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Optical Resolution of Racemic 4-Hydroxy-3-isobornyl-5-methylbenzaldehyde

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Abstract—Racemic 4-hydroxy-3-isobornyl-5-methylbenzaldehyde was separated into particular enantiomers via transformation into diastereoisomeric Schiff bases by reaction with (*R*)-1-phenylethanamine. The absolute configuration of the products was determined on the basis of the X-ray diffraction data for camphanate derived from one enantiomer of 4-hydroxy-3-isobornyl-5-methylbenzaldehyde.

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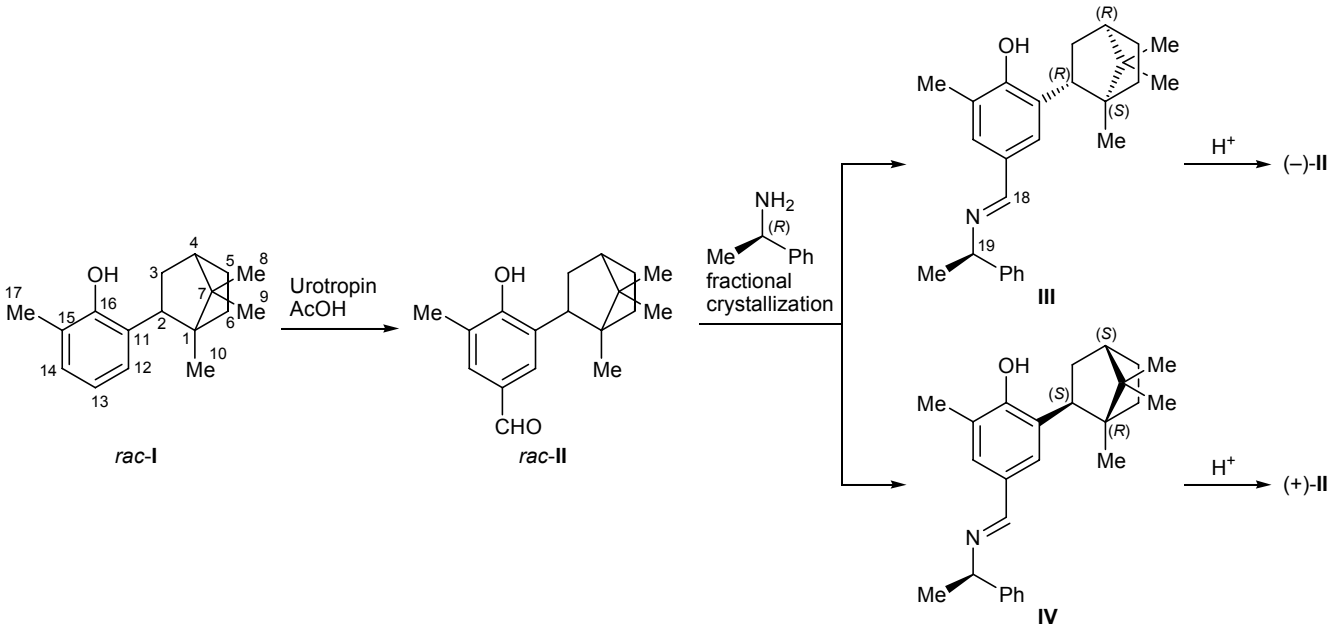
The presence of an aldehyde group in the molecules of 4-hydroxy-3,5-dialkylbenzaldehydes opens prospects in the synthesis of porphyrins [1] and fused, heterocyclic [2–4], and phosphorus-containing compounds [5] functionalized by 2,4-dialkylphenol fragments. These compounds attract interest from the viewpoint of their physiological and antioxidant properties. Racemic phenols having an isobornyl substituent are synthetically accessible, they possess antithrombogenic and antithrombocytic properties [6] and can be used as antioxidants [7]. It is desirable that both racemic and optically active derivatives of isobornylphenols be available to study their biological activity.

We previously reported on optical resolution of racemic salicylaldehydes having an isobornyl substituent with the use of (*R*)-1-phenylethanamine [8]. The

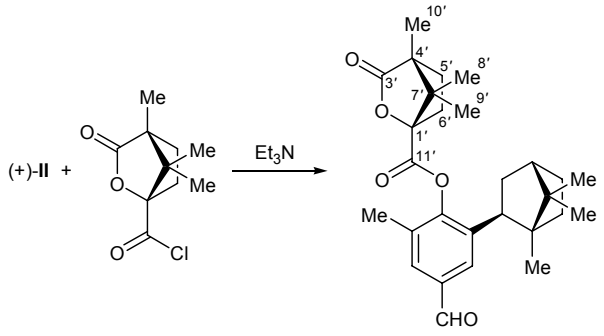
Scheme 1.



present article reports on the synthesis and optical resolution of racemic isobornylphenol possessing an aldehyde group in the *para* position with respect to the hydroxy group. Isobornylphenol *rac*-**I** was synthesized by alkylation of *o*-cresol with camphene in the presence of aluminum methylphenoxide [7]. The corresponding aldehyde *rac*-**II** was prepared by treatment of *rac*-**I** with hexamethylenetetramine (urotropin) in acetic acid (Duff reaction) according to the procedure described in [9]. Racemate **II** was separated into individual enantiomers via transformation into diastereoisomeric Schiff bases by reaction with enantiomerically pure (*R*)-1-phenylethanamine (Scheme 1). The Schiff bases were obtained in quantitative yield as mixtures of diastereoisomers **III** and **IV** at a ratio of ~1 : 1 (GLC data). By fractional crystallization from hexane we succeeded in isolating compounds **III** and **IV** enriched in one diastereoisomer. The diastereoisomeric purity was estimated by GLC.

The NOESY spectra of **III** and **IV** revealed coupling between the 18-H and 19-H protons,* indicating that these protons are spatially close to each other. These findings suggest that Schiff bases **III** and **IV** have *E* configuration with respect to the double C=N bond. Aldehydes (+)-**II** and (–)-**II** enriched in particular enantiomer were isolated by acid hydrolysis of each Schiff base. Their optical purity was estimated by analytical HPLC on a Chiralcel OD-H column.

Scheme 2.



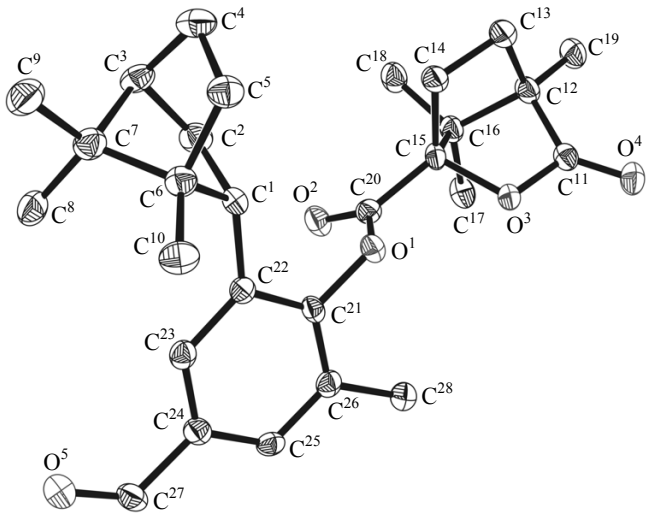
V

Ester **V** was synthesized by acylation of (+)-**II** at the hydroxy group with (1*S*)-camphanic chloride (Scheme 2). Slow evaporation of a solution of **V** in hexane–diethyl ether gave single crystals suitable for X-ray analysis (see figure). According to the X-ray diffraction data, compound **V** crystallized in $P2_1$ chiral space group. The bond lengths and bond angles in molecule **V** were similar to those found previously for other isobornylphenol derivatives [10]. However, the conformation of **V** differed considerably from that typical of structurally related compounds. The torsion angle $C^6C^1C^{22}C^{21}$ in molecule **V** is –149.2(2)° against –79.8(3) to –82.6(3)° reported in [10] for analogous compounds. Some selected geometric parameters of molecule **V** in crystal are collected in table.

The absolute configuration of compound **V** was determined on the basis of anomalous X-ray scattering; it coincided with the relative configuration assumed from the known configuration of the camphane substituent. The chiral centers in the isobornyl fragment of (+)-**II**, **IV**, and **V** have (1*R*,2*S*,4*S*) configuration. The configuration of the terpene fragment in compounds **III** and (–)-**II** is the opposite, (1*S*,2*R*,4*R*).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance II 300 spectrometer (300.17 and 75.48 MHz, respectively) from solutions in $CDCl_3$. The chemical shifts were determined relative to the solvent signals (δ 7.26 ppm, δ_C 77.00 ppm). Signals were assigned on the basis of *J*-modulation ^{13}C NMR spectra and two-dimensional spectra (HSQC, COSY, NOESY). The melting points were determined on a Kofler hot stage. The optical rotations were measured using a P3002RS Krüss Optronic automatic digital polarimeter (λ 589 nm).



Structure of the molecule of 4-formyl-2-methyl-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl}phenyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**V**) according to the X-ray diffraction data.

* For atom numbering, see Schemes 1 and 2.

Selected bond lengths and bond angles in the molecule of 4-formyl-2-methyl-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl}phenyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**V**)

Bond	*d*, Å	Angle	ω, deg
O^1–C^{20}	1.350(2)	$C^{20}O^1C^{21}$	116.52(14)
O^1–C^{21}	1.412(2)	$C^{11}O^3C^{15}$	105.92(14)
O^2–C^{20}	1.203(2)	$O^4C^{11}O^3$	121.47(19)
O^3–C^{11}	1.372(2)	$O^4C^{11}C^{12}$	131.22(18)
O^3–C^{15}	1.470(2)	$O^3C^{11}C^{12}$	107.30(16)
O^4–C^{11}	1.200(2)	$O^2C^{20}O^1$	124.40(19)
O^5–C^{27}	1.226(3)	$O^2C^{20}C^{15}$	125.01(18)
		$O^1C^{20}C^{15}$	110.55(16)
		$O^5C^{27}C^{24}$	124.1(2)

The progress of reactions was monitored by TLC on Sorbfil plates. Aldehyde spots were detected by treatment with a solution of 15 g of potassium permanganate in 300 ml of water containing 0.5 ml of concentrated sulfuric acid. Ester **V** was detected by treatment with a solution of Bromocresol Purple, followed by heating to 100–120°C. The purity of phenol **I** and aldehydes **II** was checked by GLC on a Shimadzu GC-2010AF gas chromatograph equipped with a flame-ionization detector (carrier gas helium; Agilent HP-1 capillary column, 60 m × 0.25 mm × 0.25 μm; oven temperature programming from 100 to 240°C at a rate of 6 deg/min); diastereoisomeric purity of Schiff bases **III** and **IV** was determined at an oven temperature of 270°C. Enantiomeric purity of aldehydes **II** was estimated by HPLC on an Agilent 1100 chromatograph [UV detector, λ 224 nm; 20°C; Chiralcel OD-H column (Daicel), 25 cm × 4.6 mm, 10 μm, eluent hexane–*i*-PrOH (19:1), flow rate 1.0 ml/min].

Aldehydes **II** and ester **V** were purified by column chromatography on silica gel Alfa Aesar 70/230μ (wet packing). Toluene was dried over anhydrous $CaCl_2$ and was distilled over metallic sodium. Petroleum ether with bp 65–70°C was used. Hexane was distilled just before use. Molecular sieves (4 Å) were activated by calcination at 140°C over a period of 3 h. (*R*)-(+)-1-Phenylethanamine (Alfa Aesar, ChiPros®, enantiomeric purity >99%), (1*S*)-camphanic acid chloride (Acros Organics), triethylamine (Sigma–Aldrich), 4-dimethylaminopyridine, urotropin, acetic acid, and diethyl ether of chemically pure grade were used without additional purification.

X-Ray analysis was performed for a 0.15×0.15×0.10-mm single crystal of ester **V** on a Bruker Smart Proteum automatic diffractometer with a rotating anode at 100.0(2) K (CuK_α irradiation, λ 1.54178 Å, graphite monochromator). Monoclinic crystals ($C_{28}H_{36}O_5$, *M* 452.57), space group $P2_1$, with the following unit cell parameters: a = 7.9126(2), b = 7.0320(1), c = 21.4735(5) Å; β = 93.661(1)°; V = 1192.38(4) Å^3; Z = 2; d_{calc} = 1.261 g/cm^3; μ(CuK_α) = 0.681 mm^{-1}; F(000) = 488. Total of 7933 reflections (3361 independent reflections with R_{int} = 0.0345) were measured by φ- and ω-scanning through a step of 0.5° in the range 2.06 < θ < 63.03° ($-9 \le h \le 8$, $-7 \le k \le 8$, $-22 \le l \le 24$). Correction for absorption was introduced by measuring the intensities of equivalent reflections (transmission factors min/max = 0.905/ 0.935). The structure was solved by the direct method and was refined by the full-matrix least-squares procedure in anisotropic approximation with respect to F^2 for all non-hydrogen atoms (SHELXTL-PLUS [11]). All hydrogen atoms were placed into positions calculated on the basis of geometry considerations and were refined according to the riding model. The final divergence factors were R_1 = 0.0350, wR_2 = 0.0922 for 3303 reflections with $I > 2\sigma(I)$ and R_1 = 0.0355, wR_2 = 0.0927 (for all reflections); 305 refined parameters; absolute structure parameter –0.12(17); goodness of fit 1.046; $\Delta\rho_{min/max}$ = –0.191/0.319.

4-Hydroxy-3-methyl-5-(1,7,7-trimethylbicyclo-[2.2.1]heptan-*exo*-2-yl)benzaldehyde (*rac*-II). A mixture of 3.2 g (13.1 mmol) of phenol *rac*-**I**, 1.47 g (10.5 mmol) of urotropin, and 8 ml of 90% aqueous acetic acid was heated for 3 h under reflux. The progress of the reaction was monitored by thin-layer chromatography using petroleum ether–diethyl ether (5:1) as eluent. The precipitate was filtered off, dried, and purified by column chromatography (gradient elution with petroleum ether–diethyl ether). Yield 2.6 g (73%), colorless powder, mp 155–157°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 3232 (OH), 1674 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.78 s (3H, $C^{10}H_3$), 0.85 s (3H, C^9H_3), 0.89 s (3H, C^8H_3), 1.45–1.49 m (1H, 5-H), 1.59–1.73 m (3H, 3-H, 6-H), 1.78–1.95 m (2H, 4-H, 5-H), 2.32–2.46 m (1H, 3-H), 2.32 s (3H, $C^{17}H_3$), 3.07 t (1H, 2-H, J = 8.8 Hz), 5.37 s (1H, OH), 7.53 br.s and 7.73 br.s (1H each, 14-H, 16-H), 9.82 s (1H, 18-H). ^{13}C NMR spectrum, δ_C, ppm: 12.42 (C^{10}), 16.17 (C^{17}), 20.33 (C^9), 21.30 (C^8), 27.46 (C^5), 34.21 (C^3), 40.01 (C^6), 45.45 (C^4), 45.65 (C^2), 48.23 (C^7), 49.83 (C^1); 123.52, 128.80, 129.99 (C^{11}, C^{13}, C^{15}); 128.68, 130.39 (C^{14}, C^{16}); 159.07 (C^{12}), 191.66 (C^{18}). Found, %: C 79.12; H 8.97. $C_{18}H_{24}O_2$. Calculated, %: C 79.37; H 8.88.

Enantiomerically enriched aldehydes II. A mixture of 0.3 g (0.8 mmol) of Schiff base **III** or **IV** and 5 ml of 90% aqueous acetic acid was heated for 2.5 h under reflux, 10 ml of diethyl ether was added, the organic layer was separated, washed with water (2× 7 ml) to remove acid, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by column chromatography using petroleum ether–diethyl ether as eluent.

4-Hydroxy-3-methyl-5-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}benzaldehyde (–)-(II). Yield 0.18 g (82%), enantiomeric purity 60.8%. Retention time 9.53 min. Colorless powder, mp 139–140°C (from petroleum ether), $[\alpha]_D^{23}$ = –28.3° (*c* = 0.3, $CHCl_3$).

4-Hydroxy-3-methyl-5-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}benzaldehyde (+)-(II). Yield 0.19 g (86%), enantiomeric purity 85.4%. Retention time 10.56 min. Colorless powder, mp 140–142°C (from petroleum ether), $[\alpha]_D^{23}$ = +49.4° (*c* = 0.3, $CHCl_3$).

Schiff bases III and IV. A mixture of 1.5 g (5.5 mmol) of racemic aldehyde **II** dissolved in 25 ml of toluene, 0.71 ml (5.5 mmol) of (*R*)-(+)-1-phenylethanamine and 6.5 g of molecular sieves was heated for 3.5 h under reflux while stirring in a stream of argon. The mixture was filtered through a glass filter, the precipitate (molecular sieves) was washed with $CHCl_3$, and the filtrate was evaporated. The residue was separated by fractional crystallization from hexane, the separation process being monitored by GLC.

2-Methyl-6-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}-4-{(*E*)-[(*R*)-1-phenylethylimino]methyl}phenol (III). Yield 0.4 g (19%), diastereoisomeric purity 63%. Retention time 20.1 min. Brown powder, mp 64–69°C (from hexane). IR spectrum, ν, cm^{-1}: 3408 (OH), 1640 (C=N). ^1H NMR spectrum, δ, ppm: 0.79 s (3H, $C^{10}H_3$), 0.86 s (3H, C^9H_3), 0.87 s (3H, C^8H_3), 1.28–1.52 m (2H, 5-H, 6-H), 1.59 d (3H, $C^{20}H_3$, *J* = 6.6 Hz), 1.60–1.73 m (2H, 3-H, 6-H), 1.82–1.96 m (2H, 4-H, 5-H), 2.19–2.34 m (1H, 3-H), 2.26 s (3H, $C^{17}H_3$), 3.09 t (1H, 2-H, *J* = 8.7 Hz), 4.50 q (1H, 19-H, *J* = 6.6 Hz), 5.06 br.s (1H, OH), 7.21–7.59 m (7H, 14-H, 16-H, 22-H, 22′-H, 23-H, 23′-H, 24-H), 8.26 br.s (1H, 18-H). ^{13}C NMR spectrum, δ_C, ppm: 12.38 (C^{10}), 16.11 (C^{17}), 20.37 (C^9), 21.38 (C^8), 24.80 (C^{20}), 27.52 (C^5), 34.20 (C^3), 40.05 (C^6), 45.52 (C^4), 45.73 (C^2), 48.17 (C^7), 49.78 (C^1), 69.52 (C^{19}), 123.34 (C^{13}), 126.63 and 128.32 (C^{22}, $C^{22'}$, C^{23}, $C^{23'}$, C^{24}), 127.06 and 127.76 (C^{14}, C^{16}), 128.22 (C^{15}), 128.81 (C^{11}), 145.64 (C^{21}), 155.45 (C^{12}), 159.59 (C^{18}). Found, %: C 83.31; H 8.93; N 3.87. $C_{26}H_{33}NO$. Calculated, %: C 83.15; H 8.86; N 3.73.

2-Methyl-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl}-4-{(*E*)-[(*R*)-1-phenylethylimino]methyl}phenol (IV). Yield 0.71 g (34%), diastereoisomeric purity 86%. Retention time 20.2 min. Light yellow powder, mp 127–129°C (from hexane). IR spectrum, ν, cm^{-1}: 3396 (OH), 1642 (C=N). ^1H NMR spectrum, δ, ppm: 0.79 s (3H, $C^{10}H_3$), 0.86 s (3H, C^9H_3), 0.93 s (3H, C^8H_3), 1.33–1.49 m (2H, 5-H, 6-H), 1.59 d (3H, $C^{20}H_3$, *J* = 6.6 Hz), 1.62–1.72 m (2H, 3-H, 6-H), 1.81–1.96 m (2H, 4-H, 5-H), 2.20–2.32 m (1H, 3-H), 2.27 s (3H, $C^{17}H_3$), 3.09 t (1H, 2-H, *J* = 8.7 Hz), 4.51 q (1H, 19-H, *J* = 6.6 Hz), 4.98 br.s (1H, OH), 7.20–7.54 m (7H, 14-H, 16-H, 22-H, 22′-H, 23-H, 23′-H, 24-H), 8.26 br.s (1H, 18-H). ^{13}C NMR spectrum, δ_C, ppm: 12.39 (C^{10}), 16.08 (C^{17}), 20.34 (C^9), 21.43 (C^8), 24.86 (C^{20}), 27.56 (C^5), 34.28 (C^3), 40.13 (C^6), 45.59 (C^4), 45.81 (C^2), 48.22 (C^7), 49.83 (C^1), 69.48 (C^{19}), 123.17 (C^{13}), 126.61 and 128.32 (C^{22}, $C^{22'}$, C^{23}, $C^{23'}$, C^{24}), 127.23 and 127.57 (C^{14}, C^{16}), 128.20 (C^{15}), 128.81 (C^{11}), 145.59 (C^{21}), 155.45 (C^{12}), 159.63 (C^{18}). Found, %: C 83.34; H 9.01; N 3.61. $C_{26}H_{33}NO$. Calculated, %: C 83.15; H 8.86; N 3.73.

4-Formyl-2-methyl-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl}phenyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (V). A mixture of 0.027 g (0.1 mmol) of aldehyde (+)-**II** dissolved in 3 ml of toluene, 0.032 g (0.15 mmol) of (1*S*)-camphanic acid chloride, 0.021 ml (0.15 mmol) of triethylamine, and 0.0012 g (0.01 mmol) of 4-dimethylaminopyridine was heated for 4 h under reflux with stirring in a stream of argon. The mixture was evaporated, and the residue was purified by column chromatography using petroleum ether–diethyl ether as eluent. Yield 0.039 g (87%), colorless powder, mp 142–145°C (from hexane), $[\alpha]_D^{23}$ = +9.1° (*c* = 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1798, 1764 (C=O, ester), 1706 (CH=O), 1260 (C–O). ^1H NMR spectrum, δ, ppm: 0.76–1.00 m (9H, C^8H_3, C^9H_3, $C^{10}H_3$), 1.17 s (9H, $C^{8'}H_3$, $C^{9'}H_3$, $C^{10'}H_3$), 1.23–1.34 m (1H, 5-H), 1.35–1.49 m (1H, 6-H), 1.58–1.91 m (5H, 3-H, 4-H, 5-H, 5′-H, 6-H), 1.96–2.05 m (1H, 5′-H), 2.20–2.31 m (2H, 3-H, 6′-H), 2.24 s (1H, $C^{17}H_3$), 2.50–2.60 m (1H, 6′-H), 2.82 t (1H, 2-H, *J* = 8.7 Hz), 7.60 br.s (1H, 14-H), 7.86 s (1H, 16-H), 9.94 s (1H, 18-H). ^{13}C NMR spectrum, δ_C, ppm: 9.67, 16.78, 16.95 ($C^{8'}$, $C^{9'}$, $C^{10'}$); 17.42 (C^{17}), 21.30 (C^8, C^9, C^{10}), 27.30 (C^3, C^5), 28.83 and 28.99 ($C^{5'}$, C^6), 31.82 ($C^{6'}$), 45.52 (C^4), 46.74 (C^2), 48.10 (C^1, C^7), 54.48 and 54.91

($C^{4'}$, $C^{7'}$), 90.45 ($C^{1'}$), 128.37 (C^{16}), 130.05 (C^{14}), 131.08 (C^{11}), 133.82 (C^{13}), 156.86 (C^{12}), 165.50 and 177.74 ($C^{3'}$, $C^{11'}$), 191.54 (C^{18}). Found, %: C 74.05; H 8.24. $C_{28}H_{36}O_5$. Calculated, %: C 74.31; H 8.02.

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