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Studies on the Chinese Crude Drug "Forsythiae Fructus." VII.[1)] A New Caffeoyl Glycoside from *Forsythia viridissima*

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In addition to a known caffeoyl glycoside of 3,4-dihydroxyphenethyl alcohol, acteoside (**1**), a new caffeoyl glycoside of β,3,4-trihydroxyphenethyl alcohol, designated as β-hydroxyacteoside (**2**), was isolated from the fruits of *Forsythia viridissima* LINDLEY (Oleaceae). The structure of **2** was established as β,3,4-trihydroxyphenethyl-*O*-α-L-rhamnopyranosyl-(1→3)-4-*O*-caffeoyl-β-D-glucopyranoside on the basis of analysis of the carbon-13 nuclear magnetic resonance spectrum and chemical evidence.

Keywords——*Forsythia viridissima*; Oleaceae; acteoside; caffeoyl glycoside of β,3,4-trihydroxyphenethyl alcohol; β-hydroxyacteoside; ^{13}C-NMR spectra

In previous papers,[1,2)] we reported the isolation of two new caffeoyl glycosides of 3,4-dihydroxyphenethyl alcohol and β,3,4-trihydroxyphenethyl alcohol, designated as forsythiaside (3,4-dihydroxy-β-phenethyl-*O*-α-L-rhamnopyranosyl-(1→6)-4-*O*-caffeoyl-β-D-glucopyranoside) and suspensaside (DL-β,3,4-trihydroxyphenethyl-*O*-α-L-rhamnopyranosyl-(1→6)-4-*O*-caffeoyl-β-D-glucopyranoside), from the fruits of *Forsythia suspensa* VAHL (Oleaceae). These two compounds showed antibacterial activity.

This paper describes the isolation from the fruits of *F. viridissima* LINDLEY and the structure determination of a new caffeoyl glycoside of β,3,4-trihydroxyphenethyl alcohol, designated as β-hydroxyacteoside, in addition to a known caffeoyl glycoside of 3,4-dihydroxyphenethyl alcohol, acteoside.

The extraction and separation were carried out as described in Experimental. Acteoside

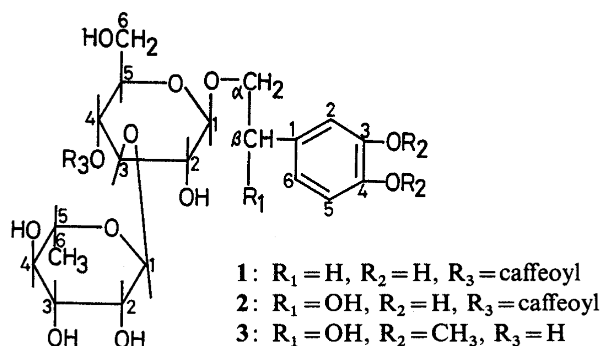

Chart 1

(**1**) was isolated as an amorphous powder, $C_{29}H_{36}O_{15}$, mp 145—150 °C, $[\alpha]_D^{20}$ −66.5° (methanol), whose molecular weight was confirmed by the observation of *m/z* 646 ($M^+ - 1 + {}^{23}Na$) on field desorption mass spectrometry (FD-MS). The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **1** was similar to that of forsythiaside,[2)] except

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that differences in the chemical shifts at carbons of the glucose moiety were observed. Compound **1** was assumed to be acteoside (3,4-dihydroxy-β-phenethyl-*O*-α-L-rhamnopyranosyl-(1→3)-4-*O*-caffeoyl-β-D-glucopyranoside). Thus, the structure of **1** was established by the comparison of its spectral data (infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and ^{13}C-NMR) with those reported in the literature.[3]

β-Hydroxyacteoside (**2**) was obtained as an amorphous powder, $C_{29}H_{36}O_{16}$, mp 177—183 °C, $[\alpha]_D^{22}$ −32.1 ° (methanol), whose molecular weight was confirmed by the observation of *m/z* 663 ($M^+ + {}^{23}Na$) on FD-MS. The ultraviolet (UV) spectrum of **2** showed absorption maxima at 218, 231, 289 and 331 nm. The bathochromic shift of the absorption maximum with base was very similar to that of **1**. The IR spectrum of **2** suggested the presence of a conjugated ester (1685 cm^{-1}) and aromatic rings (1600 and 1518 cm^{-1}), while the ^{1}H-NMR spectrum of **2** resembled that of **1** except for disappearance of the signal assigned to two benzyl protons of the phenethyl moiety. These data suggest that **2** bears a marked structural resemblance to **1**.

The ^{1}H-NMR spectrum of the acetate of **2** showed the presence of six alcoholic acetoxy (δ 1.83, 1.90 and 2.05) and four phenolic acetoxy (δ 2.25) groups, and a proton (δ 5.85, dd, $J=5, 4$ Hz) at the benzyl position bearing an acetoxy group.

Acid hydrolysis of **2** gave caffeic acid and 3,4-dihydroxyphenylacetaldehyde,[4] which were identified by comparison with authentic samples by thin-layer chromatography (TLC). The presence of D-glucose and L-rhamnose in the hydrolyzate was detected by TLC and gas chromatography (GC).

The reaction of **2** in methanol with excess diazomethane gave two compounds, deacyl-β-hydroxyacteoside dimethyl ether (**3**) as an amorphous powder, $C_{22}H_{34}O_{13}$, $[\alpha]_D^{22}$ −31.5 ° (methanol), and 4-(3′,4′-dimethoxyphenyl)-2-pyrazoline-3-carboxylic acid methyl ester.[1]

The UV spectrum of **3** showed no bathochromic shift on addition of base. The ^{1}H-NMR spectrum of **3** exhibited signals at δ 1.25 (3H, d, $J=6$ Hz) due to methyl protons of the rhamnose moiety, at δ 3.78 and 3.80 (6H, each s) due to aromatic methoxys, at δ 4.30 (1H, d, $J=8$ Hz) and 5.13 (1H, br s) due to anomeric protons of the sugar moiety, and at δ 6.80—7.00 (3H, m) due to aromatic protons.

TABLE I. ^{13}C-NMR Chemical Shifts[a]

	β,3,4-Trihydroxyphenethyl moiety				Rhamno-glucose moiety			Caffeate moiety	
	2	1	β,3,4-Trihydroxy-phenethyl alcohol		2	1		2	1
C-1	133.6	131.4	134.4	Glc-1	104.0	104.0	C-1′	127.7	127.5
C-2	114.7	116.2	114.5	Glc-2	76.0	75.8	C-2′	115.2	115.2
C-3	146.2	145.9	145.7	Glc-3	81.3	81.5	C-3′	146.8	146.6
C-4	146.0	144.4	145.4	Glc-4	70.3	70.2	C-4′	149.7	149.5
C-5	117.1	117.0	116.0	Glc-5	76.0	75.8	C-5′	116.5	116.4
C-6	119.2	121.1	118.9	Glc-6	62.2	62.2	C-6′	123.1	123.0
C-α	76.3	72.0	68.3	Rham-1	102.9	102.8	C-7′	147.9	147.8
C-β	73.7	36.3	75.4	Rham-2	72.0	72.0	C-8′	114.7	114.6
				Rham-3	72.3	72.0	C-9′	168.2	168.2
				Rham-4	73.7	73.7			
				Rham-5	70.3	70.2			
				Rham-6	18.3	18.2			

a) The spectra were taken in micro cells with a JNM-FX 60 spectrometer (15.00 MHz) in CD_3OD with TMS as an internal reference.

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TABLE II. ^{13}C-NMR Chemical Shifts[a)]

β-Hydroxy-3,4-dimethoxyphenethyl moiety				Rhamno-glucose moiety					
	3	Deacylacteoside dimethyl ether	β-Hydroxy-3,4-dimethoxyphenethyl alcohol		3	Deacylacteoside dimethyl ether		3	Deacylacteoside dimethyl ether
C-1	135.0	133.1	136.2	Glc-1	104.1	104.1	Rham-1	102.5	102.7
C-2	111.4	113.2	111.5	Glc-2	75.6	75.4	Rham-2	72.1	71.7
C-3	150.3	150.2	150.3	Glc-3	84.1	84.5	Rham-3	72.1	72.2
C-4	150.0	148.9	149.8	Glc-4	70.0	70.2	Rham-4	73.9	73.9
C-5	112.9	114.2	112.9	Glc-5	77.8	77.7	Rham-5	70.0	70.0
C-6	120.0	122.2	119.9	Glc-6	62.5	62.6	Rham-6	17.7	17.7
C-α	76.3	71.7	68.6						
C-β	73.9	36.6	75.5						
OCH_3	56.4	56.5	56.5						

a) The spectra were taken in micro cells with a JNM-FX 60 spectrometer (15.00 MHz) in CD_3OD with TMS as an internal reference.

TABLE III. Molecular Optical Rotation Differences

	$[\alpha]_D$ (°)	$[M]_D$ (°)	$\Delta [M]_D$ (°)
Deacyl-β-hydroxyacteoside dimethyl ether (3)	−31.5	−159.4	+14.1
Deacylacteoside dimethyl ether	−35.4	−173.5	
Deacylsuspensaside dimethyl ether	−36.0	−182.2	+3.0
Deacylforsythiaside dimethyl ether	−37.8	−185.2	
(+)-Phenylethane-1,2-diol	+60.3	+83.2	

The results clearly suggested that **2** consists of β,3,4-trihydroxyphenethyl moiety and a rhamno-glucose moiety containing a caffeoyl group, like suspensaside.

The ^{13}C-NMR spectra of **2** and **3** were correlated with those of known compounds, *i.e.* **1**, β,3,4-trihydroxyphenethyl alcohol, β-hydroxy-3,4-dimethoxyphenethyl alcohol and deacylacteoside dimethyl ether. Tables I and II present the ^{13}C-NMR data and their assignments.

The ^{13}C-NMR of **2** supported the attachment of the caffeate moiety at the C-4 carbon of glucose (Glc-4) and of the rhamnose moiety at the C-3 carbon of glucose (Glc-3). The chemical shifts of the C-α carbon of **2** at 76.3 ppm relative to that of β,3,4-trihydroxyphenethyl alcohol at 68.3 ppm and of the C-1 carbon of glucose (Glc-1) at 104.0 ppm suggested the linkage of the glucose moiety to the C-α position of β,3,4-trihydroxyphenethyl alcohol.

Consequently, the structure of **2** has been established as β,3,4-trihydroxyphenethyl-*O*-α-L-rhamnopyranosyl-(1→3)-4-*O*-caffeoyl-β-D-glucopyranoside.

With regard to the problem of the absolute configuration at the C-β position of the β-hydroxyphenethyl moiety, the molecular optical rotation differences of deacylacteoside dimethyl ether-deacyl-β-hydroxyacteoside dimethyl ether (**3**), deacylforsythiaside dimethyl ether-deacylsuspensaside dimethyl ether, and a related compound, (+)-phenylethane-1,2-diol ((+)-β-hydroxyphenethyl alcohol), were compared. It was expected that the molecular optical rotation value attributable to the β-hydroxyphenethyl moiety of **3** having *S*-configuration at the C-β position would probably be nearly equal to that of (+)-phenylethane-1,2-diol.

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However, a smaller value than that expected was obtained, suggesting that the β-hydroxyphenethyl moiety has both *S*- and *R*-configuration in a ratio of approximately 7 : 5.

Compounds **1** and **2** show no inhibitory activity[5] against cyclic adenosine monophosphate (cAMP)-phosphodiesterase *in vitro* (IC_{50} **1**: $>50\times10^{-5}$ mol/l, **2**: $>50\times10^{-5}$ mol/l) in contrast to forsythiaside (IC_{50} 11.0×10^{-5} mol/l) and suspensaside (IC_{50} 18.3×10^{-5} mol/l) isolated from the fruits of *F. suspensa*.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected.

The following instruments were used: optical rotation, Yanagimoto OR-10, Jasco J-20; UV spectra, Shimadzu UV-210; IR spectra, Shimadzu IR-400; ^{1}H-NMR, Hitachi R-40 with tetramethylsilane ($\delta=0$) as an internal reference; ^{13}C-NMR spectra, JEOL JNM-FX 60 equipped with a JEC-980 computer; FD-MS, JEOL JMS-DX 300; MS, Hitachi RMU-7L; GC, Shimadzu GC-6AM. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad singlet; sh, shoulder.

The conditions for GC were as follows: glass column (3 mm × 1 m), 1.5% OV-1 on Shimalite-W (80—100 mesh); column temp., 140—180 °C (3 °/min); injection and detector temp., 280 °C; carrier gas, N_2 (25 ml/min).

Pre-coated thin-layer chromatography plates, Silica gel $60F_{254}$ (Merck), were used for TLC and for preparative TLC.

Isolation——"Forsythia Fructus" (500 g, fruits of *Forsythia viridissima* LINDLEY) were crushed and extracted with hot water (2.5 l). The extract was cooled and the precipitate was filtered off. The filtrate was evaporated to dryness, and the residue was extracted with MeOH. The MeOH extractives (21.1 g) were subjected to column chromatography on Sephadex LH-20, eluting with H_2O. The fractions (10 ml each) were monitored by TLC using the upper layer of $CH_3COC_2H_5$–AcOEt–HCOOH–H_2O–C_6H_6 (4 : 3 : 1 : 1 : 2) as a developer, and those showing a TLC spot at *Rf* 0.35, which gave a greenish-blue color with dil. $FeCl_3$ soln., were concentrated to afford crude acteoside (**1**). Repeated re-chromatography on Sephadex LH-20 gave 30.7 mg of **1**.

The fractions showing a TLC spot at *Rf* 0.18, which gave a greenish-blue color with dil. $FeCl_3$ soln., were concentrated to afford crude β-hydroxyacteoside (**2**). Repeated re-chromatography on Sephadex LH-20 gave 125.8 mg of **2**.

Acteoside (1)——Amorphous powder, mp 145—150 °C, $[\alpha]_D^{20}$ $-66.5°$ ($c=1.0$ in MeOH). UV λ_{max}^{MeOH} nm (log ε): 216 (4.28) sh, 248 (3.98) sh, 290 (4.00), 332 (4.10), UV $\lambda_{max}^{MeOH+NaOH}$ nm: 300, 381. IR ν_{max}^{KBr} cm^{-1}: 3600—3100 (OH), 1700 (C=O), 1628 (C=C), 1600, 1518 (arom. C=C), FD-MS *m/z*: 646 (M^+, $C_{29}H_{36}O_{15}$, $-1+{}^{23}$Na). ^{1}H-NMR (in CD_3OD) δ: 1.10 (3H, d, $J=6$ Hz, rhamnose-CH_3), 2.77 (2H, t, $J=7$ Hz, Ar-CH_2), 4.35 (1H, d, $J=8$ Hz, glucose-anomeric H), 5.17 (1H, br s, rhamnose-anomeric H), 6.23 (1H, d, $J=15$ Hz, Ar-C$\underline{H}$=CH–), 6.4—7.1 (6H, m, arom. H), 7.55 (1H, d, $J=15$ Hz, Ar-CH=C$\underline{H}$–).

Acetate of Acteoside (1)——**1** (100.2 mg) was acetylated with acetic anhydride-pyridine in the usual way. The crude acetate was purified by preparative TLC using $CHCl_3$–AcOEt (1 : 1) as a developer to give 67.7 mg of the acetate as an amorphous powder. $[\alpha]_D^{19}$ $-43.5°$ ($c=1.1$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 217 (4.31) sh, 284 (4.22). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (C=O), 1640 (C=C), 1508 (arom. C=C). MS *m/z* (%): 918 ($M^+-2\times CH_3CO$) (5.5), 765 ($C_{35}H_{41}O_{19}^+$) (2.3), 273 ($C_{12}H_{17}O_7^+$) (100). ^{1}H-NMR (in $CDCl_3$) δ: 1.02 (3H, d, $J=6$ Hz, rhamnose-CH_3), 1.91, 1.98, 2.06 (15H, each s, alcoholic CH_3CO), 2.27 (12H, s, phenolic CH_3CO), 2.83 (2H, t, $J=7$ Hz, Ar-CH_2), 6.28 (1H, d, $J=15$ Hz, Ar-C$\underline{H}$=CH–), 6.95—7.25 (6H, m, arom. H), 7.55 (1H, d, $J=15$ Hz, Ar-CH=C$\underline{H}$–).

Deacylacteoside Dimethyl Ether——A solution of **1** (147.5 mg) in methanol was treated with excess diazomethane, and the mixture was left to stand overnight in a refrigerator. Then the reaction mixture was evaporated to dryness. The residue was purified by preparative TLC using the lower layer of $CHCl_3$–MeOH–H_2O (65 : 25 : 10) as a developer to give 35.0 mg of deacylacteoside dimethyl ether as an amorphous powder. $[\alpha]_D^{22}$ $-35.4°$ ($c=0.3$ in MeOH). UV λ_{max}^{MeOH} nm (log ε): 228 (3.83), 279 (3.42), 284 (3.37) sh. IR ν_{max}^{KBr} cm^{-1}: 3600—3100 (OH), 1608, 1590, 1518 (arom. C=C). MS: Calcd for $C_{22}H_{34}O_{12}$, 490.2048. Obsd., 490.2021. ^{1}H-NMR (in CD_3OD) δ: 1.23 (3H, d, $J=6$ Hz, rhamnose-CH_3), 2.83 (2H, t, $J=7$ Hz, Ar-CH_2), 3.75, 3.78 (6H, each s, $2\times CH_3O$), 4.25 (1H, d, $J=8$ Hz, glucose-anomeric H), 5.08 (1H, br s, rhamnose-anomeric H), 6.65—6.90 (3H, m, arom. H).

β-Hydroxyacteoside (2)——Amorphous powder, mp 177—183 °C, $[\alpha]_D^{22}$ $-32.1°$ ($c=0.8$ in MeOH). UV λ_{max}^{MeOH} nm (log ε): 218 (4.33) sh, 231 (4.21) sh, 289 (3.98), 331 (4.00). UV $\lambda_{max}^{MeOH+NaOH}$ nm: 297, 379. IR ν_{max}^{KBr} cm^{-1}: 3600—3100 (OH), 1685 (C=O), 1630 (C=C), 1600, 1518 (arom. C=C). FD-MS *m/z*: 663 (M^+, $C_{29}H_{36}O_{16}$, $+{}^{23}$Na), 623 ($[M-H_2O]^+$ +1). ^{1}H-NMR (in CD_3OD) δ: 1.10 (3H, d, $J=6$ Hz, rhamnose-CH_3), 4.46 (1H, d, $J=8$ Hz, glucose-anomeric H), 5.14 (1H, br s, rhamnose-anomeric H), 6.20 (1H, d, $J=15$ Hz, Ar-C$\underline{H}$=CH–), 6.6—7.0 (6H, m, arom. H), 7.53 (1H, d, $J=15$ Hz, Ar-CH=C$\underline{H}$–).

Acetate of β-Hydroxyacteoside (2)——**2** (113.0 mg) was acetylated with acetic anhydride–pyridine in the usual way. The crude acetate was purified by preparative TLC using $CHCl_3$–AcOEt (1 : 1) as a developer to give 57.8 mg of

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the acetate as an amorphous powder. $[\alpha]_D^{15}$ $-33.3°$ ($c=1.0$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 216 (4.16) sh, 283 (4.07). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (C=O), 1640 (C=O), 1505 (arom. C=C). MS *m/z* (%): 765 ($C_{35}H_{41}O_{19}^+$) (13.3), 273 ($C_{12}H_{17}O_7^+$) (100). ^{1}H-NMR (in $CDCl_3$) δ: 1.03 (3H, d, $J=6$ Hz, rhamnose-CH_3), 1.83, 1.90, 2.05 (18H, each s, alcoholic CH_3CO), 2.25 (12H, s, phenolic CH_3CO), 5.85 (1H, dd, $J=5$, 4 Hz, Ar-CH), 6.27 (1H, d, $J=15$ Hz, Ar-C$\underline{H}$=CH–), 7.06—7.30 (6H, m, arom. H), 7.58 (1H, d, $J=15$ Hz, Ar-CH=C$\underline{H}$–).

Acid Hydrolysis of β-Hydroxyacteoside (2)——2 in 1% H_2SO_4 soln. was heated on a water bath for 1 h, then cooled. The mixture was extracted with Et_2O. The Et_2O layer was washed and evaporated to dryness. Caffeic acid in the residue was identified by comparison with an authentic sample [*Rf* 0.85 on TLC developed with the upper layer of $CH_3COC_2H_5$–AcOEt–HCOOH–H_2O–C_6H_6 (4:3:1:1:2)]. 3,4-Dihydroxyphenylacetaldehyde in the residue was also identified by comparison with an authentic sample [*Rf* 0.48 on TLC developed with $CHCl_3$–MeOH–H_2O (65:30:10)]. The aq. layer was neutralized with $BaCO_3$ and the precipitate was filtered off. The filtrate was evaporated to dryness. The residue was examined by TLC and GC (as tetramethylsilane (TMS) ethers) to identify L-rhamnose and D-glucose.

Reaction of β-Hydroxyacteoside (2) in Methanol with Excess Diazomethane——A solution of **2** (296.8 mg) in methanol was treated with excess diazomethane, and the mixture was left to stand overnight in a refrigerator. Then the reaction mixture was evaporated to dryness. The residue (334.3 mg) was dissolved in MeOH, and divided into two portions. One portion of the solution was purified by preparative TLC using the lower layer of $CHCl_3$–MeOH–H_2O (65:35:10) as a developer to give 20.8 mg of **3**. The other portion of the solution was purified by preparative TLC using $CHCl_3$–AcOEt (1:1) as a developer to give 4-[3′,4′-dimethoxyphenyl]-2-pyrazoline-3-carboxylic acid methyl ester, which was identical with an authentic sample.

Deacyl-β-hydroxyacteoside Dimethyl Ether (3)——Amorphous powder, $[\alpha]_D^{22}$ $-31.5°$ ($c=0.3$ in MeOH). UV λ_{max}^{MeOH} nm (log ε): 229 (3.87), 278 (3.43), 282 (3.40) sh. IR ν_{max}^{KBr} cm^{-1}: 3600—3100 (OH), 1600, 1580, 1518 (arom. C=C). MS: Calcd for $C_{22}H_{34}O_{13}$, 506.1996. Obsd., 506.1960. ^{1}H-NMR (in CD_3OD) δ: 1.25 (3H, d, $J=6$ Hz, rhamnose-CH_3), 3.78, 3.80 (6H, each s, $2\times CH_3O$), 4.30 (1H, d, $J=8$ Hz, glucose-anomeric H), 5.13 (1H, br s, rhamnose-anomeric H), 6.80—7.00 (3H, m, arom. H).

(+)-Phenylethane-1,2-diol——(+)-Mandelic acid methyl ester in tetrahydrofuran was reduced with $LiAlH_4$ in the usual way. The product was purified by preparative TLC using $CHCl_3$–AcOEt (1:1) as a developer to give (+)-phenylethane-1,2-diol.

Colorless needles from MeOH, mp 55—58 °C, $[\alpha]_D^{22}$ $+60.3°$ ($c=0.7$ in $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 230 (2.70), 252 (2.33), 257 (2.40), 263 (2.35), 280 (2.28). IR ν_{max}^{KBr} cm^{-1}: 3400—3200 (OH), 1605, 1518, 1495 (arom. C=C). MS: Calcd for $C_8H_{10}O_2$, 138.0680. Obsd., 138.0685. ^{1}H-NMR (in $CDCl_3+D_2O$) δ: 3.60 (2H, m, –C$\underline{H}_2$OH), 4.66 (1H, m, Ar-C$\underline{H}$), 7.10—7.40 (5H, m, arom. H). ^{13}C-NMR (in $CDCl_3$) δ: 140.6 (C-1), 128.6 (C-3, 5), 128.0 (C-4), 126.1 (C-2, 6), 74.8 (C-β), 68.1 (C-α).

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