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# Crocipodin, a benzotropolone pigment from the mushroom *Leccinum crocipodium* (Boletales)

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ABSTRACT

Crocipodin, an unusual benzotropolone pigment, has been isolated from the fruit bodies of the mushroom *Leccinum crocipodium*. Its structure was determined by spectroscopic methods, particularly 2D NMR spectroscopy. The structure was confirmed by total synthesis, starting from 4-bromocatechol and gallic acid.



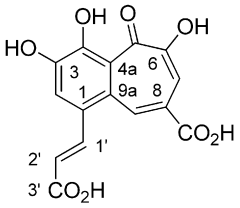
## 1. Introduction

*Leccinum crocipodium* (=*L. nigrescens*) (German: Gelber Rauhfuß) is a rare thermophilic bolete, found on loamy soil in association with oak and hornbeam trees. The mushroom is easily recognized by its bright yellow pores and the darkening of its flesh where cut or bruised. In this publication we describe the isolation, structure elucidation and synthesis of crocipodin, the orange-red pigment responsible for the yellow appearance of this mushroom.

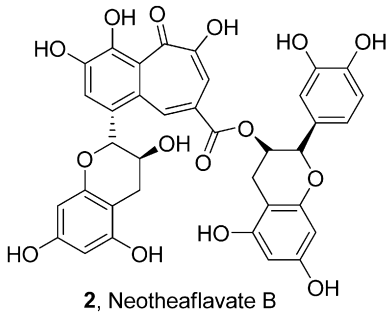
## 2. Results and discussion

### 2.1. Isolation and structure elucidation

For an investigation of the pigments, the lyophilized and defatted fruit bodies of *L. crocipodium* were extracted with acidified acetone. Chromatography of the concentrated extract with acetone on Sephadex LH-20 furnished a brownish orange fraction, which on repeated chromatography yielded almost pure crocipodin (**1**, 0.14% of dry weight). The orange-red pigment showed intense UV–vis maxima at 282 and 400 nm. In the IR spectrum (KBr), a carbonyl band at 1701 $cm^{-1}$ and aromatic vibrations at 1634 and 1602 $cm^{-1}$ could be recognized, in addition to a broad OH absorption at 3433 $cm^{-1}$.




**1**, Crocipodin




**2**, Neotheaflavate B

Crocipodin (**1**) exhibited a rather simple $^1H$ NMR spectrum. The spectrum displayed two doublets at $\delta_H$ 6.33 and 8.16 in DMSO-$d_6$, which could be assigned to a *trans* double bond ($^3J_{H,H}$=15.5 Hz). In addition, three signals for aromatic protons were present, a singlet at $\delta_H$ 7.69 and two broadened singlets at 7.68 and 8.60, which were resolved into two 1.5 Hz doublets in acetone-$d_6$. The $^{13}C$ NMR spectrum exhibited 15 resonances, which, according to DEPT measurements, could be assigned to five methine carbons at $\delta_C$ 115.8 ($\delta_H$ 7.68), 121.8 ($\delta_H$ 7.69), 123.5 ($\delta_H$ 6.33), 131.8 ($\delta_H$ 8.60), and 141.8 ($\delta_H$ 8.16), and 10 quaternary carbons at $\delta_C$ 121.5, 125.0, 126.8, 129.3, 148.2, 153.1, 154.3, 167.2, 167.8, and 185.6.

The EI mass spectrum of crocipodin (**1**) showed a molecular ion at *m*/*z* 318. After silylation with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA), a weak molecular peak at *m*/*z* 678 was

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visible, indicating the formation of a pentakis(trimethylsilyl) derivative. Unfortunately, no high-resolution mass spectra could be obtained, probably due to impurities in the samples. Assuming that crocipodin contains only oxygens as heteroatoms, the molecular formula $C_{15}H_{10}O_8$ was proposed, incorporating five methine carbons, seven quaternary carbons, three CO moieties and five hydroxy groups.

From the HMBC and NOESY correlations (Fig. 1) structure **1** could be assigned to crocipodin. Especially informative were the nuclear Overhauser effects between the side-chain proton H-1′ and H-9, and between H-2′ and H-2. From the HMBC correlations of H-2, the substitution of the benzene ring could be determined, and the correlations of the *meta*-coupled protons H-7 and H-9 allowed the assignment of the carbons of the tropolone ring. A comparison of the $^1H$ and $^{13}C$ NMR signals of crocipodin (**1**) with the corresponding resonances of the tea pigment neotheaflavate B (**2**)[1] shows excellent agreement.

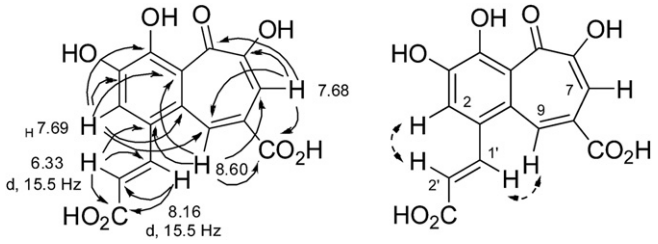
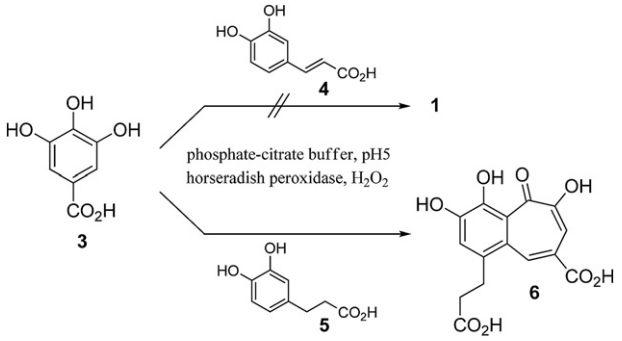



**Fig. 1.** Selected HMBC (left) and NOESY correlations (right) for **1** (in DMSO-$d_6$).

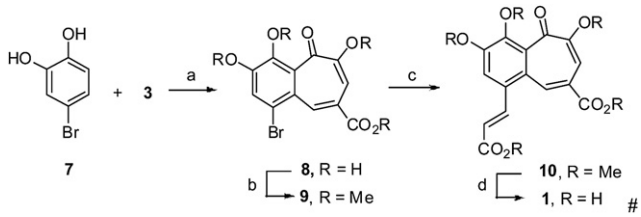
## 2.2. Total synthesis

The structure of crocipodin (**1**) points to a simple biosynthesis via oxidative condensation of gallic acid (**3**) and caffeic acid (**4**) (Scheme 1), analogous to the formation of 3,4,6-trihydroxybenzotropolones from catechols and pyrogallol.[1,2] However, neither the oxidation with potassium iodate[2a] nor the enzymatic conditions previously described by Sang et al.[1] were successful when applied to our system. This may be attributed to the electron-withdrawing effect of the conjugated carboxyl group in caffeic acid.[3] In accordance with this proposal, dihydrocrocipodin (**6**) was formed from dihydrocaffeic acid (**5**) and gallic acid (**3**) upon treatment with horseradish peroxidase and $H_2O_2$ in buffer solution at pH 5 (Scheme 1).[1]




**Scheme 1.** Attempted synthesis of crocipodin (**1**) and synthesis of dihydrocrocipodin (**6**).

In order to avoid these difficulties, a three-step synthesis of crocipodin (**1**) was envisaged, commencing from the known bromo-compound **8**,[4] which can be conveniently obtained by oxidative condensation of 4-bromocatechol (**7**) with gallic acid (**3**) in the presence of $H_2O_2$ and horseradish peroxidase (Scheme 2).[1] Methylation of **8** afforded the permethyl derivative **9**, which was submitted to Heck conditions with methyl acrylate to produce the desired (*E*)-propenoate **10** in high yield. In the final step, the methoxy groups were cleaved with $BBr_3$ to provide crocipodin (**1**). The synthetic product was identical with natural crocipodin by comparison of the IR, NMR, and mass spectra as well as co-chromatography in the HPLC.




**Scheme 2.** Synthesis of crocipodin (**1**). Reagents and conditions: (a) 3% aq $H_2O_2$, horseradish peroxidase, acetone/phosphate/citrate buffer, pH 5, 75%; (b) MeI, anhyd $K_2CO_3$, DMF, 98%; (c) $H_2C{=}CHCO_2Me$, $Pd(OAc)_2$, anhyd $K_2CO_3$, *n*-$Bu_4NCl$, DMF, $N_2$, 100 °C, 2h, 91%; (d) $BBr_3$, $CH_2Cl_2$, 75%.

## 3. Conclusion

The structure of crocipodin (**1**) has been elucidated from spectroscopic evidence and confirmed by total synthesis. The occurrence of a benzotropolone pigment in *Leccinum*[5] is exceptional. Other yellow species, such as the North American *L. rugosiceps* ssp. *corrugis* and *L. rubropunctum* owe their color to polyhydroxypulvinic acids.[6] Benzotropolones have not been isolated from boletes previously, however, they are known from the agaric *Tricholoma aurantium*[7] and the polypore *Fomes fomentarius*.[8]

## 4. Experimental section

### 4.1. General procedures and methods

Melting points (uncorrected): Büchi MP B-540 apparatus. UV–vis spectra: Perkin–Elmer Lambda-16 spectrometer. IR spectra: Perkin–Elmer FT 1000 Fourier spectrometer and Perkin–Elmer FTIR System equipped with a Smith Dura sample IR II ATR unit. The synthetic samples were measured as neat materials. Abbreviations: ss, very strong; s, strong; m, medium; w, weak; br, broad. NMR spectra: Bruker AMX 600 (used for natural **1**), Varian Mercury spectrometers operating at 300 MHz, 400 MHz, and 600 MHz (used for the synthetic samples). Chemical shifts in $\delta$ [ppm] relative to DMSO-$d_6$ ($\delta_H$=2.49, $\delta_C$=39.7) or acetone-$d_6$ ($\delta_H$=2.04, $\delta_C$=29.8) as internal standard. MS (EI, ESI): Finnigan MAT 90, Finnigan MAT 95 Q, and Varian MAT 711 spectrometer. TLC: Silica gel 60 $F_{254}$ aluminum foils (Merck). Column chromatography: Silica gel 60 (40–63 μm, Merck), Sephadex LH-20 (Pharmacia). Analytical HPLC: Waters M 6000A pump with gradient controller and photodiode array detector M 990 equipped with a Knauer Lichrosorb RP-18 column (7 μm, 250×4 mm). 4-Bromocatechol and horseradish peroxidase were purchased from Sigma–Aldrich.

### 4.2. Mushroom collection

*L. crocipodium* (Letellier) Watling was collected in August 1998 in Kist near Würzburg, Germany, and in Obernburg/Waldhaus, Germany (leg. N. Arnold/L. Kahner, det. N. Arnold).

### 4.3. Isolation procedure

The lyophilized mushrooms (30 g) were powdered, defatted with petroleum ether (40–60 °C), and extracted exhaustively with

acetone containing a few drops of concd HCl (pH=5). Concentration of the extracts under reduced pressure yielded a red-brown residue (5 g), which was dissolved in acetone (5 mL) and chromatographed on Sephadex LH-20 (eluent acetone). The first, light brown, fraction contained mainly ergosterol, the second fraction exhibited a blue fluorescence, and the third, brownish orange, fraction contained the orange-red pigments.

The third fraction was repeatedly chromatographed with acetone on Sephadex LH-20, and the resulting orange-red solid was distributed between EtOAc and $H_2O$. The aqueous phase was extracted with EtOAc (3×), and the combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure to yield crocipodin (**1**, 42 mg, 0.14%) as an orange-red solid. According to the $^1$H NMR spectrum, the compound was contaminated with traces of unidentified impurities; TLC: $R_f$=0.50 (silica gel; toluene/$HCO_2Et$/$HCO_2H$, 10:5:3); HPLC: $t_R$=23.0 min (RP-18; solvent system A: acetonitrile/water, 1:9+0.5% TFA; solvent system B: acetonitrile; gradient start: 100% A, within 60 min–100% B, then 10 min 100% B; flow rate: 1 mL/min); UV–vis (MeOH, qualitative): $\lambda_{max}$=282, 400 nm; IR (KBr): 3433 (br, ss), 1701 (s), 1634 (s), 1602 (m), 1538 (w), 1447 (m), 1402 (m), 1331 (m), 1237 (s), 1094 (w), 1025 (m), 996 (m); $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 6.33 (d, $J$=15.5 Hz, 1H, 2′-H), 7.68 (br s, 1H, 7-H), 7.69 (s, 1H, 2-H), 8.16 (d, $J$=15.5 Hz, 1H, 1′-H), 8.60 (br s, 1H, 9-H), ~10.0 (very br, OH), ~12.8 (very br, OH), 15.2 (br, OH). The OH signals experienced strong broadening due to exchange with residual $H_2O$; $^1$H NMR (600 MHz, acetone-$d_6$): $\delta$ 6.46 (d, $J$=15.5 Hz, 1H, 2′-H), 7.81 (s, 1H, 2-H), 7.89 (d, $J$=1.5 Hz, 1H, 7-H), 8.36 (d, $J$=15.5 Hz, 1H, 1′-H), 8.86 (d, $J$=1.5 Hz, 1H, 9-H), 10.0 (br, 2H, OH), 10.4 (br, 1H, OH), 12.8 (br, 2H, OH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): 115.8 (C-7), 121.5 (C-4a), 121.8 (C-2), 123.5 (C-2′), 125.0 (C-8), 126.8 (C-9a), 129.3 (C-1), 131.8 (C-9), 141.8 (C-1′), 148.2 (C-3), 153.1 (C-4), 154.3 (C-6), 167.2 (3′-$CO_2H$), 167.8 (8-$CO_2H$), 185.6 (C-5); EI-MS: $m/z$=318 $[M]^+$, 300 $[M-H_2O]^+$, 272, 255, 244, 227, 201, 183, 159, 155, 135, 126 (impurities in the sample did not allow to determine correct intensities).

Treatment of **1** (1 mg) with MSTFA (3 drops) yielded, after 10 min, the pentakis(trimethylsilyl) derivative; EI-MS: $m/z$ (%)=678 (2, $M^+$), 663 (100 $[M^+-CH_3]$), 545 (7), 501 (1), 457 (2), 147 (43), 127 (11).

### 4.4. Synthesis of dihydrocrocipodin (6)

Gallic acid (**3**, 1.87 g, 11.0 mmol) and dihydrocaffeic acid (**5**, 3.01 g, 16.5 mmol) were dissolved in acetone/pH 5.0 phosphate/citrate buffer (1:10 v/v, 50 mL). Then, horseradish peroxidase type I (25 ku) was added in three portions, 4 mg each time. Additionally, every 15 min and four times per period, 3% aq $H_2O_2$ (1.2 mL) was added. During the reaction the mixture was shaken occasionally. The precipitate **6** was collected by filtration and dried under high vacuum overnight to yield compound **6** (0.74 g, 21%) as a red solid, mp>290 °C (dec). IR (neat): 3674 (br), 3392 (br), 3220 (w), 1740 (ss), 1646 (s), 1517 (s), 1454 (m), 1401 (m), 1362 (ss), 1290 (ss), 1150 (m), 1089 (m), 972 (ss), 891 (m), 855 (m); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.55 (t, $J$=7.7 Hz, 2H), 3.18 (t, $J$=7.7 Hz, 2H), 7.43 (s, 1H), 7.61 (d, $J$=1.3 Hz, 1H), 8.57 (d, $J$=1.3 Hz, 1H), 9.73 (s, 1H), 10.26 (s, 1H), 12.71 (br, 2H), 14.70 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=30.3, 35.5, 115.7, 122.2, 123.6, 124.6, 126.1, 132.5, 135.2, 148.5, 150.4, 153.9, 168.3, 173.7, 185.9; HRMS ($ESI^-$) calcd for $C_{15}H_{11}O_8$ [M–H]: 319.0453, found: 319.0456.

### 4.5. Synthesis of crocipodin (1)

*4.5.1. 1-Bromo-3,4,6-trihydroxy-5-oxo-5H-benzocycloheptene-8-carboxylic acid (**8**).* Gallic acid (**3**, 0.6 g, 3.53 mmol) and 4-bromocatechol (**7**, 0.96 g, 5.08 mmol) were dissolved in acetone/pH 5.0 phosphate/citrate buffer (1:10 v/v, 50 mL). Horseradish peroxidase type I (25 ku) was added in three portions, 2 mg each time. Additionally, every 15 min and four times per period, 3% $H_2O_2$ (0.6 mL) was added to the reaction mixture, which was shaken by hand occasionally. The red precipitate was collected by filtration and washed with water. After drying under high vacuum overnight, **8** (0.86 g, 75%) was obtained as a red powder; dec>300 °C (lit.[4] mp 303–305 °C); IR (neat): 3674 (br), 3385 (br), 3220 (w), 1648 (s), 1520 (s), 1487 (w), 1456 (w), 1401 (w), 1361 (s), 1288 (s), 1150 (w), 1088 (w), 969 (m) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.57 (d, $J$=1.4 Hz, 1H), 7.82 (s, 1H), 8.86 (d, $J$=1.4 Hz, 1H), 9.96 (s, 1H), 10.72 (s, 1H), 12.53 (br, 1H), 14.79 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 115.6, 118.8, 122.1, 125.3, 126.0, 126.8, 135.9, 149.1, 152.0, 154.5, 168.0, 185.7; HRMS ($ESI^-$) calcd for $C_{12}H_6BrO_6$ [M–H]: 324.9348, found: 324.9349.

*4.5.2. Methyl 1-bromo-3,4,6-trimethoxy-5-oxo-5H-benzocycloheptene-8-carboxylate (**9**).* To a suspension of compound **8** (0.10 g, 0.31 mmol) and anhyd $K_2CO_3$ (0.51 g, 3.67 mmol) in anhyd DMF (4 mL), maintained at 0 °C under argon, was added dropwise iodomethane (0.15 mL, 2.45 mmol), and the mixture was stirred overnight at room temperature. Then, the reaction was quenched with water (10 mL) and the mixture stirred for 20 min. After addition of EtOAc (100 mL), the organic phase was washed with water (3×100 mL), and the combined aqueous phases were extracted with EtOAc (200 mL). Then, the combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude yellow product was purified by column chromatography (hexanes/$Et_2O$, 2:1) to afford **9** (115 mg, 98%) as a yellow solid; mp 179–180 °C; IR (neat): 3392 (br), 3225 (w), 2939 (w), 1715 (s), 1658 (w), 1620 (w), 1448 (m), 1364 (s), 1289 (s), 1219 (m), 1150 (m), 1091 (m), 1031 (m), 968 (m), 858 (w), 709 (m); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.86 (s, 3H), 3.94 (s, 3H), 3.97 (s, 6H), 6.71 (s, 1H), 7.50 (s, 1H), 8.44 (d, $J$=1.0 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 52.9, 56.5, 62.7, 65.2, 102.1, 120.1, 120.6, 124.9, 125.4, 132.3, 134.1, 145.9, 156.7, 154.4, 167.5, 185.9; HRMS (EI) calcd for $C_{16}H_{15}BrO_6$: 382.0052, found: 382.0030.

*4.5.3. Methyl (E)-3-(3,4,6-trimethoxy-8-methoxycarbonyl-5-oxo-5H-benzocyclohepten-1-yl)-2-propenoate (**10**).* A mixture of compound **9** (50 mg, 0.13 mmol), methyl acrylate (60 mg, 0.65 mmol), $Pd(OAc)_2$ (3 mg, 0.01 mmol), anhyd $K_2CO_3$ (30 mg, 0.22 mmol), and tetrabutylammonium chloride (50 mg, 0.17 mmol) in anhyd DMF (4 mL) was placed in a scintillation vial and purged for 5 min with nitrogen. Then, the mixture was heated to 100 °C for 2 h in the sealed vial. After being cooled to room temperature, the reaction mixture was diluted with $CH_2Cl_2$ (30 mL) and washed with water (3×30 mL). The combined aqueous phases were *re*-extracted with $CH_2Cl_2$ (2×50 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting yellow oil was submitted to column chromatography ($Et_2O$/hexanes, 1:1) to yield **10** (46 mg, 91%) as a yellow solid; mp 152 °C; IR (neat): 3394 (br), 2955 (m), 1698 (ss), 1665 (ss), 1621 (ss), 1584 (m), 1567 (m), 1451 (w), 1426 (m), 1310 (s), 1273 (s), 1219 (ss), 1187 (w), 1150 (w), 1093 (ss), 1033 (ss), 1007 (s), 976 (s), 900 (w), 859 (w), 759 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 3.85 (s, 6H), 3.92 (s, 3H), 3.98 (s, 6H), 6.34 (d, $J$=15.7 Hz, 1H), 6.68 (s, 1H), 7.30 (s, 1H), 8.21 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 52.0, 52.9, 56. 2, 56.3, 62.7, 101.8, 114.4, 122.5, 125.0, 125.4, 128.7, 131.0, 134.3, 141.9, 147.8, 154.3, 157.0, 166.6, 167.5, 186.6; HRMS (EI) calcd for $C_{20}H_{20}O_8$: 388.1158, found: 388.1140.

*4.5.4. (E)-3-(8-Carboxy-3,4,6-trihydroxy-5-oxo-5H-benzocyclohepten-1-yl)-2-propenoic acid, crocipodin (**1**).* To a stirred solution of **10** (58 mg, 0.15 mmol) in dry $CH_2Cl_2$ (1 mL), was added dropwise a 1 M solution of $BBr_3$ in $CH_2Cl_2$ (3 mL, 3.0 mmol) at room temperature. After 18 h of stirring, the reaction mixture was carefully

quenched upon dropwise addition of satd aq $NaHCO_3$ (30 mL). The resulting biphasic mixture was stirred for 10 min at room temperature and washed with EtOAc (2×20 mL). After phase separation, the aqueous phase was acidified with 1 N HCl and extracted with EtOAc (3×30 mL). The combined organic phases were washed with brine (50 mL), dried over $Na_2SO_4$, and concentrated. The resulting red residue was purified by HPLC: $t_R$=23.8 min (RP-18; solvent system A: water+0.5% TFA; solvent system B: MeOH; gradient start: 55% A, within 25 min–80% B, then 10 min 80% B; flow rate 1 mL/min) to yield crocipodin (**1**) as a brown-orange solid (35 mg, 73%); dec>300 °C; UV–vis (MeOH): $\lambda_{max}$ (ε) 280 (3.67), 400 (2.95), 460 (sh, 2.49); IR (neat): 3381 (ss), 3250–2875 (br), 2644 (w), 1704 (ss), 1633 (s), 1590 (s), 1512 (w), 1448 (s), 1419 (s), 1334 (s), 1260 (s), 1244 (s), 1191 (s), 1080 (m), 1000 (w), 948 (w), 861 (m), 769 (w), 696 (m); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.31 (d, $J$=15.4 Hz, 1H), 7.61 (s, 1H), 7.68 (s, 1H), 8.13 (d, $J$=15.4, 1H), 8.56 (s, 1H), 9.97 (br, 1OH), 10.51 (br, 1OH), 15.09 (sharp, 1H, 4-OH), 2 OH signals not visible; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 115.8, 121.8, 122.0, 123.8, 124.6, 126.9, 129.7, 132.2, 142.0, 148.6, 153.4, 154.6, 167.5, 168.0, 185.9; MS (ESI$^-$) $m/z$ (%)=339 [M–2H+Na] (30), 317 [M–H] (41), 315 (6), 273 (6), 194 (7); HRMS (ESI$^-$) calcd for $C_{15}H_9O_8$ [M–H]: 317.0297, found: 317.0298.

## Acknowledgements

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## Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.12.060. These data include MOL files and InChIKeys of the most important compounds described in this article.

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