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%), acetisovanillone (0.0030%), benzoyl-paeoniflorin (0.1000%), benzoyl-oxypaeoniflorin (0.0500%), and paeoniflorigenone (**5**, 0.0110%).⁷⁾

Paeonisuffrone(**1**), white powder, $[\alpha]_D -16.8^\circ$ ($c=1.5$, 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 $\text{C}_{10}\text{H}_{14}\text{O}_4$. 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, δ_c 19.2 (10-H₃)], two methylenes [δ 2.31, 2.91 (ABq, $J=18\text{Hz}$, 3-H₂); δ 2.21 (d, $J=11\text{Hz}$), 2.47 (dd, $J=7, 11\text{Hz}$) (7-H₂)], two methylenes bearing an oxygen function [δ 3.57, 3.88 (ABq, $J=10\text{Hz}$, 9-H₂); δ 3.84, 3.89 (ABq, $J=12\text{Hz}$, 8-H₂)], a ketone carbonyl (δ_c 212.9), two quart. carbons bearing an oxygen function [δ_c 82.2, 87.6 (1, 2-C)] and another one quart. carbon [δ_c 63.0 (6-C)].

Acetylation of **1** with Ac₂O-pyridine afforded the monoacetate (**1a**), white powder, $[\alpha]_D -48.9^\circ$ ($c=0.6$, EtOH), $\text{C}_{12}\text{H}_{16}\text{O}_5$, IR (KBr, cm^{-1}): 3566, 2975, 1732, 1240, 1042, ^1H NMR (CDCl_3 , δ): 1.42 (s, 10-H₃), 2.10 (s, OAc), 2.21 (d, $J=11\text{Hz}$), 2.50 (dd, $J=7, 11\text{Hz}$) (7-H₂), 2.54, 2.78 (ABq, $J=18\text{Hz}$, 3-H₂), 2.84 (d, $J=7\text{Hz}$, 5-H), 3.70, 3.92 (2H, ABq, $J=11\text{Hz}$, 9-H₂), 4.38, 4.42 (ABq, $J=12\text{Hz}$, 8-H₂), while acetylation of **1** with Ac₂O-pyridine in the presence of dimethylaminopyridine (DMAP) yielded the diacetate (**1b**), white powder, $[\alpha]_D -9.0^\circ$ ($c=0.5$, EtOH), $\text{C}_{10}\text{H}_{16}\text{O}_4$, IR (KBr, cm^{-1}): 2930, 1790, 1744, 1372, 1242, 1134, 1046, 1022, ^1H NMR (CDCl_3 , δ): 1.36 (s, 10-H₃), 2.09, 2.12 (both s, OAc₂), 2.54, 2.92 (ABq, $J=17\text{Hz}$, 3-H₂), 2.76 (2H, s, 7-H₂), 3.00 (m, 5-H), 3.72, 3.92 (ABq, $J=10\text{Hz}$, 9-H₂), 4.36, 4.40 (ABq, $J=12\text{Hz}$, 8-H₂). Reduction of **1** with NaBH₄ in MeOH furnished **2**, white powder, $[\alpha]_D -6.2^\circ$ ($c=0.3$, EtOH), $\text{C}_{16}\text{H}_{22}\text{O}_7$, IR (KBr, cm^{-1}): 3400, 2930, ^1H NMR (CD_3OD , δ): 1.22 (s, 10-H₃), 1.54 (d, $J=10\text{Hz}$), 2.03 (dd, $J=8, 10\text{Hz}$) (7-H₂), 1.78 (d, $J=16\text{Hz}$), 2.29 (dd, $J=8, 16\text{Hz}$) (3-H₂), 2.42 (dd, $J=4, 8\text{Hz}$, 5-H), 3.68, 4.62 (ABq, $J=8\text{Hz}$, 9-H₂), 3.80, 3.83 (2H, ABq, $J=12\text{Hz}$, 8-H₂), 4.11 (dd, $J=4, 8\text{Hz}$, 4-H). Acetylation of **2** with Ac₂O-pyridine-DMAP gave the triacetate (**2a**), white powder, $[\alpha]_D -1.5^\circ$ ($c=0.3$, EtOH), IR (KBr, cm^{-1}): 2924, 1740, 1250, ^1H NMR (CDCl_3 , δ): 1.27 (s, 10-H₃), 1.98 (d, $J=16\text{Hz}$), 2.51 (dd, $J=8, 16\text{Hz}$) (3-H₂), 2.06, 2.07, 2.09 (3H

each, all s, OAcx3), 2.23(d, $J=12$ Hz), 2.43(dd, $J=8, 12$ Hz) (7- H_2), 2.67(dd, $J=4, 8$ Hz, 5-H), 3.83, 4.44(2H, ABq, $J=9$ Hz, 9- H_2), 4.27, 4.39(ABq, $J=12$ Hz, 8- H_2), 5.12(dd, $J=4, 8$ Hz, 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 ; 3 α -H&5-H; 7 β -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)[$\Delta\delta$: 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)[$\Delta\delta$: negative]. Consequently, the absolute configuration at C-4 has been

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
COCH ₃			171.7	171.0				
				169.7				
COCH ₃			21.0	20.9 ^{c)}				
				21.1 ^{c)}				
OCH 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, $[\alpha]_D +39.7^\circ$ ($c=0.6$, MeOH), $\text{C}_{10}\text{H}_{14}\text{O}_5$, 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, $\text{C}_{11}\text{H}_{16}\text{O}_5$, IR(KBr, cm^{-1}): 3419, 2936, 1356, 1073, $[\alpha]_D +21.1^\circ$ ($c=0.4$, MeOH), ^1H NMR(CD_3OD , δ): 1.15(s, 10-H₃), 1.76, 2.01(d, $J=14\text{Hz}$, 2-H₂), 1.76(d, $J=13\text{Hz}$), 2.07(dd, $J=5$, 13Hz) (5-H₂), 2.34(m, 7-H), 2.70(m, 4-H), 3.25(s, OMe), 3.71(d, $J=9\text{Hz}$), 3.92(dd, $J=4$, 9Hz) (8-H₂), 5.21(d, $J=3\text{Hz}$, 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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(Received January 5, 1993)