ABSOLUTE STEREOSTRUCTURES OF PAEONISUFFRONE AND PAEONISUFFRAL, TWO NEW LABILE MONOTERPENES, FROM CHINESE MOUTAN CORTEX

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Two new labile monoterpenes named paeonisuffrone and paeonisuffral were isolated from Chinese Moutan Cortex, the dried root of *Paeonia suffruticosa* ANDREWS. The absolute stereostructures of paeonisuffrone and paeonisuffral were elucidated on the basis of chemical and physicochemical evidence which included the application of a modified Mosher's method and lipase catalyzed debenzoylation.

KEYWORDS Moutan Cortex; *Paeonia suffruticosa*; Paeoniaceae; paeonisuffrone, paeonisuffral; Mosher's method modified

During the course of our chemical studies on biologically active constituents of naturally occurring drug materials,[1] we have investigated the chemical constituents of Moutan Cortex, the root cortex of *Paeonia suffruticosa* ANDREWS (Paeoniaceae)[Botanpi in Japanese].[2] In our recent paper, we reported the isolation of five new glycosides of antioxidant activity, suffruticosides A, B, C, and D and galloyl-oxypaeoniflorin, together with a new paeonol glycoside, suffruticoside E, from the water-soluble portion of the Chinese Moutan Cortex, which is now in common use in Japan.[3] In a continuing study, we have isolated two new labile monoterpenes named paeonisuffrone(**1**) and paeonisuffral(**3**) from the lipophilic portion of the same Chinese Moutan Cortex.[4] This paper communicates the evidence consistent with the absolute stereostructures of paeonisuffrone(**1**) and paeonisuffral(**3**) as shown.[5]

The MeOH extract (prepared below 25°C) of the Cortex was partitioned into an AcOEt-water mixture. Repeated silica gel column chromatography of the AcOEt-soluble portion furnished **1**(0.0003%, from the Cortex), **3**(0.0014%), and 3-O-methylpaeonisuffral(**4**, 0.0003%)[6] together with paeonol(1.3%), resacetophenone(0.0030%), acetovanillone(0.0010%), 2, 5-dihydroxy-4-methylacetophenone(0.0020%), 2, 5-dihydroxy-4-methoxyacetophenone (0.0010%), acetoisovanillone(0.0030%), benzoyl-paeoniflorin(0.1000%), benzoyl-oxypaeoniflorin(0.0500%), and paeoniflorigenone(**5**, 0.0110%).[7]

Paeonisuffrone(**1**), white powder, $[\alpha]_D$ -16.8°(c=1.5, MeOH), showed absorption bands due to hydroxyl(3426 cm^{-1}) and ketone(1725 cm^{-1}) functions in its IR spectrum. The positive FAB-MS of **1** showed the quasimolecular ion peaks at m/z 237$(M+K)^+$ and m/z 221$(M+Na)^+$, while the negative FAB-MS showed the quasimolecular ion peak at m/z 197$(M-H)^-$. The high resolution MS measurement of **1** revealed the molecular formula $C_{10}H_{14}O_4$. The ^1H(270 MHz, CD_3OD, δ) and ^{13}C NMR(Table I) spectra of **1** showed signals ascribable to a tert.-methyl[δ 1.31, δc 19.2(10-H_3)], two methylenes [δ 2.31, 2.91(ABq, J=18Hz, 3-H_2); δ 2.21(d, J=11Hz), 2.47(dd, J=7, 11Hz) (7-H_2)] , two methylenes bearing an oxygen function [δ 3.57, 3.88(ABq, J=10Hz, 9-H_2); δ 3.84, 3.89(ABq, J=12Hz, 8-H_2)], a ketone carbonyl(δc 212.9), two quart. carbons bearing an oxygen function [δc 82.2, 87.6(1, 2-C)] and another one quart. carbon[δc 63.0(6-C)].

Acetylation of **1** with Ac_2O-pyridine afforded the monoacetate(**1a**), white powder, $[\alpha]_D$ -48.9°(c=0.6, EtOH), $C_{12}H_{16}O_5$, IR(KBr, cm^{-1}): 3566, 2975, 1732, 1240, 1042, ^1H NMR($CDCl_3$, δ): 1.42(s, 10-H_3), 2.10(s, OAc), 2.21(d, J=11Hz), 2.50(dd, J=7, 11Hz) (7-H_2), 2.54, 2.78(ABq, J=18Hz, 3-H_2), 2.84(d, J=7Hz, 5-H), 3.70, 3.92(2H, ABq, J=11Hz, 9-H_2), 4.38, 4.42(ABq, J=12Hz, 8-H_2), while acetylation of **1** with Ac_2O-pyridine in the presence of dimethylaminopyridine(DMAP) yielded the diacetate(**1b**), white powder, $[\alpha]_D$ -9.0°(c=0.5, EtOH), $C_{10}H_{16}O_4$, IR(KBr, cm^{-1}): 2930, 1790, 1744, 1372, 1242, 1134, 1046, 1022, ^1H NMR($CDCl_3$, δ): 1.36(s, 10-H_3), 2.09, 2.12(both s, OAcx2), 2.54, 2.92(ABq, J=17Hz, 3-H_2), 2.76(2H, s, 7-H_2), 3.00(m, 5-H), 3.72, 3.92(ABq, J=10Hz, 9-H_2), 4.36, 4.40(ABq, J=12Hz, 8-H_2). Reduction of **1** with $NaBH_4$ in MeOH furnished **2**, white powder, $[\alpha]_D$ -6.2° (c=0.3, EtOH), $C_{16}C_{22}O_7$, IR(KBr, cm^{-1}): 3400, 2930, ^1H NMR(CD_3OD, δ): 1.22(s, 10-H_3), 1.54(d, J=10Hz), 2.03(dd, J=8, 10Hz) (7-H_2), 1.78(d, J=16Hz), 2.29(dd, J=8, 16Hz) (3-H_2), 2.42(dd, J=4, 8Hz, 5-H), 3.68, 4.62(ABq, J=8Hz, 9-H_2), 3.80, 3.83(2H, ABq, J=12Hz, 8-H_2), 4.11(dd, J=4, 8Hz, 4-H). Acetylation of **2** with Ac_2O-pyridine-DMAP gave the triacetate(**2a**), white powder, $[\alpha]_D$-1.5° (c=0.3, EtOH), IR(KBr, cm^{-1}): 2924, 1740, 1250, ^1H NMR($CDCl_3$, δ): 1.27(s, 10-H_3), 1.98(d, J=16Hz), 2.51(dd, J=8, 16Hz) (3-H_2), 2.06, 2.07, 2.09(3H

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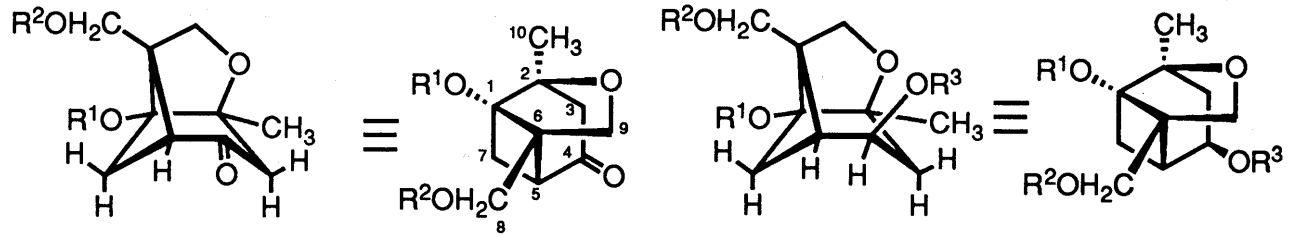
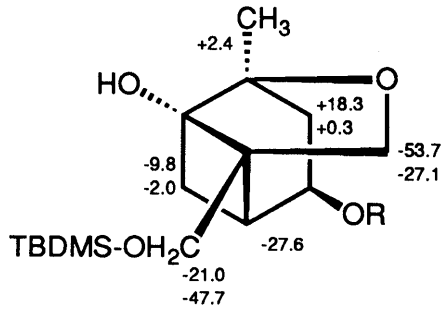


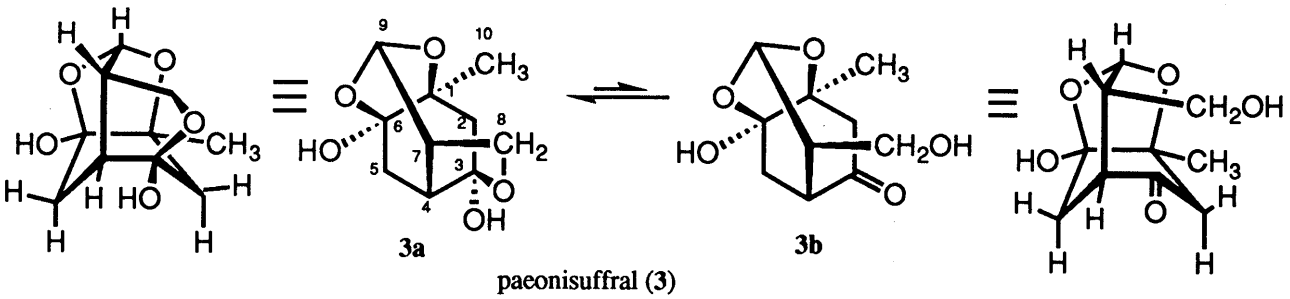
paeonisuffrone (1) : $R^1 = R^2 = H$
1a : $R^1 = H, R^2 = Ac$
1b : $R^1 = R^2 = Ac$

2 : $R^1 = R^2 = R^3 = H$
2a : $R^1 = R^2 = R^3 = Ac$
2b : $R^1 = H, R^2 = TBDMS, R^3 = H$



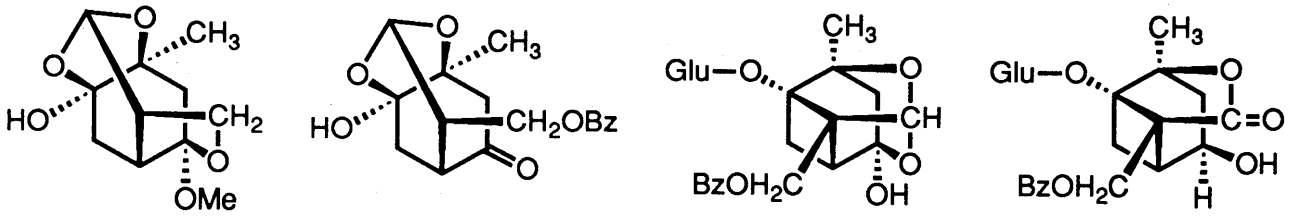
Δδ values in Hz(= δS-δR, measured in 270 MHz)

2c : R = (-)-(S)-MTPA
2d : R = (+)-(R)-MTPA



3a **3b**

paeonisuffral (3)



3-O-methylpaeonisuffral (4) paeoniflorigenone (5) paeoniflorin (6) albiflorin (7)

each, all s, OAcx3), 2.23(d, J=12Hz), 2.43(dd, J=8, 12Hz) (7-H_2), 2.67(dd, J=4, 8Hz, 5-H), 3.83, 4.44(2H, ABq, J=9Hz, 9-H_2), 4.27, 4.39(ABq, J=12Hz, 8-H_2), 5.12(dd, J=4, 8Hz, 4-H). Comparison of ^1H NMR data for **2** and **2a** with those for **1**, **1a**, and **1b** showed the presence of a partial structure(-CH_2-CO-CH-CH_2-) from C-3 to C-7.

The connectivities of the quart. carbons(C-1, 2, 6) were clarified by HMBC experiment with **1a**. Namely, the long-range correlations were observed between the following carbons and protons of **1a**(2-C: 3-H_2, 10-H_3; 1-C: 3-H_2, 5-H, 8-H_2; 6-C: 7-H_2, 8-H_2). Furthermore, the NOE correlations were observed in the pairs of protons in **2a**[3-H_2&10-H_3; 3α-H&5-H; 7β-H&8-H_2] and comparison of the ^1H-^1H coupling constants for **1** with those for paeoniflorin(**6**) and albiflorin(**7**)[8] has finally led us to formulate the stereostructure of **1** as shown.

The absolute configuration of **1** has been determined by application of a modified Mosher's method.[9] Thus, silylation of **1** with t-butyldimethylsilyl chloride(TBDMSCl) and imidazole in DMF(r.t., 1h) and subsequent reduction with $NaBH_4$ provided **2b**, which was treated with (-)-(S)- and (+)-(R)-α-methoxy-α-trifluoromethylphenylacetic acid(MTPA) and dicyclohexylcarbodiimide(DCC) in CH_2Cl_2 in the presence of DMAP to afford the (-)-(S)-MTPA ester(**2c**) and (+)-(R)-MTPA ester(**2d**), respectively. The signals due to protons on C-3 and C-10 in the (+)-(R)-MTPA ester(**2d**) appeared at higher fields than those of the (-)-(S)-MTPA ester(**2c**)[Δδ: positive], while the signals due to protons attached to C-5 and C-7 of **2d** were observed at lower fields as compared to those of (**2c**)[Δδ: negative]. Consequently, the absolute configuration at C-4 has been

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Table I. ^{13}C NMR Data for **1**, **1a**, **1b**, **2**, **3a**, **3b**, and **4**

Carbons	**1**[a]	**1**[b]	**1a**[a]	**1b**[a]	**2**[b]	**3a**[b]	**3b**[b]	**4**[b]
1	81.7	82.2	81.4	85.6	82.6	79.7	79.7	79.7
2	86.1	87.6	86.1	86.0	90.5	45.2	48.1	43.9
3	48.6	49.8	48.5	48.9	45.4	107.6	213.0	110.9
4	209.9	212.9	209.1	208.2	70.4	45.6	47.9	43.9
5	48.5	49.5	48.6	51.0	40.1	32.0	35.7	32.0
6	60.4	63.0	59.8	59.0	59.1	102.7	97.3	102.9
7	31.2	31.7	31.2	31.9	30.8	44.0	47.3	40.5
8	61.2	62.7	69.8	70.5	64.1	67.2	61.2	68.3
9	68.8	71.7	63.0	63.1	70.3	101.1	101.0	101.1
10	18.9	19.2	19.0	19.8	20.4	22.6	21.9	22.7
$\underline{C}OCH_3$			171.7	171.0				
				169.7				
$CO\underline{C}H_3$			21.0	20.9[c]				
				21.1[c]				
$O\underline{C}H_3$								49.3

The spectra were measured a) in $CDCl_3$, or b) in CD_3OD, and c) assignments may be interchangeable.

elucidated to be R and the absolute structure of paeonisuffrone(**1**) has been determined as shown.

Paeonisuffral(**3**), white powder, $[\alpha]_D$ +39.7°(c=0.6, MeOH), $C_{10}H_{14}O_5$, IR(KBr, cm^{-1}): 3400, 2936, 1719, 1356, 1071, positive FAB-MS(m/z): 215$(M+H)^+$, was obtained as a tautomeric mixture of the ketal(**3a**) and the ketone(**3b**) forms.[10] The confirmative assignments for ^1H and ^{13}C NMR spectra of **3a** and **3b** were obtained by using ^1H-^1H COSY, ^1H-^{13}C COSY and HMBC, and the ^1H and ^{13}C NMR data for **3b** were found similar to those data for paeoniflorigenone(**5**), except for some signals due to the benzoyl group of the latter. Treatment of **3** with silica gel in methanol yielded 3-O- methylpaeonisuffral(**4**), white powder, $C_{11}H_{16}O_5$, IR(KBr, cm^{-1}): 3419, 2936, 1356, 1073, $[\alpha]_D$ +21.1°(c=0.4, MeOH), ^1H NMR(CD_3OD, δ): 1.15(s, 10-H_3), 1.76, 2.01(d, J=14Hz, 2-H_2), 1.76(d, J=13Hz), 2.07(dd, J=5, 13Hz) (5-H_2), 2.34(m, 7-H), 2.70(m, 4-H), 3.25(s, OMe), 3.71(d, J=9Hz), 3.92(dd, J=4, 9Hz) (8-H_2), 5.21(d, J=3Hz, 9-H). Finally, debenzoylation of **5** with lipase(from *Candida cylindracea*) furnished **3**[a mixture (ca. 3:1) of **3a** and **3b**]. Based on this evidence, the absolute structure of paeonisuffral(**3**) has been clarified.

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10) Two tautomers(**3a** and **3b**) were distributed in CD_3OD in an approximate ratio of 3:1 as shown by ^1H NMR (500 MHz, CD_3OD, δ). **3a** : 1.14(s, 10-H_3), 1.77(d, J=14Hz), 2.01(dd, J=1, 14Hz) (2-H_2), 1.85(dd, J=1, 13Hz), 2.13(dd, J=4, 13Hz) (5-H_2), 2.33(m, 7-H), 2.46(m, 4-H), 3.64(d, J=8Hz), 3.96(dd, J=5, 8Hz) (8-H_2), 5.19(d, J=3Hz, 9-H); **3b** : 1.22(s, 10-H_3), 2.01(m, 7-H), 2.18(dd, J=2, 13Hz), 2.28(dd, J=3, 13Hz) (5-H_2), 2.48(d, J=17Hz), 2.72(d, J=17Hz) (2-H_2), 2.71(m, 4-H), 3.29(d, J=9, 11Hz), 3.47(dd, J=6, 11Hz) (8-H_2), 5.37(br s, 9-H).

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