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A CONCISE NEW SYNTHESIS OF ANGULAR FURANOCOUMARINS: ANGELICIN, OROSELONE & OROSELOL

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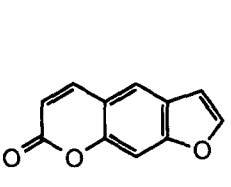
Key Words: angelicin, oroselone, oroselol

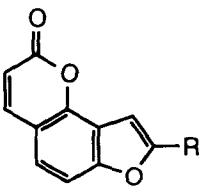
Abstract: An efficient synthesis of angular furanocoumarins has been carried out starting from dihydrobenzofuran derivatives.

Furanocoumarins have a wide range of biological properties. Many are potent photosensitizers of human skin, with valuable applications in medicine for the treatment of skin diseases, e.g., psoriasis and vitiligo.[2-4] They are also known to be phototoxic to insects, fungi, viruses and bacteria.[5-8] Psoralen (**1**) is the parent compound of a relatively large number of furanocoumarins in which the rings are linearly fused (Figure 1). Most prominent among the biological activities associated with these linear compounds is their ability to cross-link DNA via intercalation of the furocoumarin between the base pairs of the nucleic acid[9] and [2+2] photocycloaddition with the pyrimidine bases, particularly thymine.[10] Thus, undesirable side effects of photoreactions with DNA and RNA lead to mutagenicity and carcinogenicity.[11]

Figure 1



1 psoralen



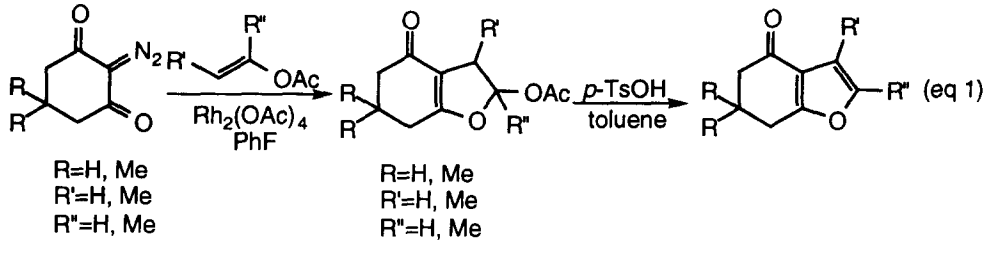
	R
2 angelicin	H
3 oroselone	$CH_2=C(CH_3)$-
4 oroselol	$(CH_3)_2(OH)C$-

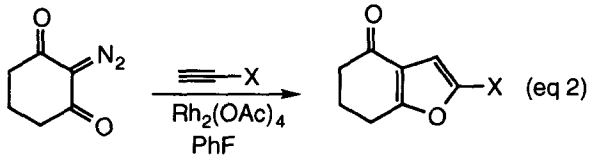
For this reason, considerable efforts have been expended to develop furocoumarins which only permit monofunctional photobinding with DNA and thereby diminish undesirable side effects. This has been accomplished by using angular furocoumarins such as angelicin (**2**), which on account of their geometry cannot crosslink with DNA,[12] and by blocking the photoreactive α-pyrone double bond with appropriate substituents [13] or by annelation of an additional aromatic ring.[14] Angelicin (**2**) is the parent compound of the much smaller and less available class of furanocoumarins that have an angular configuration and occur in a limited number of

plant species relative to the the linear class. Both classes of these compounds have evolved primarily as defense mechanisms against plant pathogens and herbivores. Recent work by Berenbaum[15] suggests that the biosynthetic pathway leading to the angular attachment of the furan ring may have been a response to selective pressures exerted by specialized herbivores that had adapted to feeding on linear furanocoumarins.

Syntheses of these angular furanocoumarins have been achieved by Claisen rearrangement of 7-allyloxycoumarin,[16] benzannulation reaction of carbene complexes with acetylenes,[17] and coupling of an acetylenic reagent with an *o*-iodohydroxycoumarin.[18] The many steps and low yields in previous work, as well as the difficulty in controlling the regiochemistry of the Claisen rearrangement have prompted a search for better syntheses. In this paper we describe a simple and convenient total synthesis of angular furanocoumarins: angelicin (**2**); oroselone (**3**); and oroselol (**4**) (Figure 1).

The rhodium-mediated decomposition of diazocarbonyl compounds has become an important method in syntheses of natural products.[19] We have recently reported that reactions of diazoketones with vinyl acetates followed by acid-catalyzed dehydration (eq 1) is an efficient route to dihydrobenzofuran derivatives as the key step in the synthesis of biologically active flavonoid nuclei such as pongamol and lanceolatin B.[20] It has been reported by Pirrung that the reactions of diazocyclohexane-1,3-dione with both cumulenes and electron-deficient or electron-rich acetylenes give only one regioisomer in moderate yield (eq 2).[21] Based on these results, we prepared the dihydrobenzofurans **5**, **6**, and **7**.

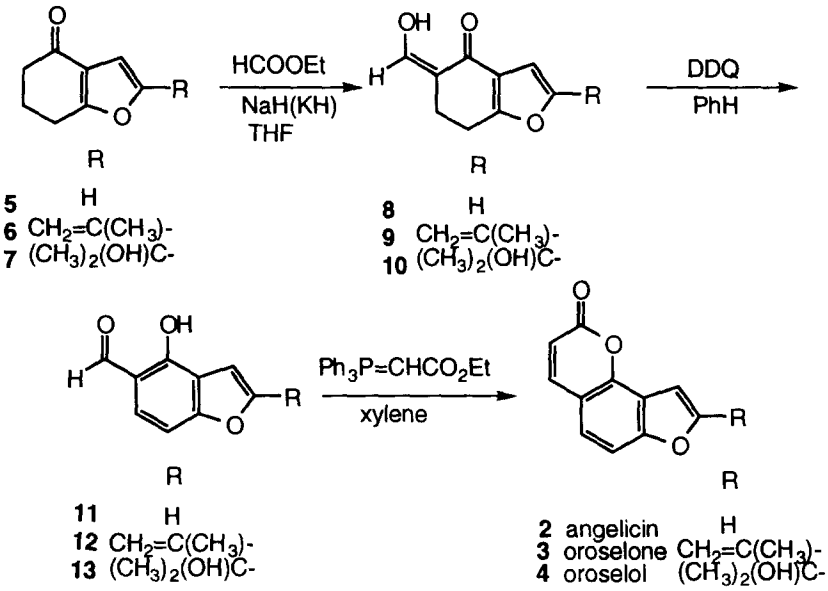




Key intermediate **5** was readily prepared in two steps from diazocyclohexane-1,3-dione. Cycloaddition with vinyl acetate using a catalytic amount (2 mol %) of Rh_2OAc_4 in fluorobenzene followed by dehydration with *p*-TsOH in toluene gave **5** in 69 % overall yield. The other substituted dihydrobenzofurans, **6** and **7**, were readily obtained in one step by reaction of diazocyclohexane-1,3-dione with isopropenyl acetylene and 2-methyl-3-butyn-2-ol using catalytic Rh_2OAc_4 (2 mol %) in fluorobenzene in 75 and 80 % yields, respectively. The dihydrobenzofuran derivatives **5**, **6**, and **7** were formylated using excess NaH in the presence of a catalytic amount of KH and ethyl formate in THF to give **8**, **9** and **10** in 92, 94, and 85 % yields, respectively (Scheme 1). The ^1H NMR spectra show a mixture of enol and keto tautomers in the ratio 2.6:1, 4.9:1, and 3.5:1. Oxidation of **8**, **9**, and **10** with DDQ in refluxing benzene proceeded smoothly to give the aromatized

compounds **11**, **12**, and **13** in 70, 72, 76 %, respectively. Next, in order to build the α–pyrone ring, we first attempted to condense aldehyde **11** with a Horner-Emmons reagent (triethyl phosphonoacetate) and base. However, this reaction was unsuccessful, possibly because of the presence of the acidic phenol group. Fortunately, we were able to introduce the α–pyrone ring in one step by reaction with (carbethoxymethylene)triphenylphosphorane in refluxing xylene.[22] Small amounts of the uncyclized α,β-unsaturated esters, as mixtures of E and Z isomers, were isolated, in addition to the major products **2**, **3**, and **4** which were obtained in 73, 71, and 79 % yields, respectively. The physical and spectroscopic properties of our products agreed well with those reported in the literature.[17, 18, 23-26]

Scheme 1



In conclusion, a route to biologically-active angular furanocoumarins has been developed from readily available dihydrobenzofurans. The process has afforded efficient syntheses of **2** (5 steps, 32 % overall yield), **3** (4 steps, 36 % overall yield), and **4** (4 steps, 41 % overall yield), which have desirable medicinal properties.

Experimental

All experiments were carried out under a nitrogen or argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Benzene and xylene were distilled from calcium hydride. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385-9 (Merck). Melting points were determined in capillary tubes on a Haake Buchler apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H

NMR) spectra were recorded on a GE Model QE-300 (300 MHz) and a Varian XL-300 (300 MHz) spectrometer, using TMS as intenal standard (0.0 ppm). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a GE Model QE-300 (75 MHz) spectrometer, and chemical shifts are reported, using $CDCl_3$ as internal standard at 77.0 ppm. IR spectra were recorded on a Bomem MB-100 Series FTIR spectrophotometer. Low-resolution EI mass spectra were performed on a Hewlett Packard 5988A spectrometer. High-resolution mass spectra (HRMS) were obtained on JEOL J MS-SX 102A spectrometer.

4,5,6,7-Tetrahydrobenzofuran-4-one (5).[20]

To a solution of rhodium acetate (192 mg, 0.434 mmol) in vinyl acetate (10.0 mL, 108 mmol) in PhF (50 mL) was added a solution of 2-diazo cyclohexane-1,3-dione (3.0 g, 22 mmol) in PhF (5 mL) at room temperature. The reaction mixture was stirred for 10 h. Evaporation and purification by silica gel chromatography with 50 % ethyl acetate in hexane as eluent afforded the acetate adduct (3.622 g, 85 %) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, J=7.5 Hz, 1H), 3.06 (dd, J=16.2, 7.5 Hz, 1H), 2.82 (d, J=16.2 Hz, 1H), 2.51 (m, 2H), 2.38 (m, 2H), 2.11 (s, 3H), 2.09 (m, 2H); IR (neat) 2947, 1759, 1647, 1405, 1361, 1261, 1213, 1163, 1138, 1050, 936 cm^{-1}

To a stirred solution of the acetate (2.0 g, 10 mmol) in dry toluene (50 mL) was added 100 mg of p-toluenesulfonic acid. The mixture was stirred at reflux for 1 h and then cooled to room temperature and added to saturated sodium bicarbonate solution (30 mL). The organic layer was separated, the aqueous layer was extracted with ether and the combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of solvent gave an oil which was purified by silica gel chromatography with 50 % ether in pentane to yield 1.125 g (81 %) of tetrahydrobenzofuran **5** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J=2.0 Hz, 1H), 6.67 (d, J=2.0 Hz, 1H), 2.89 (m, 2H), 2.50 (m, 2H), 2.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 166.7, 142.2, 120.6, 105.9, 37.2, 22.8, 22.2; IR (neat) 3131, 2948, 1677, 1595, 1516, 1447, 1414, 1294, 1242, 1184, 1119, 1026 cm^{-1}; MS (EI) 136 (M^+), 121, 108, 94, 80, 77, 63, 55, 52.

2-Isopropenyl-4,5,6,7-tetrahydrobenzofuran-4-one (6).[21]

To a solution of rhodium acetate (128 mg, 0.290 mmol) and isopropenyl acetylene (2.871 g, 43.44 mmol) in PhF (40 mL) was added a solution of 2-diazo-cyclohexane-1,3-dione (2.0 g, 15 mmol) in PhF (5 mL) at room temperature. The reaction mixture was stirred for 10 h. Evaporation and purification by silica gel chromatography with 20 % ethyl acetate in hexane as eluent afforded the tetrahydrobenzofuran **6** (1.914 g, 75 %) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.50 (s, 1H), 5.00 (s, 1H), 2.87 (m, 2H), 2.48 (m, 2H), 2.16 (m, 2H), 1.98 (s, 3H); IR (KBr) 3115, 2947, 1672, 1592, 1546, 1415, 1367, 1239, 1214, 1183, 1132, 1103, 1003, 953, 889, 818 cm^{-1}; MS (EI) 176 (M^+), 158, 148, 120, 115, 92, 77, 69, 65, 55, 51.

2-(2'-Hydroxyisopropenyl)-4,5,6,7-tetrahydrobenzofuran-4-one (7).

Reaction of 2-diazo-cyclohexane-1,3-dione (2.0 g, 15 mmol) with rhodium acetate (128 mg, 0.290 mmol) and 2-methyl-3-butyn-2-ol (3.654 g, 43.44 mmol) in PhF (40 mL) afforded **7** (2.250 g, 80 %) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1H), 2.86 (m, 2H), 2.47 (m, 2H), 2.16 (m, 2H), 1.58 (s, 6H); IR (KBr) 3394, 2963, 1665, 1599, 1576, 1449, 1413, 1365, 1219, 1179, 1128, 1090, 1055, 1005, 958, 939, 895, 848 cm^{-1}; HRMS m/z (M^+) calcd for $C_{10}H_{10}O_4$: 194.0579. Found: 194.0583

5-Hydroxymethylene-4,5,6,7-Tetrahydrobenzofuran-4-one (8).

A suspension of sodium hydride (0.371 g, 14.7 mmol, 95 %) and potassium hydride (50 mg, 35 wt % disp. in mineral oil) in dry THF (30 mL) under nitrogen was stirred and cooled in an ice-bath, whilst ethyl formate (1.2 mL, 15 mmol) was added to it. The mixture was stirred at 0 °C after which the tetrahydrobenzofuran **5** (0.40 g, 3.0 mmol) in THF (5 mL) was added dropwise to it. The reaction mixture was allowed to warm to room temperature when vigorous hydrogen evolution occurred. The reaction mixture was stirred for 2 h after which methanol (5 mL) and water (10 mL) were added to it at 0 °C. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (elution with 20 % ethyl acetate in hexane) to give **8** (0.444 mg, 92 %): ^1H NMR (300 MHz, $CDCl_3$); keto form δ 9.93 (s, 1H, CHO), 7.34 (d, J=1.8 Hz, 1H), 6.68 (d, J=1.8 Hz, 1H), 3.44 (m, 1H), 2.87 (m, 2H), 2.65 (m, 2H); enol form δ 7.34 (d, J=1.8 Hz, 1H), 7.24 (d, J=6.65 Hz, 1H, =CHOH), 6.69 (d, J=1.8 Hz, 1H), 2.87 (m, 2H), 2.65 (m, 2H); IR (neat) 3141, 2945, 2849, 1724, 1642, 1605, 1409, 1395, 1337, 1219, 1121, 1031, 968, 859 cm^{-1}; MS (EI) 164 (M^+), 163, 147, 135, 118, 107, 80, 77, 67, 63, 54, 51; HRMS m/z (M^+) calcd for $C_9H_8O_3$: 164.0473. Found: 164.0480

5-Hydroxymethylene-2-Isopropenyl-4,5,6,7-tetrahydrobenzofuran-4-one (9).

Reaction of **6** (0.50 g, 2.8 mmol) with ethyl formate (1.2 mL, 14 mmol) and NaH (KH) afforded **9** (0.545 g, 94 %) as a solid: mp 69-79 °C; ^1H NMR (300 MHz, $CDCl_3$); keto form δ 9.93 (s, 1H, CHO), 6.55 (s, 1H), 5.52 (s, 1H), 5.04 (s, 1H), 3.44 (m, 1H), 2.88 (m, 2H), 2.65 (m, 2H), 2.01 (s, 3H); enol form δ 7.24 (d, J=6.65 Hz, 1H, =CHOH), 6.52 (s, 1H), 5.52 (s, 1H), 5.04 (s, 1H), 2.88 (m, 2H), 2.65 (m, 2H), 2.00 (s, 3H); IR (KBr) 3422, 2947, 1720, 1667, 1638, 1593, 1553, 1460, 1240, 1195, 1118, 985, 935, 905, 888 cm^{-1}; MS (EI) 204 (M^+), 186, 175, 147, 135, 121, 115, 91, 77, 69, 65, 55, 51; HRMS m/z (M^+) calcd for $C_{12}H_{12}O_3$: 204.0786. Found: 204.0783

5-Hydroxymethylene-2-(2'-Hydroxyisopropenyl)-4,5,6,7-tetrahydrobenzofuran-4-one (10).

Reaction of **7** (0.220 g, 1.13 mmol) with ethyl formate (0.419 g, 5.66 mmol) and NaH (KH) afforded **10** (0.214 g, 85 %); ^1H NMR (300 MHz, $CDCl_3$); keto form δ 9.93 (s, 1H, CHO), 6.50 (s, 1H), 3.41(m, 1H), 2.86 (m, 2H), 2.64 (m, 2H), 1.59 (s, 6H); enol form δ 7.24 (d, J=6.65 Hz, 1H, =CHOH), 6.50 (s, 1H), 2.86 (m, 2H), 2.64 (m, 2H), 1.59 (s, 6H); IR (neat) 3432, 2982, 1641, 1460, 1373, 1243, 1194, 1151, 1046, 986, 958, 928 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.09

4-Hydroxybenzofuran-5-carboxaldehyde (11).

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.315 g, 1.39 mmol) was added to **8** (0.190 g, 1.16 mmol) dissolved in dry benzene (15 mL) and the mixture was heated under reflux for 3 h. The mixture was allowed to cool to room temperature and then filtered. The solids were washed with ethyl acetate and the combined filtrates were concentrared under reduced pressure. The resulting residue was dissolved in ethyl acetate (50 mL) and the solution washed with saturated aqueous sodium hydrogen carbonate (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting oil was purified by flash column

chromatography on silica gel (elution with 10 % ethyl acetate in hexane) to give **11** (0.131 g, 70 %): mp 54-56°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.60 (d, J=2.2 Hz, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H), 6.99 (d, J=2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 160.3, 157.9, 144.9, 129.7, 117.1, 115.4, 104.8, 104.7; IR (KBr) 3291, 1647, 1471, 1434, 1385, 1337, 1274, 1211, 1142, 1065, 1030, 972, 797 cm^{-1}; MS (EI) 162 (M^+), 161, 144, 133, 116, 105, 78, 77, 62, 51; HRMS m/z (M^+) calcd for $C_9H_6O_3$: 162.0317. Found: 162.0314

2-Isopropenyl-4-hydroxybenzofuran-5-carboxaldehyde (12).

Reaction of **9** (0.250 g, 1.22 mmol) with DDQ (0.333 g, 1.47 mmol) afforded **12** (0.178 g, 72 %) as a solid: mp 92-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.42 (d, J=8.6 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 6.83 (s, 1H), 5.77 (s, 1H), 5.21 (s, 1H), 2.12 (s, 3H); IR (KBr) 3445, 1650, 1587, 1460, 1434, 1388, 1341, 1314, 1270, 1207, 1158, 1110, 981, 879, 823 cm^{-1}; MS (EI) 202 (M^+), 173, 156, 131, 115, 91, 77, 63, 51; HRMS m/z (M^+) calcd for $C_{12}H_{10}O_3$: 202.0630. Found: 202.0633

2-(2'-Hydroxyisopropenyl)-4-hydroxybenzofuran-5-carboxaldehyde (13).

Reaction of **10** (0.190 g, 0.850 mmol) with DDQ (0.233 g, 1.03 mmol) afforded **13** (0.143 g, 76 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.42 (d, J=8.5 Hz, 1H), 7.10 (d, J=8.5 Hz, 1H), 6.80 (s, 1H), 1.68 (s, 6H); IR (KBr) 3448, 2965, 1650, 1455, 1376, 1322, 1276, 1260, 1205, 1157, 1094, 1074, 1046, 967, 848 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{12}O_4$: 220.0735. Found: 220.0740

Angelicin (2).

To the aldehyde **11** (0.10 g, 0.62 mmol) in dry xylene (10 mL) was added carbethoxymethylenetriphenylphosphorane (0.258 g, 0.740 mmol) and the mixture was heated under reflux for 10 h. Evaporation and purification by silica gel chromatography with 20 % ethyl acetate in hexane as eluent afforded **2** (84 mg, 73 %) as a solid: mp 134-135 °C, lit mp 137-137.5 °C;[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81(d, J=9.6 Hz, 1H), 7.69 (d, J=2.2 Hz, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.38 (d, J=8.5 Hz, 1H), 7.13 (d, J=2.0 Hz, 1H), 6.39 (d, J=9.5 Hz, 1H); IR (KBr) 3443, 3163, 1737, 1655, 1618, 1477, 1402, 1375, 1337, 1272, 1252, 1149, 1057, 1040, 998, 832 cm^{-1}

Oroselone (3).

Reaction of **12** (0.151 g, 0.740 mmol) with carbethoxymethylenetriphenylphosphorane (0.310 g, 0.890 mmol) afforded **3** (0.119 g, 71 %) as a solid: mp 177-178 °C, lit mp 164-166 °C,[18a] 175.5-180 °C,[18b] 178-180 °C,[25] 179-180 °C;[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=9.6 Hz, 1H), 7.35 (d, J=8.5 Hz, 1H), 7.33 (d, J=8.5 Hz, 1H), 6.97 (s, 1H), 6.37 (d, J=9.6 Hz, 1H), 5.83 (s, 1H), 5.25 (s, 1H), 2.14 (s, 3H); IR (KBr) 3437, 1723, 1617, 1553, 1444, 1406, 1374, 1154, 1123, 1020, 907, 831, 812 cm^{-1}; MS (EI) 226 (M^+), 198, 183, 155, 141, 115, 75, 63.

Oroselol (4).

Reaction of **13** (0.130 g, 0.590 mmol) with carbethoxymethylenetriphenylphosphorane (0.247 g, 0.710 mmol) afforded **4** (0.114 g, 79 %) as a solid: mp 149-150 °C, lit mp 149-151°C,[18a] 153.5-154 °C,[18b] 156-157

°C,[24] 155-158 °C,[25] 149-150 °C;[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=9.6 Hz, 1H), 7.36 (d, J=8.5 Hz, 1H), 7.34 (d, J=8.5 Hz, 1H), 6.94 (s, 1H), 6.38 (d, J=9.6 Hz, 1H), 1.70 (s, 6H); IR (KBr) 3453, 2986, 1725, 1615, 1446, 1372, 1274, 1142, 1020, 955, 831 cm^{-1}

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