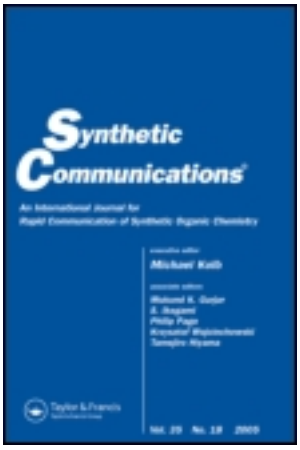

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Synthesis of Bacterial Metabolites of Polycyclic Aromatic Hydrocarbons: Benzochromenones, o-Carboxyvinylnaphthoates, and o-Substituted Aryl-α-Oxobutenoates

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Synthesis of Bacterial Metabolites of Polycyclic Aromatic Hydrocarbons: Benzochromenones, *o*-Carboxyvinylnaphthoates, and *o*-Substituted Aryl-α-Oxobutenoates

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Abstract: Bacterial metabolites of phenanthrene and anthracene include benzochromenones, *o*-carboxyvinylnaphthoates, and *o*-substituted aryl α-oxobutenoates, which were synthesized with the Wittig reaction, the Heck reaction, and coupling of aromatic aldehyde with pyruvate.

Keywords: Polycyclic aromatic hydrocarbon, metabolite, benzochromene carboxyvinylnaphthoate, oxobutenoate

Polycyclic aromatic hydrocarbons (PAHs) are global contaminants. Numerous bacterial species have been reported as PAH degraders. Phenanthrene (**1**) and anthracene (**2**) are frequently used as model compounds in bacterial metabolism studies. Bacterial degradation usually starts with dioxygenation on 1,2-, 3,4-, or 9,10-C of phenanthrene and 1,2-C of anthracene (Figure 1).[1,2] Dihydrodiols from dioxygenation are metabolized to benzochromenones (**3**, **6**) and *o*-hydroxynaphthyl-α-oxobutenoate (**4**, **7**), and *o*-carboxyvinylnaphthoates (**5**, **8**), via *meta*- and *ortho*-cleavage

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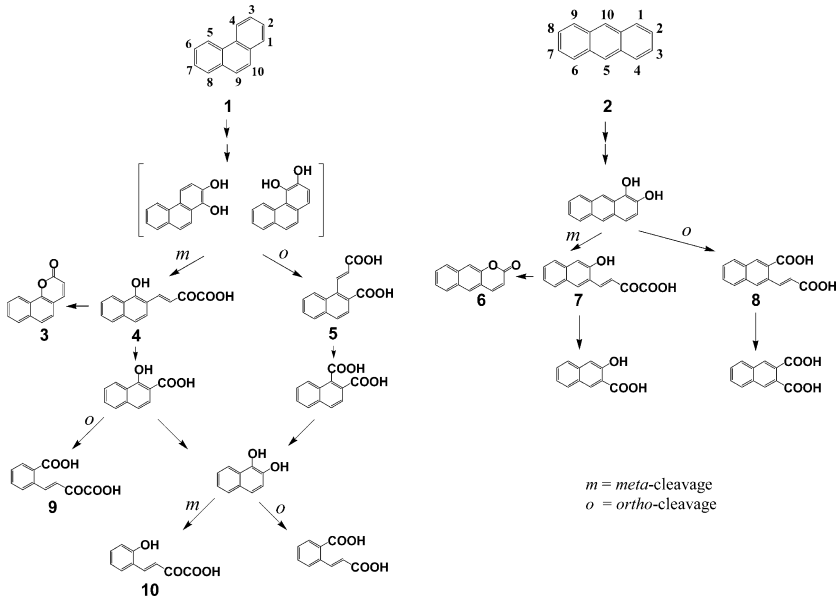
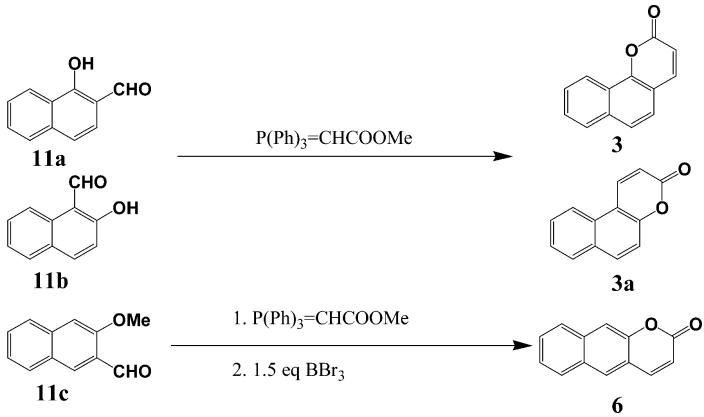


Figure 1. Bacterial metabolism of phenanthrene (**1**) and anthracene (**2**) via 3,4- and 1,2-dioxygenation.

pathways, respectively. Further degradations result in the formation of 2-(3-carboxy-3-oxoprop-1-enyl)-benzoic acid (**9**), *o*-carboxycinnamic acid, or 4-(2-hydroxyphenyl)-2-oxobut-3-enoic acid (**10**). These metabolites are usually identified by gas or liquid chromatography coupled with mass spectrometry (GC-MS or LC-MS) in their intact form or their ether/ester derivatives. However, the authentic standards of the intact chemicals (**1**–**10**) or their ether/ester derivatives are not commercially available, which limits the detailed study of their role in bacterial metabolism. In addition, their stereochemistry (*E*- or *Z*-) is also vague. This study was intended to provide proper synthetic methods of these metabolites or their derivatives for more detailed biochemical studies and instrumental analysis.

Benzochromenones and coumarins are prepared by several methods including a) coupling of trimethylsilylketene with *o*-hydroxynaphthaldehyde,[3] b) cyclization of *o*-substituted cinnamates,[4,5] and c) thermal oxidation and cyclization of *o*-hydroxyarylpropanoic acid.[6]

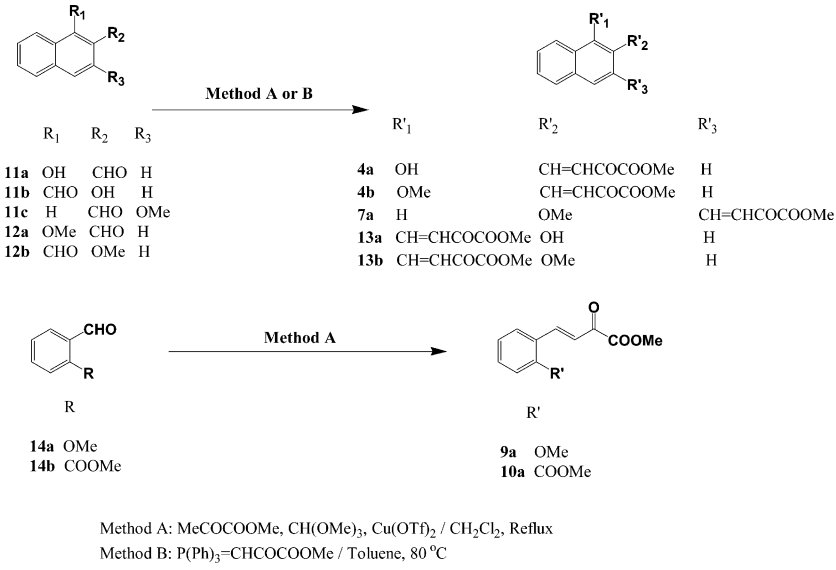
Benzochromenones **3** and **3a**, which are common metabolites of phenanthrene,[1] were prepared from *o*-hydroxynaphthaldehyde (**11a** and **11b**) through a Wittig reaction (Scheme 1). *2H*-Benzo[*g*]chromen-2-one (**6**) was synthesized from **11c**.[7] The reaction yields were 70, 78, and 69% for **3, 3a**, and **6**, respectively. Mass spectra and melting points well coincided with those in the literature.[1,2,7] Crude reaction mixtures of **3** and **3a** were analyzed with GC-MS. Approximately 20–30% of the aldehydes were



Scheme 1.

recovered as unreacted starting materials. *o*-Hydroxynaphthylpropenoates, possible Wittig reaction products, were found only at the initial stage of reaction (<2 h of reflux). Dubuffet et al.[7] prepared **3** and **3a** from *o*-methoxynaphthaldehyde via a Wittig reaction, followed by boron-mediated dealkylative ring closure, the methods of which were applied on the preparation of **6** in this study. Boron trihalide, which is very toxic and air sensitive, is usually used for the ring closure of *o*-methoxyaryl propenoates.[7,8] In this study, *o*-methoxynaphthldehyde was used for the synthesis **3** and **3a** instead of *o*-hydroxy analogues. Toluene (bp 110°C), a commonly used solvent,[7] was replaced by higher boiling xylene (bp 138°C). In the preliminary experiments for solvent selection, the reaction yields in benzene and toluene were 10 and 45% of **3**, respectively. The results suggest that higher boiling-point solvents may increase thermal rearrangement from *o*-hydroxynaphthyl propenoates to benzochromenones.

Several synthetic methods have been reported for the preparation of aryl-α-oxobutenoic acids.[9,10] The method of Dujardin et al.[9] was very simple but required a long reaction time (usually >36 h of reflux). Coupling of α-ketoylide to arylaldehyde is another possible choice of the synthesis of aryl-α-oxobutenoates.[11] The previous studies, however, were limited to the synthesis of nonsubstituted or *p*-substituted aryl analogues.[9–11] PAH metabolites, conversely, usually have *o*-hydroxy or *o*-carboxy substituents on their aromatic ring (e.g., **4**, **5**, **7**–**10**). We tested the reactivity of five arylaldehydes with *o*-hydroxy (**11a** and **b**), -methoxy (**11c**, **12a** and **b, 14a**), and methoxycarbonyl group (**14b**) in two different reaction conditions (Scheme 2). The yields of method A or B with *o*-methoxy- or *o*-carboxy-substituted arylaldehyde were 27–40% (Table 1). *o*-Hydroxyaryl aldehyde (**11a** and **b**) did not react to produce α-oxobutenoates after 36 h of reflux (Table 1). Longer heating (>72 h)



Scheme 2.

did not improve the yield. Instead of **4a** and **13a**, approximately 1–2% of benzochromenone (**3** and **3a**) was recovered from reaction mixtures. Reaction yields of method A with **11c**, **12a** and **b**, and **14a** and **b** were lower than those of nonsubstituted or *p*-substituted aldehydes,[7] which may be due to steric effects of *ortho*-substituents. Among the products derived from method A, only a single peak in each experiment, except

Table 1. Reaction condition, yield, and GC retention time of *o*-substituted aryl-*α*-oxobutenoates

Reactant	Product	Method	Reaction time (h)	GC retention time (min)	Yield (%)[a]
11a	**4a**	A	36	—	ND[b]
11b	**13a**	A	36	—	ND
11c	**7a**	A	36	58.6	32
12a	**4b**	A	48	54.78	31
	4b	B	5	54.79	34
12b	**13b**	A	48	56.66	27
	13b	B	5	56.71	38
14a	**10a**	A	36	34.28	32
14b	**9a**-*trans*	A	36	38.25	40
	9a-*cis*	A	36	35.01	1

[a]Reaction yield after column chromatography or thin-layer chromatography.
[b]Not detected.

the synthesis of **9a**, showed an expected mass spectrum of *o*-substituted aryl oxobutenoate $-[M]^+$ 220 or 270, fragments of *m/z* [M-15 (Me)], [M-31 (MeO)], [M-59 (COOMe)]. In addition to these peaks, a trace amount of benzochromenones (**3** and **3a**) was observed. In consideration of the reaction condition,[11] the C-C double bond in oxobutenoates from method A may have an *E*-configuration. Two peaks (GC retention time [Rt], 35.01 and 38.25 min) with nearly identical mass spectra were found in the reaction mixture for the synthesis of **9a**, which suggests *cis*- and *trans*-isomer, respectively.

The yields from the Wittig reaction (method B) were comparable with those in literature.[11] Although both methods A and B gave similar yields, large differences were observed in the chemical profile of reaction mixtures. More complex reaction mixtures were obtained from method A—more than 10 reaction products—and were detected in GC-MS analysis. In comparison with method A, only four to five peaks were observed in GC-MS chromatograms of reaction mixtures from method B, which can be easily assigned as unreacted aldehyde, ylide, triphenylphosphine oxide, and expected products (**4b** and **13b**). The selectivity for *E*- and *Z*-isomers in the Wittig reaction is dependent on various conditions.[12–14] Because ylide usually exists as a mixture of *E*- and *Z*-isomers, isomeric mixture of products were expected in method B. However, only a single isomer was found (**4b**) or one of isomers was the dominant product (**13b**). Because of the high steric hindrance of *ortho*-substituents, the dominant isomer may be the *E*-isomer.

o-Carboxyvinyl naphthoates (**5a**, **8a**, and **8b**) were prepared from a typical Heck reaction with *o*-bromonaphthoic acid methyl esters (Scheme 3). Among the peaks in GC-MS chromatograms of a crude reaction mixture (**5a**), only a single peak (Rt 49.50 min) showed a typical MS spectrum of the predicted product (M^+, 270). In case of the synthesis of **8a** (Rt 53.93 min), one additional peak (Rt 47.08 min) also showed a similar MS pattern. In consideration of the reaction mechanisms,[15–17] the double bond in the propenoic acid group of the dominant product (**5a** and **8a**) may be an *E*-configuration. The reaction yields were 68 and 73% for **5a** and **8a**, respectively. Approximately 30% of the reactant was recovered at the end of reaction. No other products were detected with GC-MS.

Scheme 3.

EXPERIMENTAL

General Procedures for the Preparation of Benzochromenones

Benzochromenones **3** and **3a** were prepared from **11a** and **b**, respectively, by the procedure of Dubuffet et al.[7] with some modification. Methyl triphenylphosphoranylidene acetate (10 mmol) was added to a solution of *o*-hydroxynaphthaldehyde (10 mmol) in xylene (50 ml). The mixture was refluxed for 4 h. After removing the solvent, the residues were triturated with isopropyl ether. Insoluble triphenylphosphine oxide was removed and the filtrate was concentrated. Residue was purified with silica-gel column chromatography (hexane/ethyl acetate 1/1, v/v). Purities of synthetic compounds were determined with GC-MS. Melting points were measured with a Fisher-Johns melting-point apparatus and reported without correction.

3-Methoxy-2-naphthaldehyde (**11c**) was prepared from (3-methoxynaphthalen-2-yl)-methanol by an established method.[18] *2H*-Benzo[*g*]chromen-2-one (**6**) was prepared from **11c**, according to the established procedure.[7]

***2H*-Benzo[*h*]chromen-2-one (3)**. GC-MS Rt (min): 39.53; m/z 196 (M^+, 72), 168 (100), 139 (46); ^{1}H NMR: 6.51 (*d*, 1H), 7.51 (*d*, 1H), 7.65 (*m*, 2H), 7.70 (*d*, 1H), 7.83 (*d*, 1H), 7.88 (*m*, 1H), 8.47 (*m*, 1H); purity, 98%; mp: 138–141°C, lit.: 140–141°C.[19]

***3H*-Benzo[*f*]chromen-3-one (3a)**. GC-MS Rt (min): 41.80; m/z 196 (M^+, 88), 168 (100), 139 (56); ^{1}H NMR: 6.65 (*d*, 1H), 7.45 (*d*, 1H), 7.59 (*m*, 1H), 7.68(*t*, 1H), 7.91 (*d*, 1H), 7.98 (*d*, 1H), 8.32 (*d*, 1H), 8.50 (*d*, 1H); purity, 99%; mp: 116–118°C, lit.: 115–116°C.[7]

***2H*-Benzo[*g*]chromen-2-one (6)**. GC-MS Rt (min): 41.49; m/z 196 (M^+, 100), 168 (73), 139 (60); ^{1}H NMR: 6.40 (*d*, 1H), 7.52(*m*, 1H), 7.68–7.79 (*m*, 3H), 7.90–8.00 (*m*, 1H), 8.20 (*s*, 1H); purity, 97%; mp: 124–125°C.

General Procedures for the Preparation of 4-(*o*-Methoxyaryl)-2-oxobut-3-enoates and Related Compounds

Method A: 4-(*o*-Methoxnaphthyl)-2-oxobut-3-enoates (**4b**, **7a**, and **13b**) were prepared from *o*-methoxynaphthaldehyde (**11c**, **12a**, and **b**) according to the literature method.[9] 4-(o-substituted pheny)-2-oxobut-3-enoates (**9a** and **10a**) were synthesized by the same method, using **14a** and **b**, respectively. Copper triflate [$Cu(OTf)_2$, 0.2 mmol] and trimethyl orthoformate (1.2 mmol) were added to a solution of methyl pyruvate (2 mmol) and *o*-substituted aldehyde (1 mmol) in dichloromethane (80 ml), and the mixture was heated to reflux for 36–48 h. After solvent removal, an oily residue was purified by silica-gel thin-layer chromatography (hexane/ethyl acetate 2/1, v/v).

Method B: Methyl 2-oxo-3-(triphenylphosphoranylidene)propanoate (TPPP) was prepared by a literature method.[20] TPPP (50 mmol) was added

to a solution of aldehyde (10 mmol, **12a** and **b**) in toluene (50 ml), and the mixture was stirred at 80°C for 5 h. After removing the solvent under reduced pressure, the residue was triturated with isopropyl ether. Insoluble oxide was removed and the extracts were purified with silica-gel column chromatography (hexane/ethyl acetate 1/1, v/v).

Methyl (3*E*)-4-(1-methoxy-2-naphthyl)-2-oxobut-3-enoate (4b). *m/z* 270 (M^+, 6), 255 (2), 239 (100), 211 (53), 196 (57), 168 (34); ^{1}H NMR: 3.86 (*s*, 3H), 3.95 (*s*, 3H), 7.32 (*d*, 1H), 7.47 (*d*, 1H), 7.49–7.60 (*m*, 3H), 7.85–7.90 (*m*, 2H), 8.41 (*d*, 1H); purity 96%; mp 35–36°C.

Methyl (3*E*)-4-(2-methoxy-1-naphthyl)-2-oxobut-3-enoate (13b). *m/z* 270 (M^+, 55), 239 (97), 211 (61), 196 (100), 168 (82); ^{1}H NMR: 3.84 (*s*, 3H), 3.94 (*s*, 3H), 6.37 (*d*, 1H), 7.52–7.62 (*m*, 3H), 7.75 (*d*, 1H), 7.99 (*d*, 1H), 8.04 (*d*, 1H), 8.42 (*d*, 1H); purity 98%; mp 41–42°C.

Methyl (3*E*)-4-(3-methoxy-2-naphthyl)-2-oxobut-3-enoate (7a). *m/z* 270 (M^+, 25), 255 (1), 239 (5), 211 (100), 196 (45), 168 (24); ^{1}H NMR: 3.74 (*s*, 3H), 3.87 (*s*, 3H), 7.22 (*d*, 1H), 7.44 (*t*, 1H), 7.48 (*d*, 1H), 7.67 (*t*, 1H), 7.82 (*m*, 2H), 8.08 (*d*, 1H), 8.42 (*d*, 1H); purity 95%; yellow oil.

Methyl 2-[(1*E*)-4-methoxy-3,4-dioxobut-1-enyl]benzoate (9a-*trans*). *m/z* 248 (M^+, 4), 233 (3), 217 (2), 189 (100), 145 (50); ^{1}H NMR: 3.89 (*s*, 3H), 3.92 (*s*, 3H), 7.18 (*d*, 1H), 7.48 (*m*, 1H), 7.51 (*m*, 1H), 7.64 (*m*, 1H), 7.90 (*d*, 1H), 8.37 (*d*, 1H); purity 95%; yellow oil.

Methyl 2-[(1Z)-4-methoxy-3,4-dioxobut-1-enyl]benzoate (9a-cis). *m/z* 248 (M^+, 4), 233 (4), 217 (2), 189 (100), 145 (44); ^{1}H NMR: 3.90 (*s*, 3H), 3.95 (*s*, 3H), 6.28 (*d*, 1H), 7.46–7.53 (*m*, 2H), 7.57 (*m*, 1H), 7.91 (*d*, 1H), 8.22 (*d*, 1H); purity 97%; mp 34–37°C.

Methyl (3*E*)-4-(2-methoxyphenyl)-2-oxobut-3-enoate (10a). *m/z* 220 (M^+, 7), 205 (1), 189 (1), 161 (100); ^{1}H NMR: 3.86 (*s*, 3H), 4.30 (*s*, 3H), 7.44 (*d*, 1H), 7.06–7.66 (m, 4H), 7.87 (*d*, 1H); purity 94%; yellow oil.

General Procedures for the Preparation of *o*-Carboxyvinylnaphthoates and Benzoates

Methyl esters of *o*-bromonaphthoic acids (**15a** and **b**) were prepared according to the methods of Look et al.[21] and Seki et al.,[22] followed by esterification with methyl iodide. Methyl acrylate (60 mmol), triethylamine (TEA, 60 mmol), palladium acetate (1 mmol), and tri-*o*-tolylphosphine (10 mmol) were added successively to a solution of *o*-bromonaphthoate (50 mmol) in *N,N*-dimethylformamide (50 ml). The mixture was stirred at 90°C for 5 h. After cooling, the mixture was poured into water (200 ml) and extracted with dichloromethane (80 ml × 3). After removing the solvent, residues were purified by column chromatography (silica gel, hexane/ethyl acetate).

1-[(*E*)-2-Carboxyvinyl]-2-naphthoic acid dimethyl ester (5a). GC-MS Rt (min): 49.50; *m/z* 270 (M^+, 8), 239 (9), 223 (7), 211 (100), 196 (10), 179 (10), 168 (12); ^{1}H NMR: 3.81 (*s*, 3H), 3.92 (*s*, 3H), 6.52 (*d*, 1H), 7.44–7.50

(*m*, 2H), 7.65 (*m*, 1H), 7.83 (*d*, 1H), 7.95 (*d*, 1H), 8.15 (*d*, 1H), 8.43 (*d*, 1H); purity 97%; mp 54–56°C.

3-[(*E*)-2-Carboxyvinyl]-2-naphthoic acid dimethyl ester (8a). GC-MS Rt (min): 53.93; m/z 270 (M^+, 14), 255 (3), 239 (9), 223 (26), 211 (100), 196 (13), 168 (16); ^{1}H NMR: 3.55 (*s*, 3H), 3.82 (*s*, 3H), 6.13 (*d*, 1H), 7.44–7.74 (*m*, 3H), 7.84–8.06 (*m*, 2H), 8.21 (*d*, 1H), 8.43 (*s*, 1H); purity 97%; mp 77–78°C.

3-[(*Z*)-2-Carboxyvinyl]-2-naphthoic acid dimethyl ester (8b). GC-MS Rt (min): 47.08; m/z 270 (M^+, 24), 255 (5), 239 (8), 223 (29), 211 (100), 196 (18), 168 (16); purity 91%.

Instrumental Analysis

GC-MS analyses were performed with a Varian QP-5000 gas chromatograph and a Saturn-2000 Ion trap mass spectrometer. ZB-1 column (60 m, 0.25 μm) was used. Initial column temperature was set at 120°C (held for 2 min) and raised to 280°C at a rate of 2°C/min (held for 10 min). Injector and detector temperatures were 270 and 280°C, respectively. Helium was the carrier gas at a rate of 2 ml/min. Melting point was measured with a Fisher-Johns melting-point apparatus and is reported without correction. ^{1}H NMR spectra were recorded on a Varian Mercury-Plus 300-MHz NMR for solutions in $CDCl_3$.

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