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Regioselective Hydrolysis of Diacetoxynaphthalenes Catalyzed by *Pseudomonas* sp. Lipase in an Organic Solvent

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Abstract—Depending on the relative positions of the acetyl groups in the aromatic rings, the *Pseudomonas* sp. lipase-catalyzed hydrolysis of diacetoxynaphthalenes in *tert*-butylmethyl ether proceeds regioselectively to afford the corresponding monoacetates.

Introduction

The lipase-catalyzed hydrolysis of esters and acylation of alcohols is nowadays a well recognized chemoenzymatic methodology with a great variety of applications in organic synthesis.[1] We have, for instance, used the *Pseudomonas* sp. lipase (PSL) for the regio and stereoselective acylation of naphthyl alcohols,[2] under the conditions of irreversible transesterification in organic solvents.[3] The chemoselectivity of the enzymatic reactions with hydroxyalkylphenols as substrates has shown that it is possible to differentiate between the two hydroxy groups in the same aromatic molecule.[4] In another report, it has been demonstrated that in the case of dihydroxynaphthalenes regioselective acylations may be carried out in the presence of the *Chromobacterium viscosum* lipase (CVL) in an organic solvent.[5] We have confirmed for other lipases,[6] including PSL, that the acylation procedure does not furnish satisfactory results in terms of conversion and regioselectivity. Thus, we decided to study the regioselectivity of the lipase-catalyzed hydrolysis of diacetoxynaphthalenes and, among the lipases tested,[6] PSL was the enzyme of choice. In an acetone/buffer system, PSL catalyzed the complete hydrolysis to diols, so we turned our attention to water-saturated solvents.[7] The best results were obtained in *tert*-butylmethyl ether (*t*-BuOMe) and we describe here the results of this investigation.

Keywords: *Pseudomonas* sp. lipase; regioselectivity; monoacetoxynaphthalenes.

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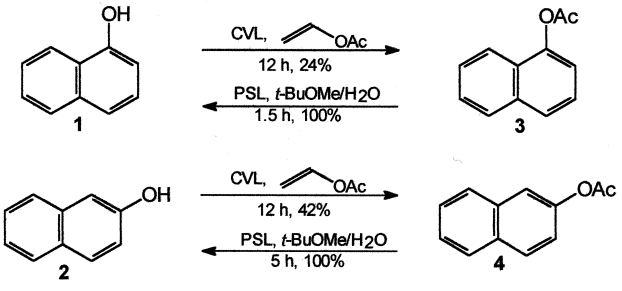
Results and Discussion

Hydrolysis of 1- and 2-acetoxynaphthalenes

Different rates of hydrolysis for naphthalene esters have been reported for α- and β-naphthyl sulphates in the presence of an immobilized sulfatase,[8] and in the cited work[5] it has been shown that in a cyclohexane–tetrahydrofuran mixture the CVL-catalyzed acylation of 1-naphthol **1** (24%, 12 h) is slower than that of the 2-isomer **2** (42%, 12 h). The PSL-catalyzed hydrolysis of the isomeric acetoxynaphthalenes **3** and **4** proceeded with the opposite regioselection, since the complete hydrolysis of **3** required 1.5 h, compared with the 5 h necessary for compound **4**. Although the two lipases have been purified from two different microorganisms, the observed reversal of the regioselectivity going from hydrolysis to esterification is consistent with results obtained from regioisomeric substrates[9] (Scheme 1).

Regioselective hydrolysis of the 1-acetoxy group (α-hydrolysis)

We then examined a series of diacetoxynaphthalenes **5a,b** and **6a–c**, that were completely hydrolyzed in 0.6–2.5 h to



Scheme 1.

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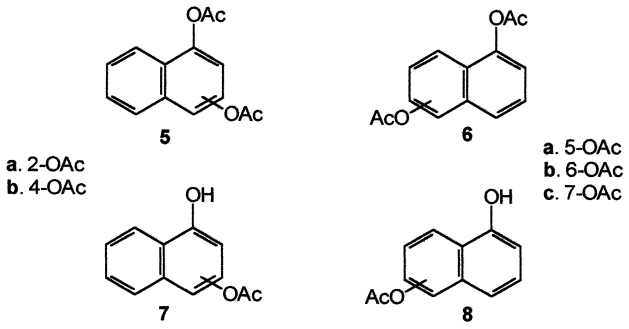


Scheme 2. The correct nomenclature of compound **7b** and **8a** is, in effect, 1-acetoxy-4-hydroxy- and 1-acetoxy-5-hydroxy-naphthalene, respectively.

the corresponding monoacetates **7a,b** and **8a–c** characterized by the fact that the 1-acetoxy group of the diacetates was regioselectively hydrolyzed (α-hydrolysis). It should be noted that the control of the chemical hydrolysis is often difficult and mixtures of monoacetates and diol are obtained. For instance, the monoacetates **7a** and **7b**, that can be obtained almost quantitively by the selective enzymatic α-hydrolysis of the diacetates **5a** and **5b**, have been obtained either as by-products[10] or prepared by controlled hydrolysis of the diacetate[11] (Scheme 2).

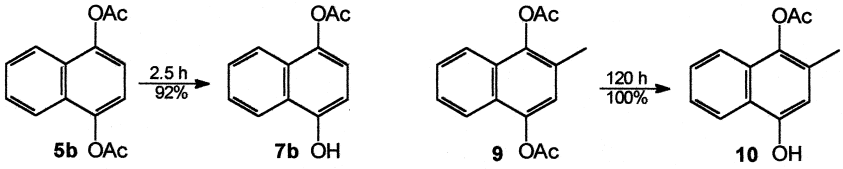
We have also prepared the 2-methyl-1,4-diacetoxynaphthalene **9** from menadione and submitted this to the enzymatic hydrolysis. Compared to the diacetate **5b** the hydrolysis of compound **9** was extremely slow (120 h) and the 4-acetoxy group was selectively hydrolyzed to afford exclusively the monoacetate **10** (Scheme 3).

This result is not unexpected since, due to the steric hindrance of the 2-methyl group, the hydrolysis of the 1-acetate of compound **9** should be less favoured. Another interesting compound is the monoacetate **8a** that was prepared from the diacetate **6a** (40% yield; 60% of diol); in fact this monoprotected naphthalenediol is an important intermediate for the synthesis of 1,5-dihydroxynaphthalene-based polyethers employed as templates for the construction of molecular assemblies or supramolecular arrays.[12] We have, therefore, tried to improve the yields of the monoacetate **8a** using various solvents and different experimental conditions without any success. The best result was obtained from the enzymatic hydrolysis of the dibutyrate **11** that afforded in *t*-BuOMe the monoester **12** in 65% isolated yield (Scheme 4).

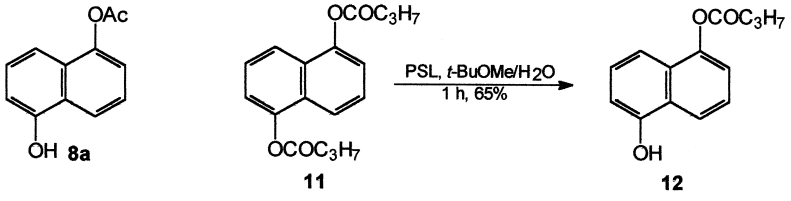
Regioselective hydrolysis of the 2-acetoxy group (β-hydrolysis)

We assumed that, according to the α-hydrolysis mechanism, the 1,3-diacetate **13** should afford the 3-acetoxy-1-hydroxynaphthalene **14** but, surprisingly, the 1-acetoxy-3-hydroxynaphthalene **15** was formed (1 h, 84%), as established by an accurate ^{1}H NMR study with NOE experiments. Enhancement of the signals at δ 7.74 and 6.90 (C-8 and C-2 hydrogens, respectively) by irradiation of the acetate signal (δ 2.44) was observed, whereas the signal at δ 6.95 (C-4 hydrogen) did not show any NOE (Scheme 5).

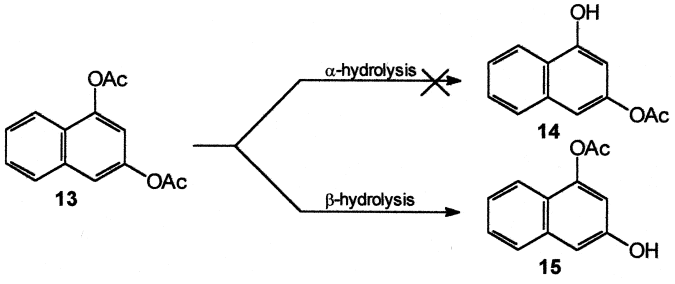
The hydrolysis of the 3-acetoxy group could constitute an unexpected example of β-hydrolysis that was probably determined by the peculiar stereoelectronic properties of



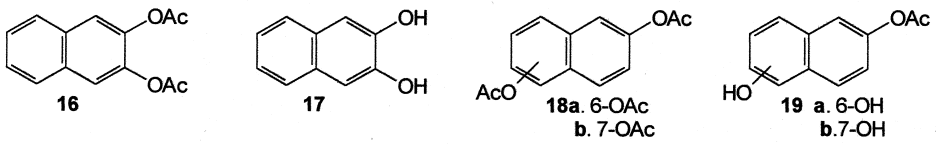
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

Table 1. Lipase-catalysed regioselective hydrolysis of diacetates (In all cases the reaction was interrupted at the disappearance of the starting diacetate. The reactions did not take place in absence of enzyme)

Substrate	Ratio[a] Monoacetate/diol	time (h)	Product
5a	100:0	1	7a
5b	92:8	2.5	7b
6a	40:60	2.5	8a
6b[b]	56:44	0.75	8b
6c[b]	80:20	0.6	8c
9	100:0	120	10
13	84:16	1	15
16	0:100	14	17
18a	95:5	1	19a
18b	48:52	1	19b

[a] Determined by HPLC analysis.
[b] Minute amounts (5–7%) of the other regioisomer were detected by HPLC.

the substrate. However, this result prompted us to investigate the hydrolysis of other diacetates that should proceed according to a β-mechanism. This was expected to be slower than the α-hydrolysis, as suggested by the behaviour of the acetates **3** and **4**. In fact, the diacetate **16** reacted completely in 14 h, but in this case only the dihydroxynaphthalene **17** was formed (Scheme 6).

From compounds **18a,b** the monoacetates **19a,b** could be obtained with chemical yields depending on the structure. The reactions were as fast as those of the α-hydrolysis examples. The results obtained from all the diacetoxynaphthalenes examined in the present work are collected in Table 1.

Conclusions

We have shown that the enzymatic hydrolysis of diacetoxynaphthalenes generally proceeds with good to excellent regioselectivity to afford monoacetates that have not been previously described or that in some cases could not be prepared by chemical methods in a straightforward manner. At present there are no plausible explanations for the results, according to the two mechanisms of regiopreference, i.e. α- versus β-hydrolysis. A rationale for the interaction of the substrate within the catalytic site of PCL, taking into account the particular shape of the molecules and stereoelectronic effects, could rely upon molecular modelling studies that have been recently carried out for the enzyme used in the present work.[13]

Experimental section

All reagents were obtained from commercial sources and used without further purification. *Pseudomonas* sp. lipase (PSL) was obtained from Amano Pharmaceutical Co. The starting naphthols were purchased (Aldrich) and the acetates **6a–c, 13, 16, 18a, 18b** were obtained by usual acetylation with acetic anhydride in pyridine. The acetates **5a, 5b, 9** were otained by reductive acetylation of the corresponding naphthoquinone[14] (Aldrich) and the butyrate **11** was obtained by reaction with butyryl chloride in dichloromethane and 4-dimethylaminopyridine as catalyst. All compounds were identified by their physical and/or spectroscopic data. Melting points were recorded on a Stuart Scientific SMP3 instrument and are uncorrected. IR spectra were recorded on a Nicolet 510 Fourier transform spectrophotometer. NMR spectra were recorded on a Bruker AM-500 spectrometer operating at 500.13 MHz for proton and 125.76 MHz for carbon. The ^{1}H NMR spectra are referenced to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.24 ppm. The ^{13}C NMR spectra are referenced to the middle peak of the solvent $CDCl_3$ at 77.00 ppm. Mass spectra (electron impact) were recorded on a Hewlett Packard 5988A spectrometer by direct inlet at an ionising voltage of 70 eV. The progress of all reactions and column chromatography were monitored by TLC and HPLC. HPLC analyses were carried out on a Merck superspher 100 RP-18 column (4 mm×15 cm) the eluent was H_2O/MeOH (50:50, v/v) except for compound **11** (H_2O/MeOH, 20:80, v/v). The flow rate was 1 ml/min and detection was at 230 nm. TLC was carried out on Merck silica gel 60 F_{254} microplates eluting with hexane/ethyl acetate (80:20, v/v).

Enzyme-mediated hydrolysis of diacetates. General procedure

PSL (200 mg) was added to a solution of the diacetate (10 mmol) in *t*-BuOMe (150 ml) containing water (20 mol eq). The suspension was stirred at 25°C and, after disappearance of the starting diacetate, the enzyme was filtered off and the solvent removed at reduced pressure. The crude product was purified by flash chromatography[15] with Merck Kieselgel-60 (230–400 mesh) eluting with hexane/ethyl acetate (80:20; v/v). Monoacetates were obtained as viscous oils or solids that were pure enough to be characterized by mp. Monoacetates **7a** and **10** did not require flash chromatography and were crystallized as described.

2-Acetoxy-1-hydroxynaphthalene (7a). Yield: 98%; white solid, mp 134–135°C (from dichloromethane/hexane) (lit.[10a] mp 136–138°C); ν_{max} (KBr) 3442, 1740, 1602 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.64 (1 H, d, *J*=8.4 Hz, 8-H), 7.56 (1 H, d, *J*=8.4 Hz, 5-H), 7.51 (1 H, d, *J*=9.1 Hz, 3-H), 7.34 (1 H, dd, *J*=8.4 and 8.4 Hz, 6-H), 7.20 (1 H, dd, *J*=8.4 and 8.4 Hz, 7-H), 7.08 (1 H, d, *J*=9.1 Hz, 4-H), 2.35 (3H, s, OCO*CH*$_3$); δ_C (125.76 MHz, $CDCl_3$) 169.76, 145.16, 136.24, 128.69, 128.05, 127.70, 126.69, 126.56, 123.35,

119.50, 118.47, 20.28; *m/z* (EI) 202 (M^+, 7), 160 (110), 131 (46), 114 (11), 103 (15), 77 (20).

1-Acetoxy-4-hydroxynaphthalene (7b). Yield: 89%, white solid, mp 131–132°C (lit.10[b] mp 130–131.5°C); ν_{max} (KBr) 3420, 1739, 1603 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.15 (1 H, dd, *J*=7.7 and 1.4 Hz, 5-H), 7.64 (1 H, dd, *J*=7.7 and 1.4 Hz, 8-H), 7.40 0(1 H, ddd, *J*=7.7, 7.7 and 1.4 Hz, 7-H), 7.37 (1 H, ddd, *J*=7.7, 7.7 and 1.4 Hz, 6-H), 6.93 (1 H, d, *J*=8.4 Hz, 2-H), 6.68 (1 H, d, *J*=8.4 Hz, 3-H), 2.41 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 170.65, 150.99, 147.88, 138.97, 127.32, 126.60, 125.14, 122.53, 120.59, 117.92, 106.87, 20.64; *m/z* (EI) 202 (M^+, 8), 160 (100), 131 (36), 115 (4), 103 (18), 77 (32).

1-Acetoxy-5-hydroxynaphthalene (8a). Yield: 40%, white solid, mp 149–150°C (lit.[16] mp 156°C); ν_{max} (KBr) 3439, 1728, 1602 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.00 (1 H, d, *J*=7.7 Hz, 2-H), 7.39 (1 H, dd, *J*=7.7 and 7.7 Hz, 3-H), 7.35 (1 H, d, *J*=8.4 Hz, 8-H), 7.22 (1 H, d, *J*=7.7 Hz, 4-H), 7.19 (1 H, dd, *J*=8.4 and 8.4 Hz, 7-H), 6.56 (1 H, d, *J*=8.4 Hz, 6-H), 2.45 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 170.35, 150.98, 147.21, 128.05, 126.69, 125.84, 124.56, 120.04, 118.64, 113.43, 109.12, 21.00; *m/z* (EI) 202 (M^+, 10), 160 (100), 131 (35), 115 (6), 103 (25), 77 (27).

6-Acetoxy-1-hydroxynaphthalene (8b). Yield: 54%, viscous oil; (Found: C, 71.4; H, 4.8. $C_{12}H_{10}O_3$ requires C, 71.28; H, 4.98%); ν_{max} (thin film) 3437, 1734, 1602 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.13 (1 H, d, *J*=9.1 Hz, 8-H), 7.47 (1 H, d, *J*=2.1 Hz, 5-H), 7.32 (1 H, d, *J*=7.7 Hz, 4-H), 7.23 (1 H, dd, *J*=7.7 and 7.7 Hz, 3-H), 7.17 (1 H, dd, *J*=9.1 and 2.1 Hz, 7-H), 6.68 (1 H, d, *J*=7.7 Hz, 2-H), 2.35 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 170.01, 151.64, 148.70, 135.15, 126.77, 125.80, 123.65, 120.02, 118.93, 118.13, 108.36, 21.14. *m/z* (EI) 202 (M^+, 12), 160 (100), 131 (40), 115 (6), 103 (29), 77 (34).

7-Acetoxy-1-hydroxynaphthalene (8c). Yield: 78%, viscous oil; (Found: C, 71.3; H, 5.1. $C_{12}H_{10}O_3$ requires C, 71.28; H, 4.98%); ν_{max} (thin film) 3440, 1741, 1604 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.68 (1 H, d, *J*=9.1 Hz, 5-H), 7.62 (1 H, d, *J*=7.7 Hz, 4-H), 7.27 (1 H, dd, *J*=7.7 and 7.7 Hz, 3-H), 7.17 (1 H, d, *J*=7.7 Hz, 2-H), 7.08 (1 H, d, *J*=2.1 Hz, 8-H), 6.99 (1 H, dd, *J*=9.1 and 2.1 Hz, 6-H), 2.36 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 170.03, 155.08, 145.34, 129.81, 129.36, 128.05, 125.84, 122.35, 118.80, 118.38, 102.82, 20.73; *m/z* (EI) 202 (M^+, 10), 160 (100), 131 (39), 115 (4), 103 (13), 77 (19).

1-Acetoxy-2-methyl-4-hydroxynaphthalene (10). Yield: 98%, brown solid, mp 122–123°C (from dichloromethane/hexane) (lit.[17] mp 120–122°C); ν_{max} (KBr) 3412, 1734, 1601 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.96 (1 H, d, *J*=8.4 Hz, 5-H), 7.63 (1 H, d, *J*=8.4 Hz, 8-H), 7.47 (1 H, dd, *J*=8.4 and 8.4 Hz, 7-H), 7.37 (1 H, dd, *J*=8.4 and 8.4 Hz, 6-H), 6.34 (1 H, s, 3-H), 2.43 (3H, s, OCOCH_3), 2.16 (3 H, s, CH_3); δ_C (125.76 MHz, $CDCl_3$) 170.34, 149.37, 137.48, 127.53, 126.93, 126.38, 124.56, 123.83, 122.09, 120.31, 110.94, 20.61, 16.26; *m/z* (EI) 216 (M^+, 10), 174 (100), 145 (12), 131 (19), 115 (25), 105 (21), 77 (18).

1-Butyryloxy-5-hydroxynaphthalene (12). Column chromatography purification (light petroleum/ethyl acetate, 90:10, v/v) of the crude product affords compound **12** (65%) as a white solid, mp 112–113°C; (Found: C, 73.1; H, 6.3. $C_{14}H_{14}O_3$ requires C, 73.03; H, 6.13%); ν_{max} (KBr) 3410, 1740, 1601 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.98 (1 H, d, *J*=7.7 Hz, 2-H), 7.38 (1 H, dd, *J*=7.7 and 7.7 Hz, 3-H), 7.33 (1 H, d, *J*=7.7 Hz, 8-H), 7.21 (1 H, d, *J*=7.7 Hz, 4-H), 7.18 (1 H, dd, *J*=7.7 and 7.7 Hz, 7-H), 6.54 (1 H, d, *J*=7.7 Hz, 6-H), 2.73 (2 H, t, *J*=7.0 Hz, OCOC$H_2$$CH_2CH_3$), 1.90 (2 H, tq, *J*=7.0 and 7.0 Hz, $OCOCH_2CH_2CH_3$) 1.12 (3 H, t, *J*=7.0 Hz, $OCOCH_2CH_2CH_3$); δ_C (125.76 MHz, $CDCl_3$) 173.25, 152.67, 147.06, 128.69, 127.39, 126.70, 125.02, 120.97, 119.18, 113.73, 109.97, 37.03, 19.33, 14.45; *m/z* (EI) 230 (M^+, 6), 160 (100), 131 (28), 115 (5), 103 (15), 77 (22).

1-Acetoxy-3-hydroxynaphthalene (15). Yield: 80%, viscous oil. ν_{max} (thin film) 3395, 1736, 1603 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.74 (1 H, d, *J*=8.4 Hz, 8-H), 7.59 (1 H, d, *J*=8.4 Hz, 5-H), 7.40 (1 H, dd, *J*=8.4 and 8.4 Hz, 6-H), 7.32 (1 H, dd, *J*=8.4 and 8.4 Hz, 7-H), 6.95 (1 H, d, *J*=2.8 Hz, 4-H), 6.90 (1 H, d, *J*=2.8 Hz, 2-H), 2.44 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 169.73, 153.05, 147.42, 135.15, 127.05, 126.58, 123.95, 122.64, 121.04, 110.73, 107.94, 21.0; *m/z* (EI) 202 (M^+, 12), 160 (100), 131 (33), 115 (4), 103 (13), 77 (22).

2-Acetoxy-6-hydroxynaphthalene (19a). Yield 93%, white solid, mp 148–149°C (lit.[18] mp 153–154°C); ν_{max} (KBr) 3402, 1743, 1604 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.60 (1 H, d, *J*=9.1 Hz, 8-H), 7.57 (1 H, d, *J*=9.1 Hz, 4-H), 7.40 (1 H, d, *J*=2.1 Hz, 1-H), 7.09 (1 H, dd, *J*=9.1 and 2.1 Hz, 3-H), 7.06 (1 H, d, *J*=<1 Hz, 5-H), 7.05 (1 H, dd, *J*=9.1 and<1 Hz, 7-H), 2.30 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 170.30, 154.29, 146.22, 132.79, 129.11, 128.51, 127.60, 121.24, 118.88, 118.31, 109.24, 21.07; *m/z* (EI) 202 (M^+, 12), 160 (100), 131 (26), 115 (2), 103 (10), 77 (15).

2-Acetoxy-7-hydroxynaphthalene (19b). Yield: 45%, white solid, mp 165–166°C (lit.[19] mp 171–172°C); ν_{max} (KBr) 3400, 1740, 1602 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.73 (1 H, d, *J*=9.1 Hz, 4-H), 7.68 (1 H, d, *J*=9.1 Hz, 5-H), 7.34 (1 H, d, *J*=2.1 Hz, 1-H), 7.05 (1 H, d, *J*=2.1 Hz, 8-H), 7.03–7.00 (2 H, m, 3-H and 6-H), 2.34 (3H, s, OCOCH_3); δ_C (125.76 MHz, $CDCl_3$) 170.20, 154.30, 147.86, 135.25, 129.22, 128.20, 118.81, 117.80, 116.76, 115.10, 108.84, 20.91. *m/z* (EI) 202 (M^+, 12), 160 (100), 131 (29), 115 (3), 103 (9), 77 (13).

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