21 (3H, s, 21-CH3), 1.19 (3H, s, 38-CH3), 0.99 (3H, s, 19-CH3), 0.96 (6H, s, 38-30-CH3), 0.70 (3H, s, 29-CH3). 13C-NMR (67.8 MHz, CDCl3): Table I.
Fig. 3. Possible Biosynthetic Pathways of Viburnols

Viburnol I Methyl Ester (4a): An amorphous powder, [α]D 20 +20.0° (c = 0.3, CHCl3). IR (CHCl3) cm⁻¹: 3545, 2958, 2928, 1738, 1713, 1673, 1612. UV λmax (MeOH) nm (log ε): 241.0 (3.94). EI-MS m/z: 514 (M − H₂O)⁺. FAB-MS m/z: 533 (M + H)⁺. HR-MS m/z: 514.3232 (M⁺ − H₂O, Caled for C₁₇H₃₀O₄: 514.3229), m/z: 417.2674 (M⁺ − H₂O − C₃H₅O, Caled for C₁₄H₂₈O₄: 417.2641), m/z: 287.1970 (M⁺ − H₂O − C₃H₅O − C₃H₅O₂, Caled for C₁₀H₁₆O₅: 287.2011). 1H-NMR (270 MHz, CDCl₃) δ: 6.04 (1H, brt, J = 1.0 Hz, 24-H), 4.99 (1H, d, J = 2.5 Hz, 1-H), 4.33 (1H, s, 20-ØH), 3.84 (3H, s, COOCH₃), 3.73 (1H, d, J = 11.9, 11.0, 5.0 Hz, 11-H), 2.61, 2.53 (2H, t, J = 16.5 Hz, 22-Ch₂), 2.36 (1H, m, 12-H), 2.34 (1H, d, J = 2.5 Hz, 1-ØH), 2.16 (3H, d, J = 1.0 Hz, 27-Ch₂), 2.10 (1H, d, J = 11.9 Hz, 9-H), 1.91 (3H, d, J = 1.0 Hz, 26-ØCH₂), 1.37 (3H, s, 29-ØCH₃), 1.25 (3H, s, 28-ØCH₃), 1.19 (3H, s, 21-ØCH₃), 1.07 (3H, s, 19-ØCH₃), 0.97 (3H, s, 18-ØCH₃), 0.96 (3H, s, 30-ØCH₃). 13C-NMR (67.8 MHz, CDCl₃) Table 1.

Viburnol J (5) An amorphous powder, [α]D 20 +45.5° (c = 0.2, CHCl₃). IR (CHCl₃) cm⁻¹: 3546, 2965, 1718, 1673, 1611. UV λmax (MeOH) nm (log ε): 241.0 (3.93), EI-MS m/z: 438 (M − H₂O)⁺. FAB-MS m/z: 457 (M⁺ + H)⁺. HR-MS m/z: 438.3112 (M⁺ − H₂O, Caled for C₁₃H₂₈O₄: 438.3134), 1H-NMR (270 MHz, CDCl₃) δ: 6.05 (1H, brs, 24-H), 4.92 (1H, t, J = 1.7 Hz, 29-ØH), 4.68 (1H, brs, 29-ØH), 4.42 (1H, d, J = 11.6, 11.4, 5.0 Hz, 11-H), 4.38 (1H, s, 20-ØH), 2.57 (2H, s, 22-Ch₂), 2.54 (1H, d, J = 16.0 Hz, 1-H), 2.39 (1H, d, J = 12.0, 5.0, 3.0 Hz, 12-ØH), 2.17 (3H, s, 27-Ch₂), 2.16 (1H, d, J = 16.0 Hz, 1-H), 1.92 (3H, d, J = 1.3 Hz, 26-Ch₂), 1.79 (1H, d, J = 11.6 Hz, 9-H), 1.75 (3H, brs, 28-ØCH₃), 1.21 (3H, s, 21-CH₃), 1.06 (6H, s, 18, 19-CH₃), 0.97 (3H, s, 30-CH₃).

13C-NMR (67.8 MHz, CDCl₃) Table 1.

Viburnol K (6) An amorphous powder, [α]D 20 +25.5° (c = 0.4, CHCl₃). IR (CHCl₃) cm⁻¹: 3452, 2943, 1718, 1674, 1614. UV λmax (MeOH) nm (log ε): 241.0 (3.80). EI-MS m/z: 398 (M − H₂O)⁺. FAB-MS m/z: 417 (M⁺ + H)⁺. HR-MS m/z: 398.2831 (M⁺ − H₂O, Caled for C₁₅H₂₈O₅: 398.2821), 1H-NMR (270 MHz, CDCl₃) δ: 6.04 (1H, brt, J = 1.0 Hz, 24-H), 4.39 (1H, d, J = 11.9, 10.6, 5.0 Hz, 11-H), 4.37 (1H, s, 20-ØH), 2.56 (2H, s, 22-ØCH₂), 2.38 (1H, m, 12-ØH), 2.34 (1H, d, J = 17.2 Hz, 1-H), 2.17 (3H, d, J = 1.0 Hz, 27-Ch₂), 1.86 (1H, d, J = 17.2 Hz, 1-H), 1.92 (3H, d, J = 1.0 Hz, 26-Ch₂), 1.78 (1H, d, J = 11.9 Hz, 9-H), 1.21 (3H, s, 21-CH₃), 1.12 (3H, s, 19-CH₃), 1.04 (3H, s, 18-CH₃), 0.95 (3H, s, 30-CH₃). 13C-NMR (67.8 MHz, CDCl₃) Table 1.

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References and Notes