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On the Constituents of Rehmanniae Radix. (3). Absolute Stereostructures of Rehmaniaosides A, B, and C, and Rehmapicroside, Biologically Active Ione Glucosides and a Monoterpene Glucoside Isolated from Chinese Rehmanniae Radix

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Following the characterization of the iridoid and iridoid glycoside constituents in Chinese Rehmanniae Radix, the dried root of Rehmannia glutinosa Libosch. [Kan-jio in Japanese], we investigated the structures of biologically active iionone glucosides, rehmaniaosides A, B, and C, and a monoterpene glucoside, rehmapicroside. Their absolute stereostructures were determined on the basis of chemical and physicochemical evidence, which included the result of application of the exciton chirality method to the allylic benzylo derivitives.

Key words Rehmanniae Radix; Rehmannia glutinosa; iionone glucoside; monoterpene glucoside; rehmaniaosides; rehmapicroside

As a part of our continuing chemical studies on the processing of Rehmanniae Radix, 3) we have investigated the chemical constituents of Chinese Rehmanniae Radix, whose botanical origin was identified as Rehmannia glutinosa Libosch. (Scrophulariaceae). We have so far reported the isolation of four iridoids (rehmaglutalins A, 4) B, 4) C, 5) and D 5), a chlorinated iridoid glycoside (glutinoside 1,5)), three ionone glucosides [rehmaniaosides A (1), 6) B (2), 6) and C (3) 6)], and a monoterpenel glucoside [rehmapicroside (10) 6]), together with eight known glycosides. Among them, rehmaniaosides A (1) and B (2) were found to induce contraction of the isolated bladder and urethral smooth muscle of mice. 6) We have described the absolute stereostructures of rehmaglutalins A, B, C, and D, and glutinoside 1,4,5).

This paper presents a full account of the structure elucidation of three ionone glucosides, rehmaniaosides A (1), B (2), and C (3), and a monoterpene glucoside, rehmapicroside (10). 6)

Rehmaniaosides A (1), B (2), and C (3) The infrared (IR) spectra of rehmaniaosides A (1) and B (2) were very similar and showed absorption bands ascribable to hydroxy and olefin functions. The liquid secondary ionization mass spectra (liquid SIMS) of 1 and 2 showed the same quasimolecular ion peaks at m/z 391 (M+H) + , 413 (M+Na) + , and 483 (M+H+glycerol) + . The high-resolution liquid SIMS measurement of 1 and 2 revealed their molecular formula to be C19H33O8.

Rehmaniaoside C (3) was obtained as colorless prisms of mp 217-218°C and the molecular formula C19H33O8 was determined by elemental analysis. The ultraviolet (UV) and IR spectra of 3 showed absorption due to an enone function at 232 nm (ε 10700) and 1680 cm -1 , respectively. Reduction of 3 with NaBH4 in methanol yielded rehmaniaosides A (1) and B (2) in a 1:1 ratio, while 3 was obtained by oxidation of 1 and 2 with CrO3 in pyridine. Acetylation of 3 with acetic anhydride and pyridine provided the pentaacetate (3a). The proton nuclear magnetic resonance (1H-NMR) spectrum of 3a showed signals assignable to four methyl groups, two olefinic protons, and a β-glucopyranosyl moiety. Hydrolysis of 3 with β-glucosidase afforded an aglycone (5), which was found to be identical with the synthetic ionone derivative (5), 5) except for the sign of the specific rotation [α]D_5 - 54°; 5, [α]D_5 + 55°. Based on this evidence, the structure of the aglycone (5) was concluded to be the antipode of 5.

A detailed comparison of the 13C-NMR data (Table 1) for 3 with those for 3a and 5 led us to consider that the glucopyranosyl residue in 3 was attached to the 2'-hydroxyl group. Consequently, the structure of rehmaniaoside C (3) has been determined to be as shown.

The plane structure of rehmaniaoside C (3) was identical with that proposed for a dihydroxy-β-ionone glucoside which was isolated from Aeginetia indica L. var. gracilis Nakai. 9) The physicochemical properties of 3 were found to be identical with those reported for the dihydroxy-β-ionone glucoside. Therefore, we concluded that the dihydroxy-β-ionone glucoside has the same absolute stereostructure as rehmaniaoside C (3).

Next, the structures of rehmaniaosides A (1) and B (2) were investigated. Treatment of 1 and 2 with 4.5% hydrogen chloride in dry methanol provided an epimeric mixture of the 2-methoxy derivative (4), which gave the pentaacetate (4a) on usual acetylation. Comparison of the 13C-NMR data (Table 1) for 4 with those of 4a and the observation of a nuclear Overhauser effect (NOE) (14.1%) between 2-OCH3 and 2-H substantiated the structure 4. Methanalysis of 4 with 9% hydrogen chloride in dry methanol liberated 6, 10) 7, 10) and methyl glucoside.

Hydrolysis of rehmaniaoside A (1) and B (2) with β-glucosidase afforded 8 (from 1) and 9 (from 2), which were obtained in a 1:1 ratio from 5 by NaBH4 reduction. Based on the above-mentioned evidence, the structures of rehmaniaosides A (1) and B (2) were elucidated, except for the absolute stereostructure at the 2-position.

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In order to elucidate the C2-configuration in 1 and 2, the allylic benzoate exciton chirality method\textsuperscript{13} was applied to 1b and 2b, which were prepared from rehmaionoside C pentacetate (3a). Namely, reduction of 3a with NaBH\(_4\) in methanol yielded 1a and 2a in a 1:1 ratio. Benzylation of 1a and 2a with benzoyl chloride in pyridine afforded the 2-benzoyl derivatives, 1b (from 1a) and 2b (from 2a), respectively. Since deacetylation of 1b and 2b with 1% NaOMe in methanol regenerated 1 and 2, the structures of 1b and 2b were corroborated.

The \( ^1H \)-NMR spectrum of 1b in \( CD_3OD \) exhibited a signal due to benzyloxy-bearing methine [\( \delta \) 5.64, dq,
$J_{2,3} = 6.1$ Hz, $J_{1,2} = 6.4$ Hz]. The circular dichroism (CD) spectrum of 1b in methanol gave a positive first Cotton effect at 226 nm (ε 13100). Consequently, the preferred configuration (a) around the 2-benzyloxy-3-ene moiety in 1b was presumed to be as shown in Fig. 1, and the 25 configuration in 1b was determined.

On the other hand, the $J_{2,3}$ value in the $^1$H-NMR spectrum of 2b was 5.8 Hz and the CD spectrum of 2b showed a negative first Cotton effect at 226 nm (ε -15200). Thus, the 2R configuration (b) in 2b was concluded to be as shown in Fig. 1. Based on the above evidence, the absolute configurations of rehmaionosides A (1) and B (2) were determined to be as shown.

Rehmapicroside (10) Rehmapicroside (10) was obtained as colorless prisms of mp 127—129 ºC. The IR spectrum of 10 showed absorption bands due to hydroxyl groups and an $\alpha$, $\beta$-unsaturated carboxylic moiety at 3405, 1691, and 1637 cm$^{-1}$. The molecular formula $C_{18}H_{26}O_8$ was confirmed by the quasimolecular ion peaks at $m/z$ 347 (M + H)$^+$, 369 (M + Na)$^+$, and 439 (M + H + glycero)$^+$ in the liquid SIMS and by the elemental analysis measurement.

The $^1$H- and $^{13}$C-NMR spectra of 10 showed signals assignable to one olefinic methyl group, two tertiary methyl groups, a tetrasubstituted olefin moiety, an $\alpha,\beta$-unsaturated carbonyl group, and a $\beta$-glucopyranosyl moiety. Ordinary acetylation of 10 yielded the tetraacetate (10a), while methylation of 10 with diazomethane in methanol gave the monomethyl ester (10b).

Methanolyis of 10 with 9% hydrogen chloride in dry methanol liberated a racemic 3-methoxyl derivative (11) and methyl glucoside. Hydrolysis of 10b with $\beta$-glucosidase liberated an aglycone methyl ester (12), which gave the known enone (12b) by oxidation with CrO$_3$ in pyridine. Thus, the plane structure of rehmapicroside (10) was confirmed.

Finally, the absolute stereostructure of rehmapicroside (10) was determined by the application of the allylic benzoate exciton chirality method as described for rehmaionosides A (1) and B (2). Namely, benzylation of an aglycone methyl ester (12) with benzyol chloride in pyridine furnished the monobenzoate (12a). The CD spectrum of 12a gave a positive first Cotton curve ($\theta_{D29}$ +26500). Thus, the 3R configuration of 12a was determined.

Furthermore, the absolute stereostructure of 10 was substantiated by its partial synthesis from $\alpha$-ionone. The enone methyl ester (13), which was prepared from $\alpha$-ionone, was treated with NaBH$_4$ in methanol to afford racemic 12. Glycosidation of racemic 12 with 1-bromo-2,3,4,6-tetra-O-acetylglucopyranose and Hg(CN)$_2$ and subsequent deacetylation reaction gave the 3-epimeric mixture, which was further subjected to high-performance liquid chromatographic (HPLC) purification to provide 10b (30% yield from 13) and the diastereoisomer (14, 31%). Hydrolysis of 10b with 10% KOH in aqueous methanol furnished rehmapicroside (10, 69%).

![Chart 2](image-url)

Chart 2
Table 2. $^{13}$C-NMR Data for 10a, 10b, 10b, 11, 12, and 14 (in Pyridine-$d_5$)

<table>
<thead>
<tr>
<th>Carbon</th>
<th>10a</th>
<th>10b</th>
<th>10b</th>
<th>11</th>
<th>12</th>
<th>14</th>
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<td>142.0 (s)</td>
<td>139.1 (s)</td>
<td>141.0 (s)</td>
<td>137.4 (s)</td>
<td>138.9 (s)</td>
</tr>
<tr>
<td>2</td>
<td>129.8 (s)</td>
<td>128.9 (s)</td>
<td>132.6 (s)</td>
<td>130.8 (s)</td>
<td>135.9 (s)</td>
<td>133.3 (s)</td>
</tr>
<tr>
<td>3</td>
<td>73.1 (d)</td>
<td>76.4 (d)</td>
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<td>77.8 (d)</td>
<td>68.1 (d)</td>
<td>74.7 (d)</td>
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<td>24.2 (t)</td>
<td>23.6 (t)</td>
<td>29.4 (t)</td>
<td>24.3 (t)</td>
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<tr>
<td>5</td>
<td>33.7 (t)</td>
<td>33.8 (t)</td>
<td>34.0 (t)</td>
<td>34.8 (t)</td>
<td>35.2 (t)</td>
<td>34.0 (t)</td>
</tr>
<tr>
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<td>32.7 (t)</td>
<td>33.5 (t)</td>
<td>33.3 (t)</td>
<td>33.5 (t)</td>
<td>33.8 (t)</td>
<td>33.4 (t)</td>
</tr>
<tr>
<td>1-OCOO</td>
<td>171.7 (s)</td>
<td>170.2 (s)</td>
<td>170.2 (s)</td>
<td>172.3 (s)</td>
<td>170.7 (s)</td>
<td>170.3 (s)</td>
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<tr>
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<td>18.5 (q)</td>
<td>18.2 (q)</td>
<td>18.4 (q)</td>
<td>18.3 (q)</td>
<td>18.5 (q)</td>
</tr>
<tr>
<td>6-CH$_3$</td>
<td>26.9 (q)</td>
<td>27.0 (q)</td>
<td>27.1 (q)</td>
<td>27.6 (q)</td>
<td>27.8 (q)</td>
<td>27.2 (q)</td>
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<tr>
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<tr>
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<td>78.3 (d)</td>
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<tr>
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<td>62.4 (t)</td>
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<td>62.9 (t)</td>
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<tr>
<td>O-CH$_3$</td>
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<td>56.5 (q)</td>
<td>50.9 (q)</td>
<td>50.9 (q)</td>
<td>50.9 (q)</td>
<td>50.9 (q)</td>
</tr>
</tbody>
</table>

Based on the above evidence, the absolute configuration of rehmapiicoside (10) was determined to be as shown.

Experimental

The instruments used to obtain physical data and the experimental conditions for chromatography were the same as described in our previous paper.\(^\dagger\)

Rehmapiicosides A (1), B (2), C (3), and Rehmapiicoside D (10) Rehmapiicoside (1): Hygroscopic amorphous powder. [a]$\text{D}^{20} = +93.3^\circ$ (c = 1.03, MeOH). Anal. Caled for C$_{41}$H$_{40}$O$_{2}$·2H$_2$O·C$_{12}$·H$_{12}$·C$_{12}$·H$_{12}$: C, 53.51; H, 8.98. Found: C, 53.72; H, 8.93. High-resolution liquid SIMS: Caled for C$_{41}$H$_{40}$O$_{2}$·2H$_2$O·C$_{12}$·H$_{12}$·C$_{12}$·H$_{12}$: C = 53.51; H = 8.98. 1H-NMR (90 MHz, pyridine-$d_5$) was monitored at room temperature (23°C) under an N$_2$ atmosphere for 20 min, then neutralized with Dowex 50 W×8 (H$^+$ form). The resin was removed by filtration. After removal of the solvent from the filtrate under reduced pressure, the product was purified by HPLC (Zorbax ODS, MeOH-H$_2$O$_2$ (3:2)) to yield 1 (5 mg) and 2 (5 mg). These products were shown to be identical with authentic rehmapiicosides A and B, which were isolated from Chinese Rehmanniaceae Radix, by TLC (Silica gel 60 F$_{254}$ pre-coated TLC (ordinary phase TLC): CHCl$_3$-MeOH-H$_2$O$_2$ (65:35:10, lower phase), n-BuOH-AcOEt-H$_2$O$_2$ (4:1.5, upper phase)), and silylated silica gel 60 F$_{254}$, pre-coated TLC (reversed phase TLC): MeOH-H$_2$O$_2$ (1:1) and IR (KBr) comparisons.

CrO$_2$ Oxidation of Rehmapiicoside A (1) A solution of 1 (7 mg) in pyridine (1.0 ml) was treated with CrO$_2$ (21 mg, pyridine-$d_5$ (0.5 ml)) and the mixture was stirred at room temperature (23°C) under an N$_2$ atmosphere for 3 h. The reaction mixture was treated with isopropyl alcohol (1.0 ml) and stirred for 3 h as above, then filtered to remove the inorganic precipitate. Concentration of the filtrate under reduced pressure yielded a product (11 mg), which was purified by column chromatography [$\text{SiO}_2$ 200 mg, CHCl$_3$-MeOH-H$_2$O$_2$ (10:3:1, lower phase)] to provide 3 (5 mg). This product was shown to be identical with authentic rehmapiicoside C obtained from Chinese Rehmanniaceae Radix by TLC (ordinary phase TLC: CHCl$_3$-MeOH-H$_2$O$_2$ (7:3:1, lower phase), CHCl$_3$:MeOH (10:1) and CHCl$_3$:n-BuOH (1:1)). IR (KBr), and 1H-NMR (90 MHz, pyridine-$d_5$) comparisons.

CrO$_2$ Oxidation of Rehmapiicoside B (2) A solution of 2 (8 mg) in pyridine (1.0 ml) was treated with CrO$_2$ (21 mg, pyridine-$d_5$ (0.5 ml)) and the mixture was stirred at room temperature (23°C) under an N$_2$ atmosphere for 3 h. Isopropyl alcohol (1.0 ml) was added and the mixture was stirred, then filtered as described in connection with the oxidation of 1. Concentration of the filtrate under reduced pressure yielded a product (3 mg), which was isolated by column chromatography [[$\text{SiO}_2$ 200 mg, CHCl$_3$-MeOH-H$_2$O$_2$ (10:3:1, lower phase)] to furnish 3 (mg). This was shown to be identical with authentic rehmapiicoside C by TLC (as described above), IR (KBr), and 1H-NMR (90 MHz, pyridine-$d_5$) comparisons.

Acetylation of Rehmapiicoside C (3) A solution of 3 (13 mg) in pyridine (1.0 ml) was treated with Ac$_2$O (1.0 ml) and the mixture was stirred at room temperature (23°C) under an N$_2$ atmosphere for 3 h, isopropyl alcohol (1.0 ml) was added and the mixture was stirred, then filtered as described in connection with the oxidation of 1. Concentration of the filtrate under reduced pressure yielded a product (3 mg), which was isolated by column chromatography [[$\text{SiO}_2$ 200 mg, benzene-acetone (6:1)] to furnish 5 (4 mg).

5: mp 115–116°C (colorless crystals from benzene). [a]$\text{D}^{20} = +3.6^\circ$ (c = 0.10, EtOH). High-resolution liquid SIMS: Caled for C$_{41}$H$_{39}$O$_{2}$·2MeOH·M$^+$ (M$^+$): 226,157. Found: 226,154. IR (KBr): 3400, 2450, 1670, 1620 cm$^{-1}$. 1H-NMR (900 MHz, CDCl$_3$) δ: 0.83, 1.13, 1.23 (3H each, all s, 2,6,6'-Br$_2$-C$_6$H$_3$), 2.31 (3H, s, 1-CH$_3$), 6.34, 7.33 (1H each and both, J = 16 Hz, 3-H$_4$). 13C-NMR: see Table 1. Acid Treatment of Rehmapiicoside A (1) A solution of 1 (11 mg) in dry MeOH (1.0 ml) was treated with 9% HCl-dry MeOH and the mixture was stirred at room temperature (23°C) under an N$_2$ atmosphere for 8 h, then neutralized with Dowex 1 × 2 (OH$^-$/form) and filtered. Removal of the solvent from the filtrate under reduced pressure gave a product (13 mg), which was purified by column chromatography [$\text{SiO}_2$ 500 mg, CHCl$_3$:MeOH (10:1)] to furnish 4 (8 mg).
Acetalysis of 4

A solution of 4 (12 mg) in pyridine (0.5 ml) was treated with Ac₂O (0.5 ml) and the mixture was stirred at room temperature (23°C) under an N₂ atmosphere for 8 h, then poured into ice-water. The whole was extracted with AcOEt. The AcOEt extract was worked up as described above for the acetalysis of 3 to furnish 4a (18 mg).

4a: mp 111—113°C (colorless prisms from acetone), [α]₂⁰D +81.5° (c = 0.42, MeOH). Anal. Calcd for C₃₀H₄₂O₁₂: C, 58.62; H, 7.54. Found: C, 58.18; H, 7.79. IR (CHCl₃): 2934, 1751, 1600, 1035 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) (δ): 0.84, 1.03, 1.14 (3H each, all s, 2,6,6′-β-Ch₂). 1.25 (3H, d, J = 6 Hz, 1-CH₂), 1.99 (3H), 2.02, 2.03 (6H each) (all s, OAc, δ = 4.19, 4.22, 4.29, 4.39, 4.48, 4.68 (1H, d, J = 7 Hz, 1'-H)). 5.26 (1H, d, J = 18 Hz, 6-H). 6.14 (1H, d, J = 16 Hz, 4-H). ¹³C-NMR (22.5 MHz, pyridine-d₅); δ: 20.4 (2C), 20.5 (2C), 20.8 (1C) and others as given in Table 1.

Benzoylation of 1a

A solution of 1a (3 mg) in pyridine (0.4 ml) was treated with benzoic chloride (0.015 ml) and the mixture was stirred at room temperature (30°C) under an N₂ atmosphere for 8 h, then poured into ice-water. The whole was extracted with AcOEt. The AcOEt extract was worked up with 2N HCl, aqueous saturated NaHCO₃, and brine, and then dried over MgSO₄. After removal of the solvent under reduced pressure, the product was purified by column chromatography on SiO₂ (1 g, benzene-AcOEt (4:1)) to furnish 2b (3 mg).

2b: Colorless oil, [α]₂⁰D +21.9° (c = 0.33, MeOH). High-resolution liquid SimS: Calculated for C₂₉H₂₅O₃ (M⁺): 430.1855. Found: 430.1856. UV nm (μm): 228 (14000), CD (MeOH): [θ]₂⁰D (5 nm) +13000 (226) (pos. max.) (IR) (KBr): 2935, 1753, 1716, 1600, 1272, 1034 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) (δ): 0.78, 0.90, 1.16 (3H each, all s, 2,6,6′-β-Ch₂). 1.47 (3H, d, J = 6 Hz, 1'-CH₂), 1.97, 1.99, 2.00 (3H each), 2.01 (6H) (all s, OAc x 5), 2.59 (1H, d, J = 6, 16 Hz, 4-H), 6.13 (1H, d, J = 16 Hz, 4-H). ¹³C-NMR (500 MHz, CDCl₃); δ: 22.5 (2C), 22.6 (2C), 23.0 (1C), 24.3 (2C), 20.5 (2C), 20.8 (1C) and others as given in Table 1.
was removed by filtration. After removal of the solvent from the filtrate under reduced pressure, the product was purified by column chromatography [SiO₂, 100 mg, CHCl₃-MeOH-H₂O (7:3:1) to furnish 1 (1 mg), which was identical with rehmaonide A obtained from Chinese Rehmanniae Radix in terms of TLC (as described above for the NaBH₄ reduction of 3) and HPLC [Zorbax ODS, MeOH-H₂O (3:2) behavior].

Decylation of 2b A solution of 2b (3 mg) in 1% NaOMe-MeOH (0.5 ml) was stirred at room temperature (27°C) under a N₂ atmosphere for 30 min and neutralized with Dowex 50 W×8 (H⁺ form). Work-up of the reaction mixture as described above for the decylation of 1b, gave a product, which was purified by column chromatography [SiO₂, 100 mg, CHCl₃-MeOH-H₂O (7:3:1, lower phase)] to furnish 2 (1 mg); this was identical with authentic rehmaonide B obtained from Chinese Rehmanniae Radix in terms of TLC (as described above) and HPLC (as described above) behavior.

Acetylation of Rehmaipicoside (10) A solution of 10 (16 mg) in pyridine (1.0 ml) was treated with Ac₂O (1.0 ml) and the mixture was stirred at room temperature (23°C) under an N₂ atmosphere for 2 h, then poured into ice-water. The whole was extracted with AcOEt. Work-up of the AcOEt extract as described above in connection with the acetylation of 3 furnished 10a (22 mg).

Decyclation of (10) A colorless prisms from Et₂O, [α]D 🇧 = +15.8º (c = 0.36, CHCl₃). Anal. Calc'd for C₁₃H₁₇O₂: C, 73.3; H, 9.1. Found: C, 73.2; H, 9.2.

13: Colorless oil, High-resolution MS: Calc'd for C₁₃H₁₇O₂ (M⁺): 198.126. Found: 198.127. IR (CHCl₃): 2924, 2816, 1685, 1078 cm⁻¹. 1H-NMR (500 MHz, CDCl₃) δ: 1.14, 1.16 (3H, each, both s, 6x,6x-CH₃), 1.83 (3H, s, 2-CH₃). 3.39 (3H, s, O-CH₃). 5.36 (1H, t, J = 5 Hz, 3H).

14: Colorless powder, [α]D 🇧 = +16.4º (c = 0.84, MeOH).

15: Colorless powder, [α]D 🇧 = +3.8º (c = 0.24, CHCl₃).

References and Notes

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6) Yoshikawa M., Fukuda Y., Yaniyama T., Cha B. C., Yaniyama I.


10) Detailed comparison of the physical data for 6 and 7 indicated that these compounds are epimeric at the 2-position. However, their absolute configurations have not been determined.

