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DIHYDROFUROCOUMARIN GLUCOSIDES FROM *ANGELICA ARCHANGELICA* AND *ANGELICA SILVESTRIS*

JOHN LEMMICH, SVEND HAVELUND and OLE THASTRUP

Department of Chemistry BC, Royal Danish School of Pharmacy, 2 Universitetsparken, DK-2100 Copenhagen, Denmark

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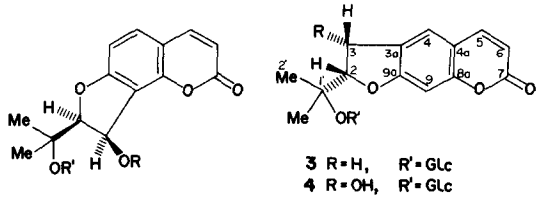
Key Word Index—*Angelica archangelica* subsp. *litoralis*; *A. silvestris*; Umbelliferae; dihydrofurocoumarins; coumarin glycosides; coniferin; ^{13}C NMR data.

Abstract—A water-soluble root extract of *Angelica archangelica* subsp. *litoralis* afforded, in addition to adenosine, coniferin and the two known dihydrofurocoumarin glycosides, apterin and 1′-*O*-β-D-glycopyranosyl-(*S*)-marmesin (marmesinin), two new dihydrofuranocoumarin glycosides, 1′-*O*-β-D-glucopyranosyl-(2*S*, 3*R*)-3-hydroxymarmesin, and 2′-β-D-glucopyranosyloxymarmesin. For the latter a 2*S*-configuration was demonstrated, the stereochemistry at position 1′ remaining undefined. Roots of *A. silvestris* similarly afforded 1′-*O*-β-D-glucopyranosyl-(2*S*, 3*R*)-3-hydroxymarmesin. By correlation with the aglycone (2*S*,3*R*)-3-hydroxymarmesin obtained in this work, the absolute configurations (2*S*,3*R*) were established for the known dihydrofurocoumarin diesters smirniorin and smirnioridin.

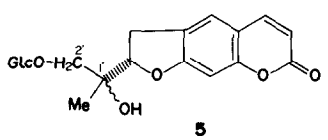
INTRODUCTION

As part of our current work on the chemistry of Umbelliferae, the two *Angelica* species occurring in Denmark, *A. archangelica* L. subsp. *litoralis* (Fr.) Thell. and *A. silvestris* L. have been examined for their content of coumarin glycosides. Earlier a number of non-glycosidic coumarins were obtained from these plants [1–5]. Our interest, especially in searching for new dihydrofurocoumarins in water-soluble extracts of these plants has been stimulated by the recent finding [6] that the diester archangelicin (**1**), earlier obtained from *A. archangelica* subsp. *litoralis* [2], and related dihydrofurocoumarins are potent coronary vasodilatators which act, at least partially, by inhibition of cAMP-phosphodiesterase.



1 R = R′ = Ang
2 R = H, R′ = Glc
6 R = R′ = H

3 R = H, R′ = Glc
4 R = OH, R′ = Glc
7 R = OH, R′ = H
8 R = OAc, R′ = Ac
9 R = OAng, R′ = Ac



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RESULTS AND DISCUSSION

The glycosides, reported in this paper, were obtained collectively as a blue fluorescent chromatographic fraction, which was only slightly retained by polyamide upon elution with water. They were separated from each other by Si gel chromatography. Thus, roots of *A. archangelica* subsp. *litoralis* afforded, in addition to adenosine and coniferin, four crystalline coumarin glycosides, two of which, apterin, (**2**) [7] and *O*-β-D-glucopyranosyl-(*S*)-marmesin (marmesinin), (**3**) [8, 9] were known compounds.

The derivation of the two other glycosides from 7-hydroxycoumarin and their non-phenolic nature were apparent from their blue fluorescence and UV spectral data. D-Glucose was the only sugar liberated upon acid hydrolysis. The structure **4** was deduced for one of these new glycosides mainly by ^1H NMR spectroscopy. Thus the only major differences in its ^1H NMR spectrum in comparison with that of **2** were attributable to the presence of aromatic protons in *para*-positions instead of *ortho*-positions. Notably, a *cis*-configuration of the dihydrofuran protons in **4** was inferred from their coupling constant ($J = 6$ Hz), and a β-configuration of the glucopyranosyl linkage from the coupling constant ($J = 7.6$ Hz) observed for the anomeric proton. Position 1′-*O* as the point of attachment for glucose, and thus the absence of a free tertiary hydroxyl group in **4**, was demonstrated by the ready formation of its penta-acetate, and also by the large acetylation shift (1 ppm) observed for the benzylic methine proton. Also the ^{13}C NMR data of **4** were in full agreement with the assigned structure, showing the expected relationships to the chemical shifts reported for marmesin [10] and methyl β-D-glucopyranoside. In particular, the high field position (δ97.7) of the signal corresponding to the anomeric carbon in **4** was indicative of a *tert*-*O*-β-D-glucopyranoside [11]. Proof of a (2*S*,3*R*)-configuration in **4** was obtained by palladium-catalysed hydrogenation of its penta-acetate. This hydrogenation, which proceeded with concomitant hydrogenolysis of the benzylic oxygen function, afforded a product, still bearing a tetra-acetylglucopyranosyl group, and convertible into (*S*)-5,6-dihydromarmesin by acid hydrolysis. The latter

compound was identified by comparison with its enantiomer, obtained by hydrogenation of authentic (*R*)-marmesin, (nodakenetin). Thus, **4** was shown to be (2*S*, 3*R*)-2, 3-dihydro-3-hydroxy-2-[1′-(β-D-glucopyranosyloxy)-1′-methylethyl]-7*H*-furo(3, 2-g)(1)benzopyran-7-one.

The other new coumarin glycoside was a minor constituent of *A. archangelica* subsp. *litoralis*. Its structure (**5**) was deduced from its MW 424 (FDMS) and from its ^{1}H NMR data, compared with those of **3**. In particular, the presence of a $-CH_2-O-$ grouping in **5** instead of one of the two methyl groups in **3**, was evident from the spectrum of the tetra-acetate of **5** prepared under normal acetylation conditions. This spectrum showed an AB pair of doublets at δ3.83 and 3.74 (J = 9.5 Hz), attributable to the diastereotopic protons at C-2′. Additionally, the position of these signals and the resistance to acetylation of the fifth hydroxyl group in **5** pointed to the primary oxygen function of the aglycone as the site of glucose attachment. Again, a β-configuration of the glucopyranosyl linkage was inferred from the doublet (J = 7.4 Hz) observed for the anomeric proton in the spectrum of **5**, itself. Thus, **5** was shown to be 2,3-dihydro-2-[2′-(β-D-glucopyranosyloxy)-1′-hydroxy-1′-methylethyl]-7*H*-furo(3,2-g)(1)benzo-pyran-7-one. A 2*S*-configuration was tentatively assigned to **5** by comparison with **3**, as similar CD-extrema, assignable to the 7-oxycoumarin chromophore, were observed for these compounds. The configuration at the asymmetric centre, C-1′ in **5**, remote from the chromophore was not established.

Roots of *A. silvestris* similarly afforded a blue fluorescent glycoside fraction. From this fraction, which was found to be very complex, only **4** was isolated in a pure state. It was known that **2** as well as esters of the corresponding diol, **6**, upon chemical hydrolysis, instead of **6**, afforded a range of solvolysis, elimination and dimerization products [7, 12]. Furthermore, as enzymic hydrolysis of **2** by means of β-glucosidase from almonds was too slow to be practical, it had been necessary to use an enzyme preparation from the plant from which this glycoside had been isolated [7, 13]. Similar difficulties were encountered during our attempts to convert **4** into the parent diol **7** until it was discovered that *Helix pomatia* digestive juice, in the form of the rather crude sulfatase–glucuronidase preparations of commerce, readily hydrolysed **2** and **4** to the parent diols. This ready access to the diols, **6** and **7** is important in our studies on cAMP phosphodiesterase inhibitory activity of dihydrofurocoumarins related to **1** as they may serve as starting materials for the preparation of new potentially active diesters.

Two diesters of *cis*-3-hydroxymarmesin had earlier been obtained from *Smirniopsis aucheri* (Umbelliferae) [14, 15], but the question of their absolute stereochemistry was hitherto unsettled. For one of these esters, the diacetate (−)-smirniorin, the absolute configuration (2*S*,3*R*) is now established, because the diacetate **8**, prepared from the diol **7** by acetylation under forcing conditions, turned out to be the same laevorotatory enantiomer. By optical comparison, and in view of the co-occurrence of these esters, the absolute configuration (2*S*,3*R*) is also tentatively assigned to the other, the angelate acetate (−)-smirnioridin (**9**). It may be mentioned, that a coumarin (prandiol), at least constitutionally identical with the aglycone of **5**, has been shown to occur naturally [16].

EXPERIMENTAL

D-Glucose was identified by TLC and by the D-glucose oxidase test.

Plant material was collected near Copenhagen: *A. archangelica* subsp. *litoralis* at the seashore by the mouth of Tryggevaelde brook; *A. silvestris* by the lake, Furesø.

Extraction and isolation. Dried and ground roots of *A. archangelica* (1350 g) were extracted with MeOH. An aq. soln of the MeOH concentrate was washed with EtOAc and evaporated. The residue (217 g) was chromatographed on Polyamide-6 columns (4 × 220 g) with a H_2O–MeOH gradient affording, after a first fraction containing mainly sugars, two fractions, A (3 g) and B (0.7 g) containing blue and yellow fluorescent glycosides, respectively. Further eluates containing mainly phenolic glycosides were discarded. Further CC of fraction A on Si gel with a gradient of CH_2Cl_2–MeOH–H_2O (90 → 35): (10 → 55): (0 → 10) followed by rechromatography and crystallization afforded: coniferin 340 mg; adenosine, 33 mg; **2**, 200 mg; **3**, 5 mg; **4**, 124 mg; **5**, 2.3 mg (calcd. yields, corrected for partial work-up of subfractions). Dried roots of *A. silvestris* (2500 g) similarly afforded **4**, 47 mg.

Adenosine and apterin, **2**. Identified by comparison with authentic samples.

(E)-3-(4′-β-D-*Glucopyranosyloxy*-3′-*methoxyphenyl*)-2-*propen*-1-*ol* (*coniferin*). Mp (EtOH–H_2O) 183–185°, (lit. [17]: mp 187°); $[\alpha]_D^{25}$ −61° (MeOH; *c* 0.4), (lit. [17] −60°); UV λ_{max}^{MeOH} nm (log ε): 258.5 (4.26), 292(sh) (3.75), no NaOMe shift; ^{1}H NMR (270 MHz, 1% D_2O, int. standard MeCN δ 2.00): δ 7.12 (*br s*) 7.06 (*d*), 7.00 (*br d*) overlapping (3H, ABC-pattern, H-2′, H-5′, H-6′ respectively), 6.54 (1H, *d*, J = 16 Hz, H-3), 6.22 (1H, *dt*, J = 16, 6 Hz, H-2), 4.20 (2H, *d*, J = 6 Hz, H-1), 5.05 (1H, *m*, anomeric H), 3.95–3.45 (9H, *m*, residual $H_{glucose}$ and OMe (δ3.83); ^{13}C NMR (67.9 MHz, D_2O 50°, int. standard dioxane 67.4 ppm): δ149.9 (C-4′), 146.1 (C-3′), 133. 6 (C-1′), 131.0 (C-3), 128.8 (C-2), 120.6 (C-6′), 117.5 (C-5′), 111.8 (C-2′), 63.0 (C-1), 57.0 (OMe), 101.5, 77.0, 76.5, 73.8, 70.3, 61.5 (β-D-glucopyranosyloxy) (assignment based on lignan models [18]). Upon acid hydrolysis (0.25 N HCl, refluxed for 2 hr) D-glucose was detected.

1′-O-β-D-*Glucopyranosyl*-(2S)-*marmesin* (*marmesinin*), (**3**), $[\alpha]_D^{20}$ −64.3° (H_2O; *c* 0.3), (lit. [8] −60°); UV λ_{max}^{MeOH} nm (log ε): 335 (4.20), 300(sh) (3.75), 259 (3.49), 249 (3.58), 226 (4.01); CD extrema: $\Delta\varepsilon_{231}$ + 0.9, $\Delta\varepsilon_{250}$ − 0.5, $\Delta\varepsilon_{335}$ − 1.7 (MeOH; *c* 7 × 10^{-5} M); FDMS *m/z*: 408 $[M]^+$ and 409 $[M+H]^+$; EIMS *m/z* (rel. int.): 408 $[M]^+$ (4), 246 $[M_{aglycone}]^+$ (48), 229 (17), 228 (15), 188 (92), 187 (100), 160 (18); ^{1}H NMR (90 MHz; 0.2% in D_2O, int. standard MeCN δ 2.00): δ 7.89 (1H, *d*, J = 9.6 Hz, H-5), 7.41 (1H, *s*, H-4), 6.77 (1H, *s*, H-9), 6.22 (1H, *d*, J = 9.6 Hz, H-6), 4.90 (1H, *t*, J = 9.0 Hz, H-2), 1.36 and 1.23 (each 3H, *ss*, gem-dimethyl), *ca* 4.7 (anomeric H, partially obscured by DOH-signal), 3.5–3.0 (8H, *m*, H-3 and residual $H_{glucose}$). Upon acid hydrolysis (0.3 N HCl, refluxed for 2 hr) D-glucose was detected. Identity of **3** was further secured by ^{1}H NMR spectral comparison with its authentic epimer 1′-*O*-β-D-glucopyranosyl-(2R)-marmesin (nodakenin).

1′-O-β-D-*Glucopyranosyl*-(2S,3R)-3-*hydroxymarmesin*, (**4**). $[\alpha]_D^{20}$ −14°, $[\alpha]_{436}^{20}$ −41° (pyridine; *c* 0.5); UV λ_{max}^{MeOH} nm (log ε): 327 (4.21) 300 (sh) (3.97), 259 (3.49), 249 (3.55), 225 (4.13), no NaOMe shift; ^{1}H NMR (270 MHz, DMSO-d_6): δ 8.03 (1 H, *d*, J = 10.0 Hz, H-5), 7.67 (1H, *s*, H-4), 6.94 (1H, *s*, H-9), 6.27 (1H, *d*, J = 10.0 Hz, H-6), 5.24, [2H, *m*, OH-3 and H-3, + CF_3COOD → 1H, *d*, J = 6.3 Hz (H-3)], 5.01 (1H, *d*, J = 4.6 Hz, OH-2″), 4.92 (1H, *d*, J = 5.4 Hz, OH-3″), 4.89 (1H, *d*, J = 3.0 Hz, OH-4″), 4.55 (1H, *d*, J = 6.3 Hz, H-2), 4.53 (1H, *d*, J = 7.8 Hz, H-1″), 4.33 (1H, *t*, J = 5.3 Hz, OH-6″), 3.33 (2H, *m*, H-6″), 3.26–3.06 (3H, *m*, H-3″, H-4″, H-5″), 2.87 (1H, *m*, + CF_3COOD → *t*, J = 8.1 Hz, H-2″),

1.47 (6H, *s*, gem-dimethyl), OH-signals removed upon addition of CF_3COOD; ^{13}C NMR (67.9 MHz, DMSO-d_6, 30°): δ 162.4 (C-9a), 160.6 (C-7), 156.1 (C-8a), 144.9 (C-5), 128.6 (C-3a), 125.7 (C-4), 112.9 (C-4a), 111.8 (C-6), 97.7 (C-1″ or C-9), 97.3 (C-9 or C-1″), 91.9 (C-2), 77.5 (C-3), 76.9 (C-3″ or C-5″), 76.7 (C-5″ or C-3″), 73.4 (C-2″), 70.1 (C-4″ or C-1′), 69.8 (C-1′ or C-4″), 60.8 (C-6″), 24.6 and 22.8 (gem-dimethyl); FDMS *m/z*: 424 $[M]^+$ and 425 $[M+H]^+$; EIMS *m/z* (rel. int.): 424 (11), 246 (5), 245 (22), 244 (5), 229 (7), 228 (12), 227 (18), 213 (7), 204 (24), 203 (13), 191 (6), 189 (13), 188 (26), 187 (100), 186 (16), 145 (9), 127 (6). Upon acid hydrolysis (0.25 N HCl, refluxed for 45 min) D-glucose was detected.

Acetylation (pyridine–Ac_2O, 25°) of **4** (17 mg) for 24 hr afforded a non-crystalline penta-acetate of **4** (23 mg), ^1H NMR (90 MHz, $CDCl_3$): δ 7.56 (1H, *d*, *J* = 9.5 Hz, H-5), 7.51 (1H, *s*, H-4), 6.79 (1H, *s*, H-9), 6.22 (1H, *d*, *J* = 6.5 Hz, H-3), 6.21 (1H, *d*, *J* = 9.5 Hz, H-6), 4.46 (1H, *d*, *J* = 6.5 Hz, H-2), 1.52 and 1.45 (6H, *ss*, gem-dimethyl), 5.27–4.84 (4H, *m*, H-1″, H-2″, H-3″, H-4″), 4.12 (2H, *m*, H-6″), 3.73 (1H, *m*, H-5″), 2.04–2.03 (15H, 5 × OAc).

5,6-*Dihydro*-(S)-*marmesin from* **4**. Hydrogenation of the penta-acetate of **4** (20 mg) over 10% Pd–C (200 mg) in EtOAc (7 ml) at 0° for 80 min and chromatography [Si gel; CH_2Cl_2–Et_2O (9:1) with 0.05% HCOOH] afforded 1′-O-β-D-glucopyranosyl-5,6-dihydro-(*S*)-marmesin tetra-acetate (10.5 mg); $[\alpha]_D^{20}$ + 9.5° ($CHCl_3$; *c* 0.3); ^1H NMR (90 MHz, $CDCl_3$): δ 6.90 (1H, *s*, H-4), 6.43 (1H, *s*, H-9), 4.61 (1H, *t*, *J* = 9.5 Hz, H-2), 3.05 (2H, *d*, *J* = 9.5 Hz, H-3), 2.82 (4H, *m*, H-5, H-6), 1.36 and 1.24 (6H, *ss*, gem-dimethyl), 5.13–4.82 (4H, *m*, H-1″, H-2″, H-3″, H-4″), 3.80–3.11 (3H, *m*, H-6″, H-5″), 2.06–2.00 (12H, 4 × OAc). Sequential hydrolysis (9.5 mg) in H_2O–dioxane–CF_3COOH (0.5 + 0.5 + 0.1 ml) under N_2 (95°, 17 hr), evaporation and chromatography [Si gel; CH_2Cl_2–EtOAc (5:2) with 0.05% HCOOH] gave 5,6-dihydro-(*S*)-marmesin (1.3 mg); ^1H NMR (90 MHz, $CDCl_3$): δ 6.91 (1H, *s*, H-4), 6.49 (1H, *s*, H-9), 4.62 (1H, *t*, *J* = 9.0 Hz, H-2), 3.10 (2H, *d*, *J* = 9.0 Hz, H-3), 2.81 (4H, *m*, H-5, H-6), 1.32 and 1.19 (6H, *ss*, gem-dimethyl); CD extrema: $\Delta\varepsilon_{245} - 0.6$, $\Delta\varepsilon_{303} - 0.6$ (0.1 N NaOH in MeOH; *c* 1.7×10^{-4} M).

5,6-*Dihydro*-(R)-*marmesin*. (*R*)-Marmesin (nodakenetin), $[\alpha]_D^{20}$ −25.3° ($CHCl_3$; *c* 1.3), prepared by hydrolysis of authentic nodakenin, upon hydrogenation (40 mg) and chromatography as described above afforded 5,6-dihydro-(*R*)-marmesin (26 mg), mp 125–127°; ^1H NMR as for *S*-form: CD extrema: $\Delta\varepsilon_{245} + 0.8$, $\Delta\varepsilon_{303} + 0.7$ (0.1 N NaOH in MeOH; *c* 1.6×10^{-4} M).

2′-β-D-*Glucopyranosyloxymarmesin* (**5**). $[\alpha]_D^{20}$ −23°, $[\alpha]_{436}^{20}$ −88° (MeOH; *c* 0.1); UV λ_{max}^{MeOH} nm (log ε): 334 (4.16), 300 (sh) (3.88), 258.5 (3.66), 248.5 (3.76), 226 (4.10), no NaOMe shift; CD extrema: $\Delta\varepsilon_{230} + 1.9$, $\Delta\varepsilon_{251} - 0.2$, $\Delta\varepsilon_{335} - 1.0$ (MeOH; *c* 7×10^{-5} M); ^1H NMR (90 MHz, 0.2% in D_2O, int. standard MeCN δ 2.00): δ 7.86 (1H, *d*, *J* = 9.5 Hz, H-5), 7.39 (1H, *s*, H-4), 6.73 (1H, *s*, H-9), 6.21 (1H, *d*, *J* = 9.5 Hz, H-6), 5.00 (1H, *t*, *J* = 8.4 Hz, H-2), 1.22 (3H, *s*, Me-1′), 4.42 (1H, *d*, *J* = 7.4 Hz, anomeric H), 3.9–3.2 (10H, *m*, residual glucose protons, H-3, H-2′); FDMS: 424 $[M]^+$ and 425 $[M+H]^+$. EIMS *m/z* (rel. int.): 424 $[M]^+$ (7), 262 $[M_{aglycone}]^+$ (30), 227 (15), 226 (32) 213 (19), 198 (11), 188 (100), 187 (92), 186 (27), 158 (11), 131 (11). Upon acid hydrolysis (0.3 N HCl, refluxed for 2 hr) D-glucose was detected. Acetylation (pyridine–Ac_2O, 25°, 24 hr) of **5** and evaporation of reagents afforded the tetra-acetate of **5** (non-crystalline); ^1H NMR (90 MHz 0.2% in $CDCl_3$): δ 7.75 (1H, *d*, *J* = 9.6 Hz, H-5), 7.22 (1H, *s*, H-4), 6.67 (1H, *s*, H-9), 6.18 (1H, *d*, *J* = 9.6 Hz, H-6), 5.14 (*t*, *J* = 9.0 Hz, H-2, partially obscured by H-2″, H-3″, H-4″), 3.83, 3.74 (AB-pair *J* = 9.5 Hz, H-2′, partially obscured by H-5″), 3.24 (2H, *d*, *J* = 9.0 Hz, H-3), 1.09 (3H, *s*, Me-1′), 5.2–4.8 (4H, *m*, H-2″, H-3″, H-4″, partially obscured by H-2), 4.55 (1H, *d*, *J* = 7.4 Hz, H-1″), 4.19 (2H, *m*, H-6″), 3.71 (*m*, H-5″, partially obscured by H-2′), 2.08–2.01 (12H, 4 × OAc).

Enzymic hydrolysis of **4**. To **4** (10 mg) in H_2O (25 ml) 0.1 ml of *Helix pomatia* β-glucuronidase–sulfatase (Sigma) was added. After 24 hr at 25°, the soln was passed through a Sep-Pak C-18 cartridge (Waters). After washing with H_2O, elution with H_2O–MeOH (17:3) evaporation and chromatography [Si gel; CH_2Cl_2–EtOAc–*tert*-BuOH (44:5:1)] **7** (5.4 mg) was afforded.

(2S, 3R)-3-*Hydroxymarmesin*, (**7**). Mp 176° (dec.), softening at 159°; $[\alpha]_D^{20}$ + 43°, $[\alpha]_{436}^{20}$ + 82° (MeOH; *c* 0.2); ^1H NMR (90 MHz, $CDCl_3$): δ 7.63 (1H, *d*, *J* = 9.5 Hz, H-5), 7.49 (1H, *s*, H-4), 6.80 (1H, *s*, H-9), 6.22 (1H, *d*, *J* = 9.5 Hz, H-6), 5.38 (1H, *d*, *J* = 6.2 Hz, H-3), 4.36 (1H, *d*, *J* = 6.2 Hz, H-2); 1.60 and 1.58 (6H, *ss*, gem-dimethyl).

Smirniorin (**8**). Acetylation [pyridine–Ac_2O (1:1) 250 μl, 4-dimethylaminopyridine 6 mg, 5°, 20 hr] of diol **7** (4.6 mg) and chromatography [Si gel; toluene–EtOAc (0 → 10%)] afforded **8** (1.8 mg); mp 145.5–147°, (lit. [14]: mp 143–145°); $[\alpha]_D^{20}$ − 102° (EtOH; *c* 0.05), $[\alpha]_D^{20}$ − 127° ($CHCl_3$; *c* 0.05), (lit.[14]: $[\alpha]_D$ − 138°, EtOH); ^1H NMR data identical with those reported [14].

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