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Successive Michael reactions on chromone derivatives with dimethyl 1,3-acetonedicarboxylate: one-pot synthesis of functionalized benzophenones, benzo[*c*]chromones and hydroxybenzoylfuroates

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ABSTRACT

Chromones were reacted with dimethyl acetonedicarboxylate in the presence of DBU in THF at room temperature to furnish good yields of products, their structure depending on the substituent at 3-position. Unsubstituted chromones lead to methyl 7-hydroxy-6-oxo-6*H*-benzo[*c*]chromone-8-carboxylates **2**, whereas by using 3-bromochromone, the methyl furoate **3c** along with the unexpected furylcyclopropyl-chromene carboxylate **4c** was isolated. Finally, from 3-formyl-chromones functionalized benzophenones **5** were isolated, in good yields. Plausible mechanisms are proposed.

1. Introduction

Besides forming the basic nucleus of an entire class of natural products, i.e., flavones,[1] the chromone moiety forms the important component of pharmacophores of a large number of molecules of medicinal significance.[2] Consequently, considerable attention is being devoted to isolation from natural resources, chemistry, and synthesis of chromone derivatives, and evaluation of their biological activity with emphasis on their potential medicinal applications.[2–4] Moreover, chromones can be readily converted into a broad range of heterocyclic systems, e.g., xanthones[5] and pyranobenzopyranones[6] by cycloaddition strategies, pyrazolopyrimidines,[7] pyridopyrimidines,[8] pyrimidopyrimidines,[9] benzopyranobenzothiazepines, -oxazepines, -diazepines,[10] furobenzopyranones,[11] *o*-hydroxyphenyl substituted pyrazoles,[12] and pyrimidines[13,14] through reaction with several nucleophiles, and particularly bis-nucleophiles.

The reaction between 3-acyl-2-methylthio-chromones and acetylacetone or diethyl 1,3-acetonedicarboxylate in the presence of potassium *tert*-butoxide leading to xanthone derivatives has been studied by Eiden et al.[15] in 1984. Shortly after, the reaction of 3-cyano-chromones with acetonedicarboxylates in the presence of piperidine, leading to isolation of benzopyranopyridines, was reported.[16] In addition, it was reported that 3-formyl-chromones react with various active methylene compounds in basic media to produce mainly Knoevenagel-type condensation products.[17] Recently, the reaction between the chromone and the dianion of ethyl acetoacetate or its electroneutral equivalent, 1,3-bis(trimethylsilyloxy)-1,3-butadiene, was attempted.[18] Eventually, through a three-step reaction sequence involving activation of the chromone moiety through formation of benzopyrylium triflates, their subsequent reaction with 1,3-bis(trimethylsilyloxy)-1,3-butadienes and finally ring closure with triethylamine, benzo[*c*]chromen-6-ones were isolated, instead of the expected 1-hydroxy-xanthones. Moreover, the reaction between the 3-formyl-chromone with the dianion of benzoylacetone was found to result to the formation of complex reaction mixtures.[19] However, functionalized benzophenones were isolated through formation of benzopyrylium triflates and subsequent reaction with 1,3-bis-silyl-enol ethers[19] or by domino 'Michael–retro-Michael–Wittig' reactions of dioxobutylidenetriphenylphosphoranes with 3-formyl-chromones.[20]

Functionalized benzophenones are of considerable interest as pharmacologically relevant natural products and natural product analogs and represent[21,22] versatile synthetic building blocks. Functionalized benzophenones are also used as photosensitizers[23] and as active ingredients of commercial agents, which protect the

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skin or color against UV irradiation.[24] Their classical synthesis through Friedel–Crafts acylation[25] leads frequently to unsatisfactory results, especially when it is applied to substituted derivatives. Other benzophenone syntheses rely on the reaction of organometallic reagents with aldehydes and subsequent oxidation. A more recent modification of this approach involves the SmI_2 mediated reaction of benzaldehydes with benzylhalides and subsequent oxidation.[26]

On the other hand, benzo[*c*]chromen-6-ones are present in a number of pharmacologically relevant natural products such as autumnariol,[27] autumnariniol,[28] alternariol,[29]and altenuisol.[30] Benzo[*c*]chromen-6-ones are specific inhibitors of the growth of endothelic cells[31] and represent estrogen receptors.[32] Therefore, various methods have been employed for their synthesis, such as cyclization of bromobenzoic acids with phenols,[33] palladium catalyzed coupling reactions,[34] Suzuki reactions,[35] and recently retro-Michael aldol lactonization reactions.[18]

In the light of this literature information, we speculated that the synthesis of benzo[*c*]chromones and functionalized benzophenones would be possible by a one-pot reaction from readily available starting materials, namely through Michael reaction between chromones and 3-formyl-chromones with dimethyl acetonedicarboxylate.

2. Results and discussion

When chromones **1a** and **1b** were allowed to react with equimolar amounts of dimethyl acetonedicarboxylate in the presence of 1.3 equiv of the base 1,8-diazabicyclo[5.4.0]undecane-7 (DBU) in the aprotic non-polar solvent THF at room temperature for 2 h the dibenzopyrane derivatives **2a** and **2b** were isolated in good yields (50–65%, Scheme 1). However, chromones bearing a methyl group at C-2, namely 2-methylchromone and 6-bromo-2-methylchromone, failed to undergo the above reaction even with heating for extended reaction periods. To the contrary, when the reaction was repeated[36] with 3-bromochromone (**1c**), approximately 10% of the starting material **1c** was recovered along with the furan derivative **3c** isolated in 19% yield, whereas a highly unexpected product containing a cyclopropyl ring, namely the furylcyclopropyl-chromene carboxylate **4c**, was the main reaction product in 42% yield (Scheme 1). When the same reaction was repeated at room temperature with 2 equiv of DBU, complete conversion of the chromone **1c** was observed. In this case the yield of **4c** was increased to 65%, whereas **3c** was formed in only 6% yield. In addition, it was possible to convert the furan derivative **3c** to the cyclopropyl derivative **4c** by reacting it with an additional equivalent of chromone **1c** and DBU at room temperature, proving thus that **3c** constitutes the intermediate for the formation of **4c** (see also proposed mechanism).

Finally, from the 3-formyl-chromones (**1d**–**1g**) functionalized hydroxy-benzophenones **5** were isolated (Scheme 1), instead of the expected Knoevenagel-type condensation products.[17]

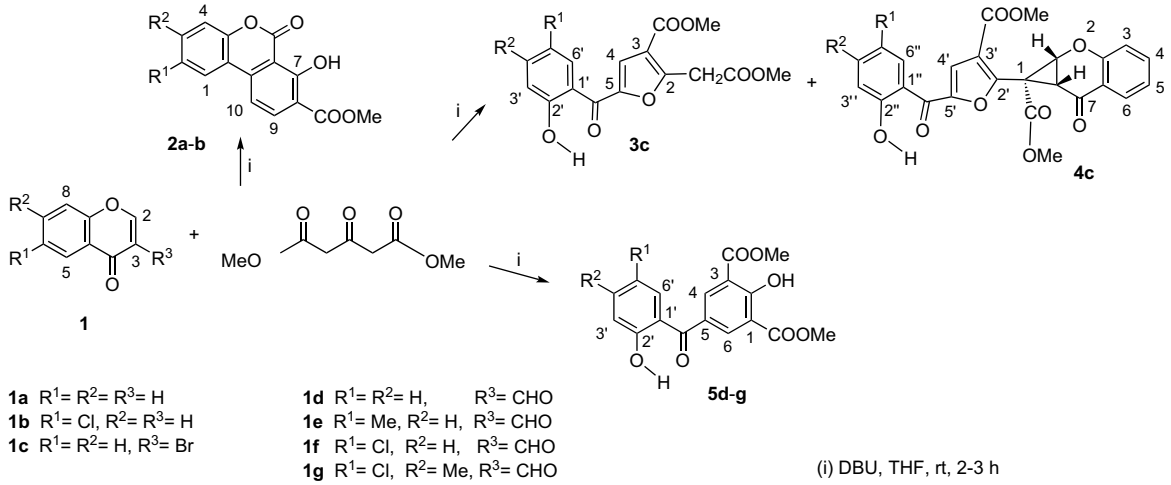
For the formation of products **2** a plausible mechanism depicted in Scheme 2 can be proposed. The reaction is most probably initiated by an attack of the base-activated nucleophilic acetonedicarboxylate to the C-2 chromone carbon, being a Michael acceptor, followed by chromone ring opening, forming thus the open chain intermediate **6a**. Subsequent ring closure, via an intramolecular Michael reaction (path a), leads to intermediate **7**, from which **8b** can be formed by loss of methanol. Dehydration to **9** and tautomerization of the β-keto-ester group leads to the isolated lactone **2**. To the contrary, the formation of a 10-membered ring **10** (path b) by lactonization of the intermediate **6**, followed by a subsequent transannular aldol condensation, appears to be less likely (Scheme 2). PM3 MO calculations predict that the described transformations **7a** to **7b**, and **9** to **2a** (path a) are energetically favored and also that path a is favored over path b.

In the case of the 3-bromo-substituted chromone **1c**, Michael attack on C-2 forms the analogous enolate intermediate **11** from which, most probably through a second intramolecular Michael attack of the enolate oxygen to the bromine bearing carbon (O-alkylation), **12** can be formed. Subsequent pyrane ring opening, results to the isolated furan derivative **3c** (Scheme 3). However, in the presence of an excess of DBU, a new enolate anion **13** is most probably formed, which reacts with a second bromochromone molecule to give **14**. Through [1,3-*H*] shift to intermediate **15** and nucleophilic attack at the bromine bearing carbon, the isolated product **4c** is formed containing a three-membered ring. The formation of the cyclopropyl derivative **4c** at room temperature is remarkable and, needless to note, unexpected.

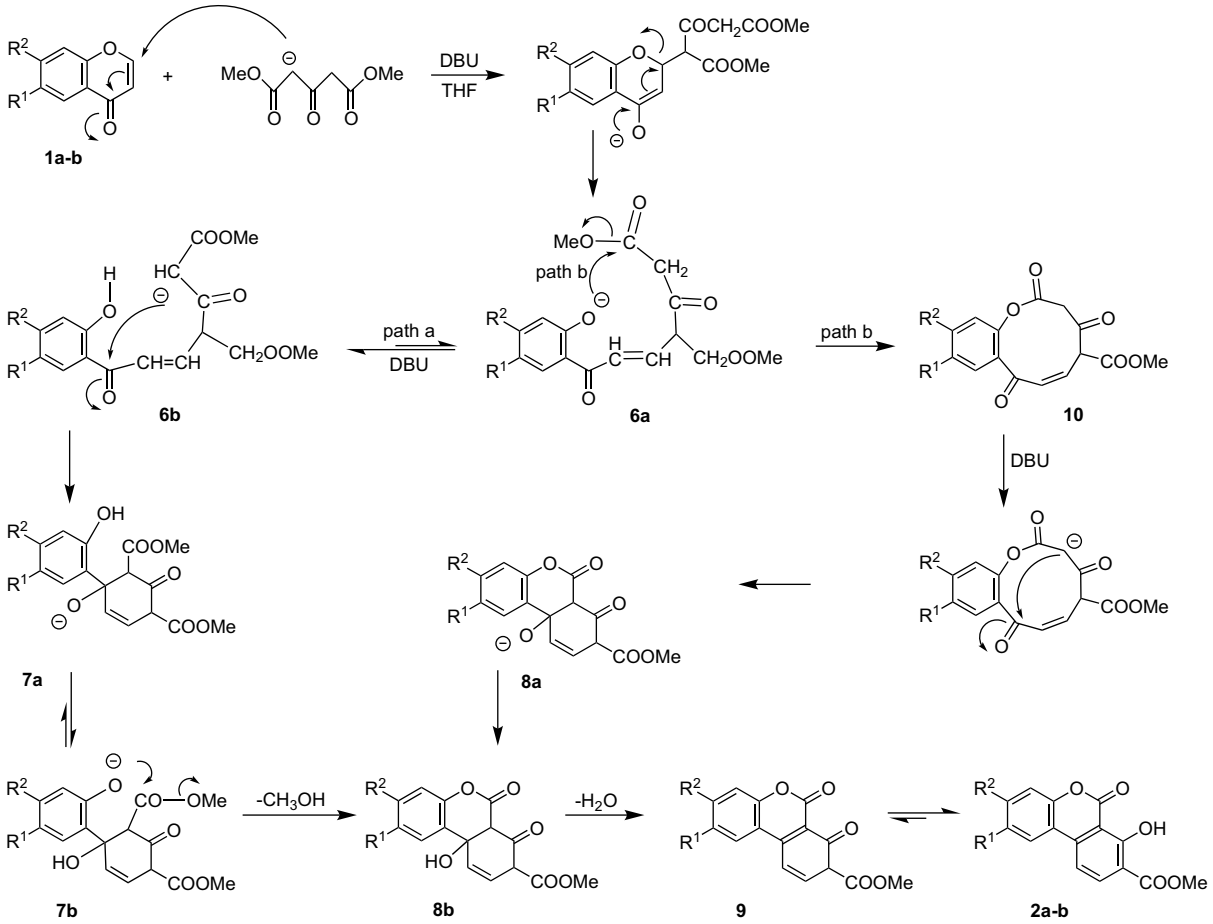
Finally, in the case of formyl-chromones the corresponding enolate anion **16**, formed at the side-chain methylene carbon, leads through a second intramolecular Michael reaction to the formation of the new six-membered ring (intermediate **17**). By loss of water to **18** and tautomerization, the isolated products **5** (Scheme 4) are formed.

2.1. Structure assignments of the new compounds

The assigned molecular structures of the new compounds **2**, **4**, and **5** were based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR and COLOC), MS, and



Scheme 1. Reaction between differently 3-substituted chromones with dimethyl acetonedicarboxylate under the same reaction conditions.



Scheme 2. Plausible reaction mechanism proposed for the formation of compounds **2**.

elemental analysis data. In Figure 1 the COLOC correlations of protons with carbons via ^{2}J and ^{3}J coupling constants for compounds **2a**, **3c**, and **4c** are depicted.

In addition, since the formation of a cyclopropane ring at room temperature seemed most improbable the structure of **4c** was undoubtedly elucidated by crystal structure analysis[38] (Fig. 2). The structure of **5d** was also confirmed by crystal structure analysis[38] (Fig. 3).

3. Conclusions

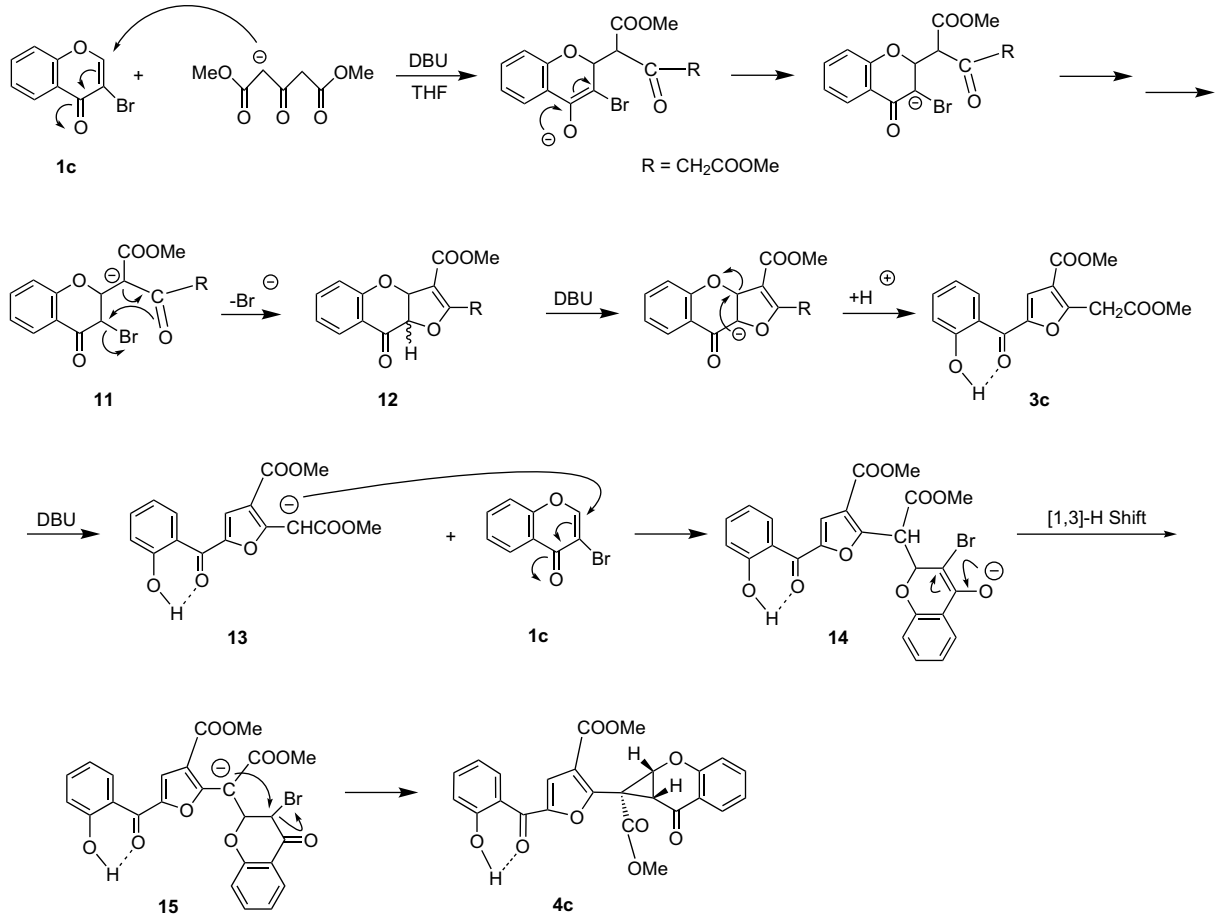
In conclusion, we have shown that from cheap, easily accessible starting materials, namely chromones, dimethyl acetonedicarboxylate, and DBU, and very mild reaction conditions, very interesting products can be isolated in good yields through a one-step reaction, the type of the isolated product depending on the substituent at chromone 3-position. Moreover, the present work demonstrates the versatility of chromones in bringing about one-pot synthetic procedures.

By using unsubstituted chromones 7-hydroxy-6-oxo-6*H*-benzo[*c*]chromene-8-carboxylates are formed. Analogous compounds are reported in the literature though a three-step reaction sequence[18] involving the formation of benzopyrylium triflates and subsequent reaction with 1,3-bis(trimethylsilyloxy)-1,3-butadiene. By applying the same reaction conditions on 3-formyl-chromones functionalized benzophenones (2-hydroxybenzoylphenols) were isolated. Again, analogous products are reported from reactions either between 1,3-bis-silylenol ethers and benzopyrylium triflates[19] or dioxobutylidenetriphenylphosphoranes with 3-formyl-chromones.[20] Finally, by using 3-bromochromone the unexpected and otherwise inaccessible furylcyclopropyl-chromene carboxylate was synthesized along with hydroxybenzoylfuran.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether–ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature (rt) on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^{n}J are reported in Hertz. Second order ^{1}H spectra in the aromatic region, where it was possible, were analyzed by simulation.[37] IR spectra were recorded on a Perkin–Elmer 297 spectrometer or on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra were recorded on a 6890N GC/MS system (Agilent Technology) and elemental analyses performed with a Perkin–Elmer

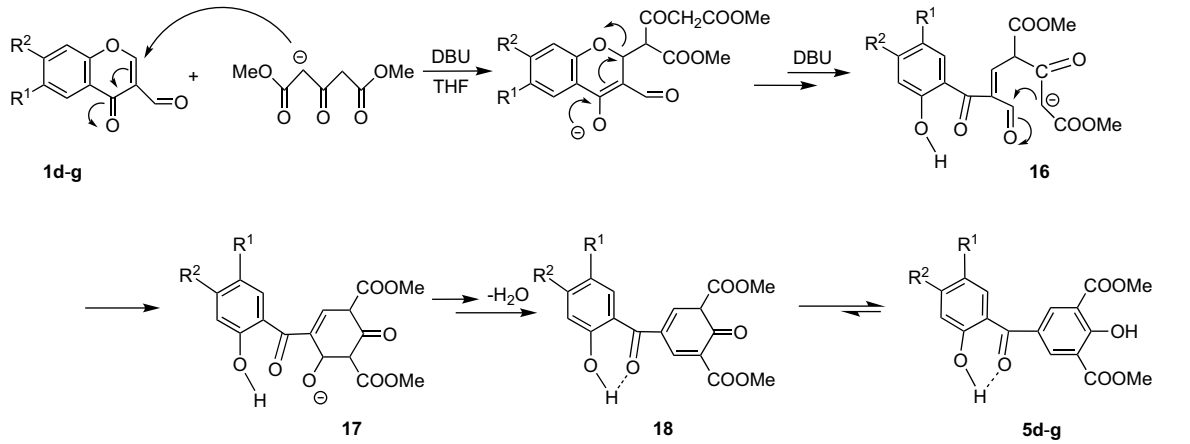


Scheme 3. Plausible reaction mechanism proposed for the formation of compounds **3c** and **4c**.

2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS, and NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HETCOR, and COLOC).

4.2. General procedure for the reaction of chromones (1a–1g) with dimethyl acetonedicarboxylate

To a stirred reaction mixture of chromone **1** (1.0 mmol) and dimethyl acetonedicarboxylate (0.22 g, 1.1 mmol) in THF (20 mL), DBU (0.20 mL, 1.3 mmol) was added via a syringe at room temperature. Stirring was continued until chromone **1** was consumed completely (followed by TLC, approximately 2–3 h). The reaction mixture was quenched with aqueous solution of 10% NH_4Cl, washed with water, dried (Na_2SO_4), the solvent was distilled off in vacuo, and the resulting residue was subjected to column chromatography on silica gel using petroleum ether–AcOEt (7:1) as eluent, slowly increasing the polarity up to 4:1 to give the isolated products.



Scheme 4. Plausible reaction mechanism proposed for the formation of compounds **5**.

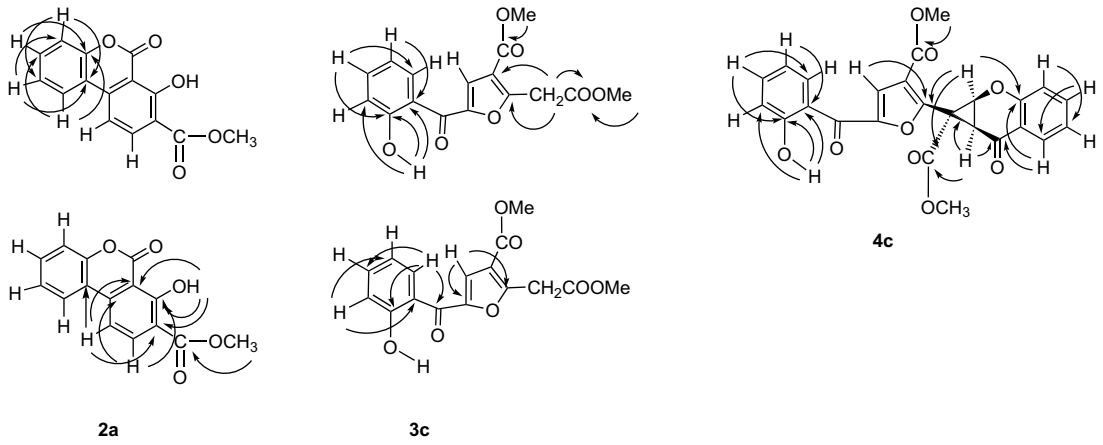


Figure 1. Critical COLOC correlations via ^{2}J and ^{3}J for the structure identification of compounds **2a**, **3c**, and **4c**.

*4.2.1. Methyl 7-hydroxy-6-oxo-6H-benzo[c]chromene-8-carboxylate (**2a**)*

0.152 g, 56% yield, white solid, mp 203–205 °C (CH_2Cl_2–pet. ether); IR (KBr) ν_{max}: 3444 (br), 1719, 1670, 1624 cm^{-1}. ^{1}H NMR: 3.98 (s, 3H, 8-OCH_3), 7.37 (dd, J=8.2, 1.2 Hz, 1H, 4-H), 7.39 (ddd, J=7.8, 7.4, 1.2 Hz, 1H, 2-H), 7.56 (ddd, J=8.2, 7.4, 1.5 Hz, 1H, 3-H), 7.59 (d, J=8.6 Hz, 1H, 10-H), 8.04 (dd, J=7.8, 1.5 Hz, 1H, 1-H), 8.30 (d, J=8.6 Hz, 1H, 9-H), 12.57 (s, 1H, 7-OH). ^{13}C NMR: 52.5 (OCH_3), 107.3 (C-6a), 111.6 (C-10), 116.5 (C-8), 117.4 (C-10b), 117.8 (C-4), 123.9 (C-1), 125.4 (C-2), 131.8 (C-3), 139.0 (C-9), 139.8 (C-10a), 151.2 (C-4a), 163.3 (C-7), 164.0 (C-6), 166.0 (8-C=O). EIMS m/z (%) 270 (91, $M^{+\bullet}$), 253 (5), 239 (100), 210 (25), 182 (15), 155 (20), 154 (19), 139 (5), 126 (40). Anal. Calcd for $C_{15}H_{10}O_5$ (270.24): C, 66.67; H, 3.73%. Found: C, 66.46; H, 3.60%.

*4.2.2. Methyl 2-chloro-7-hydroxy-6-oxo-6H-benzo[c]chromene-8-carboxylate (**2b**)*

0.171 g, 56% yield, white solid, mp 227–229 °C (CH_2Cl_2–pet. ether); IR (Nujol) ν_{max}: 3440 (br), 1697, 1668 cm^{-1}. ^{1}H NMR: 4.00 (s, 3H, 8-OCH_3), 7.36 (d, J=8.8, 1H, 4-H), 7.52 (dd, J=8.8, 2.2 Hz, 1H, 3-H), 7.57 (d, J=8.4 Hz, 1H, 10-H), 8.03 (d, J=2.2 Hz, 1H, 1-H), 8.34 (d, J=8.4 Hz, 1H, 9-H), 12.51 (s, 1H, 7-OH). ^{13}C NMR: 52.6 (OCH_3), 107.5 (C-6a), 111.8 (C-10), 117.4 (C-8), 118.9 (C-10b), 119.3 (C-4), 123.7 (C-1), 131.0 (C-2), 131.9 (C-3), 138.6 (C-10a), 139.1 (C-9), 149.7 (C-4a), 163.3 (C-7), 163.4 (C-6), 166.0 (8-C=O). Anal. Calcd for $C_{15}H_9ClO_5$ (304.68): C, 59.13; H, 2.98%. Found: C, 59.29; H, 3.13%.

*4.2.3. Reaction of chromone (**1c**) with dimethyl acetonedicarboxylate*

4.2.3.1. In the presence of 1.3 mmol DBU. The reaction was repeated as above to give after column chromatography on silica gel using petroleum ether–AcOEt (7:1) as eluent, slowly increasing the polarity up to 4:1, in elution order:

Unreacted **3-bromochromone** 0.022 g, 10%.

Methyl 5-(2-hydroxybenzoyl)-2-(2-methoxy-2-oxoethyl)-3-furoate (**3c**). Yield 0.061 g, 19%, yellow solid, mp 206–208 °C (CH_2Cl_2–ether); IR (Nujol) ν_{max}: 3250, 1735, 1715 cm^{-1}. ^{1}H NMR: 3.77 (s, 3H, 2-OCH_3), 3.89 (s, 3H, 3-OCH_3), 4.23 (s, 2H, 2-CH_2), 6.98 (ddd, J=8.1, 7.4, 1.1 Hz, 1H, 5′-H), 7.05 (dd, J=8.5, 1.1 Hz, 1H, 3′-H), 7.53 (ddd, J=8.5, 7.4, 1.6 Hz, 1H, 4′-H), 7.60 (s, 1H, 4-H), 8.13 (dd, J=8.1, 1.6 Hz, 1H, 6′-H), 11.82 (s, 1H, OH). ^{13}C NMR: 34.0 (2-CH_2), 52.1 (3-OCH_3), 52.7 (2-OCH_3), 117.8 (C-3), 118.5 (C-1′), 118.6 (C-3′), 119.3 (C-5′), 120.9 (C-4), 131.2 (C-6′), 136.6 (C-4′), 150.1 (C-5), 158.1 (C-2), 162.7 (3-C=O), 163.3 (C-2′), 168.0 (2-C=O), 184.5 (5-C=O). EIMS m/z (%) 318 (40, $M^{+\bullet}$), 286 (80), 259 (25), 254 (40), 244 (45), 226 (50), 216 (15), 213 (75), 199 (20), 186 (18), 171 (22), 158 (22), 131 (20), 121 (100), 120 (55), 109 (30). Anal. Calcd for $C_{16}H_{14}O_7$ (318.28): C, 60.38; H, 4.43%. Found: C, 60.56; H, 4.48%.

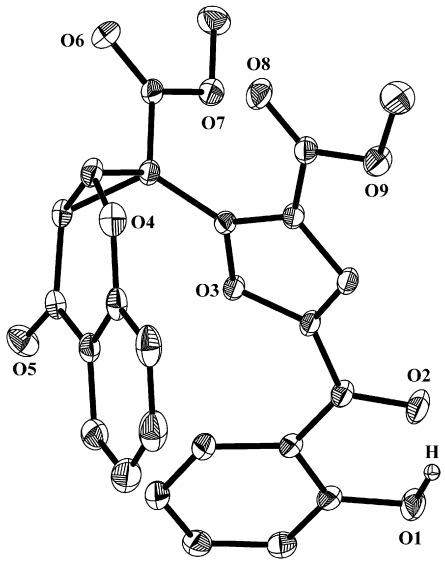


Figure 2. ORTEP of compound **4c**.

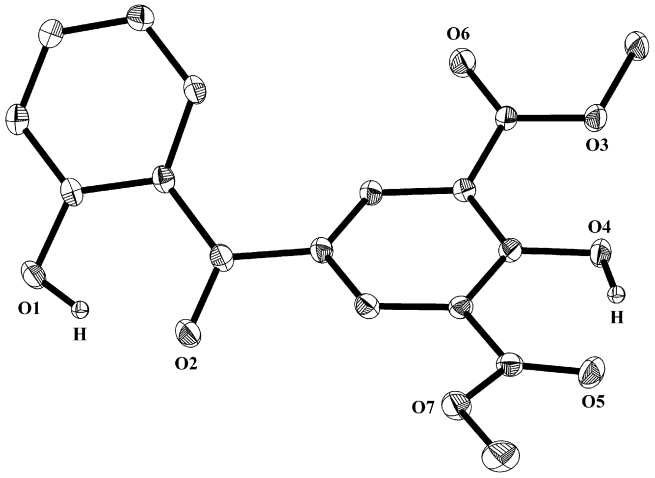


Figure 3. ORTEP of compound **5d**.

Methyl 1-[5-(2-hydroxybenzoyl)-3-(methoxycarbonyl)-2-furyl]-7-oxo-1,1a,7,7a-tetrahydrocyclopropa[*b*]chromene-1-carboxylate (**4c**). Yield 0.097 g, 42%, yellow solid, mp 210–212 °C (CH_2Cl_2–ether); IR (Nujol) ν_{max}: 3444, 1741, 1715, 1684 cm^{-1}. ^1H NMR: 3.76 (s, 3H, 1-OCH_3), 3.99 (s, 3H, 3′-OCH_3), 3.45 (br d, 1H, *J*=6.7 Hz, 7a-H), 5.23 (d, 1H, *J*=6.7 Hz, 1a-H), 6.75 (dd, *J*=8.4, 1.0 Hz, 1H, 3-H), 6.82 (ddd, *J*=8.1, 7.3, 1.0 Hz, 1H, 5-H), 7.01 (dd, *J*=8.5, 0.9 Hz, 1H, 3″-H), 7.07 (ddd, *J*=8.2, 7.1, 0.9 Hz, 1H, 5″-H), 7.28 (ddd, *J*=8.4, 7.3, 1.7 Hz, 1H, 4-H), 7.29 (s, 1H, 4′-H), 7.54 (ddd, *J*=8.5, 7.1, 1.7 Hz, 1H, 4″-H), 7.60 (dd, *J*=8.1, 1.7 Hz, 1H, 6-H), 7.92 (dd, *J*=8.2, 1.7 Hz, 1H, 6″-H), 11.87 (s, 1H, OH). ^{13}C NMR: 27.3 (C-1), 37.9 (C-7a), 52.4 (OCH_3), 53.8 (OCH_3), 65.1 (C-1a), 117.0 (C-3), 118.0 (C-1″), 118.5 (C-3″), 118.7 (C-3′), 119.4 (C-5″), 120.3 (C-4′), 122.1 (C-6a), 122.5 (C-5), 126.1 (C-6), 131.4 (C-6″), 136.3 (C-4), 136.9 (C-4″), 151.5 and 151.7 (C-2′ and C-5′), 157.4 (C-2a), 161.7 (3′-C=O), 163.6 (C-2″), 168.8 (1-C=O), 183.2 (C-7), 183.6 (5′-C=O). LC/MS (ESI, 3.5 eV) *m*/*z* (%) 463 (100, $M^{+\bullet}$+1), 431 (71), 403 (33). Anal. Calcd for $C_{25}H_{18}O_9$ (462.41): C, 64.94; H, 3.92%. Found: C, 64.78; H, 4.01%.

4.2.3.2. In the presence of 2.0 mmol DBU. The reaction was repeated as above to give, after column chromatography on silica gel using petroleum ether–AcOEt (7:1) as eluent, slowly increasing the polarity up to 4:1, in elution order: Compound **3c**, yield 0.019 g, 6%, and **4c**, yield 0.150 g, 65%.

*4.2.4. Reaction of **3c** with dimethyl acetonedicarboxylate*

To a stirred reaction mixture of the furoate **3c** (0.032 g, 0.1 mmol) and 3-bromochromone (0.025 g, 0.11 mmol) in THF (3 mL), DBU (0.020 mL, 0.013 mmol) was added via a syringe at room temperature. Stirring was continued until **3c** was consumed completely (followed by TLC, approximately 2–3 h). The reaction mixture was quenched with aqueous solution of 10% NH_4Cl, washed with water, dried (Na_2SO_4), the solvent was distilled off in vacuo, and the resulting residue was subjected to column chromatography on silica gel using petroleum ether–AcOEt (7:1) as eluent, slowly increasing the polarity up to 4:1 to give **4c**, yield 0.036 g, 78%.

*4.2.5. Dimethyl 5-(2-hydroxybenzoyl)-2-hydroxyisophthalate (**5d**)*

Yield 0.243 g, 65%, white solid, mp 81–83 °C (CH_2Cl_2–ether); IR (Nujol) ν_{max}: 3443, 1701, 1676 cm^{-1}. ^1H NMR: 3.99 (s, 6H, 2×CH_3), 6.94 (ddd, *J*=8.1, 7.1, 1.2 Hz, 1H, 5′-H), 7.10 (dd, *J*=8.6, 1.2 Hz, 1H, 3′-H), 7.55 (dd, *J*=8.1, 1.7 Hz, 1H, 6′-H), 7.55 (ddd, *J*=8.6, 7.1, 1.7 Hz, 1H, 4′-H), 8.45 (s, 2H, 4,6-H), 11.75 (s, 1H, 2′-OH), 12.29 (s, 1H, 2-OH). ^{13}C NMR: 52.8 (2×CH_3), 116.7 (C-5), 118.7 (C-3′), 118.8 (C-1′), 119.0 (C-5′), 128.3 (C-1,3), 132.7 (C-6′), 136.5 (C-4′), 137.4 (C-4,6), 163.1 (C-2′), 164.1 (C-2), 167.3 (1,3-C=O), 198.1 (5-C=O). EIMS *m*/*z* (%) 330 (69, $M^{+\bullet}$), 298 (100), 267 (37), 254 (45), 238 (83), 210 (42), 121 (60). Anal. Calcd for $C_{17}H_{14}O_7$ (330.28): C, 61.82; H, 4.27%. Found: C, 62.09; H, 4.32%.

*4.2.6. Dimethyl 2-hydroxy-5-(2-hydroxy-5-methyl-benzoyl)-isophthalate (**5e**)*

51% yield, white solid, mp 158–159 °C (CH_2Cl_2–pet. ether); IR (Nujol) ν_{max}: 3443, 1716, 1685 cm^{-1}. ^1H NMR: 2.27 (s, 3H, 5′-CH_3), 3.98 (s, 6H, 2×CH_3), 6.99 (d, *J*=8.5 Hz, 1H, 3′-H), 7.30 (d, *J*=1.0 Hz, 1H, 6′-H), 7.35 (dd, *J*=8.5, 1.0 Hz, 1H, 4′-H), 8.44 (s, 2H, 4,6-H), 11.55 (s, 1H, OH), 12.27 (s, 1H, OH). ^{13}C NMR: 20.5 (CH_3), 52.8 (2×CH_3), 116.6 (C-5), 118.4 (C-1′,3′), 128.2 (C-1,3), 128.5 (C-5′), 132.4 (C-6′), 137.3 (C-4,6), 137.6 (C-4′), 161.0 (C-2′), 164.0 (C-2), 167.4 (1,3-C=O), 198.1 (5-C=O). EIMS *m*/*z* (%) 344 (60, $M^{+\bullet}$), 312 (100), 280 (30), 268 (25), 252 (91), 224 (25), 205 (15), 134 (35). Anal. Calcd for $C_{18}H_{16}O_7$ (344.32): C, 62.79; H, 4.68%. Found: C, 63.01; H, 4.71%.

*4.2.7. Dimethyl 2-hydroxy-5-(5-chloro-2-hydroxy-benzoyl)-isophthalate (**5f**)*

Yield 0.243 g, 65%, white solid, mp 156–158 °C (CH_2Cl_2–ether); IR (Nujol) ν_{max}: 3443, 1718, 1685 cm^{-1}. ^1H NMR: 4.00 (s, 6H, 2×CH_3), 7.07 (d, *J*=9.3 Hz, 1H, 3′-H), 7.47 (dd, *J*=9.3, 2.3 Hz, 1H, 4′-H), 7.50 (d, *J*=2.3 Hz, 1H, 6′-H), 8.44 (s, 2H, 4,6-H), 11.60 (s, 1H, 2′-OH), 12.32 (s, 1H, 1-OH). ^{13}C NMR: 53.0 (2×CH_3), 116.9 (C-5), 119.4 (1′), 120.4 (C-3′), 123.8 (C-5′), 127.7 (C-1,3), 131.6 (C-6′), 136.5 (C-4′), 137.3 (C-4,6), 161.6 (C-2′), 164.4 (C-2), 167.2 (1,3-C=O), 197.2 (5-C=O). EIMS *m*/*z* (%) 364/366 (29, $M^{+\bullet}$), 332/334 (100), 300/302 (30), 288/290 (18), 272/274 (90), 244/246 (30), 205/207 (35), 155/157 (50). Anal. Calcd for $C_{17}H_{13}ClO_7$ (364.73): C, 55.98; H 3.59%. Found: C, 55.79; H, 3.66%.

*4.2.8. Dimethyl 5-(5-chloro-2-hydroxy-4-methyl-benzoyl)-2-hydroxyisophthalate (**5g**)*

Yield 0.202 g, 52%, white solid, mp 146–149 °C (CH_2Cl_2–ether); IR (Nujol) ν_{max}: 3443, 1752, 1690 cm^{-1}. ^1H NMR: 2.43 (s, 3H, CH_3), 4.00 (s, 6H, 2×CH_3), 7.00 (s, 1H, 3′-H), 7.49 (s, 1H, 6′-H), 8.43 (s, 2H, 4,6-H), 11.65 (s, 1H, 2′-OH), 12.32 (s, 1H, 2-OH). ^{13}C NMR: 20.9 (4′-CH_3), 53.0 (2×OCH_3), 116.8 (C-5), 117.7 (1′), 120.8 (C-3′), 124.5 (C-5′), 127.9 (C-1,3), 132.0 (C-6′), 137.2 (C-4,6), 146.1 (C-4′), 161.6 (C-2′), 164.3 (C-2), 167.3 (1,3-C=O), 196.9 (5-C=O). EIMS *m*/*z* (%) 378/380 (45, $M^{+\bullet}$), 346/348 (100), 314/316 (40), 302/304 (30), 286/288 (73), 258/260 (30), 205 (20), 169/171 (40). Anal. Calcd for $C_{18}H_{15}ClO_7$ (378.76): C, 57.08; H 3.99%. Found: C, 56.89; H, 4.03%.

References and notes

1. (a) Dewick, P. M. In *The Flavonoids: Advances in Research Since 1986*; Harborne, J. B., Ed.; Chapman & Hall: New York, NY, 1994; pp 117–238; (b) Gill, M. In *The Chemistry of Natural Products*, 2nd ed.; Thomson, R. H., Ed.; Blackie: Surrey, 1993; pp 60–105; (c) *Flavonoids in the Living Systems: Advances in Experimental Medicine and Biology*; Manthey, J. A., Buslig, B. S., Eds.; Plenum: New York, NY, 1998; Vol. 439.
2. (a) Korkina, G. L.; Afanas'ev, I. B. In *Advances in Pharmacology*; Sies, H., Ed.; Academic: San Diego, 1997; Vol. 38, pp 151–163; (b) *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon: New York, NY, 1990; Vol. 6.
3. (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904–7905; (b) Valenti, P.; Bisi, A.; Rampa, A.; Belluti, F.; Gobbi, S.; Zampiron, A.; Carrara, M. *Bioorg. Med. Chem.* **2000**, *8*, 239–246; (c) Singh, G.; Singh, L.; Ishar, M. P. S. *Tetrahedron* **2002**, *58*, 7883–7890.
4. (a) Larget, R.; Lockhart, B.; Renard, P.; Largeron, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 835–838; (b) Groweiss, A.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod.* **2000**, *63*, 1537–1539; (c) Pietta, P. G. *J. Nat. Prod.* **2000**, *63*, 1035–1042.
5. (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075–3082; (b) Sandulache, A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron* **2002**, *58*, 105–114.
6. Eiden, F.; Breugst, J. *Chem. Ber.* **1979**, *112*, 1791–1817.
7. Quiroga, J.; Mejía, D.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *J. Heterocycl. Chem.* **2002**, *39*, 51–54.
8. Quiroga, J.; Rengifo, A.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A. *Tetrahedron Lett.* **2002**, *43*, 9061–9063.
9. Vanden Eynde, J. J.; Hecq, N.; Kataeva, O.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 1785–1791.
10. Fitton, A. O.; Houghton, P. G.; Suschitzky, H. *Synthesis* **1979**, 337–339.
11. Cremmins, P. J.; Hayes, R.; Wallace, T. W. *Tetrahedron* **1991**, *47*, 9431–9438.
12. (a) Borrell, J. I.; Teixidó, J.; Schuler, E.; Michelotti, E. *Tetrahedron Lett.* **2001**, *42*, 5331–5334; (b) Sabitha, G.; Babu, R. S.; Yadav, J. S. *Synth. Commun.* **1998**, *28*, 4571–4576; (c) Abdel-Rahman, A. H.; Hammouda, M. A. A.; El-Desoky, S. I. *Heteroat. Chem.* **2005**, *16*, 20–27.
13. Bruno, O.; Schenone, S.; Ranise, A.; Bondavalli, F.; Barocelli, E.; Ballabeni, V.; Chiavarini, M.; Bertoni, S.; Tognolini, M.; Impicciatore, M. *Bioorg. Med. Chem.* **2001**, *9*, 629–636.
14. Clarke, P. D.; Fitton, A. O.; Kosmirak, M.; Suschitzky, H.; Suschitzky, J. L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1747–1756.
15. Eiden, F.; Rademacher, G.; Schünemann, J. *Arch. Pharm.* **1984**, *317*, 539–547.
16. Kubo, K.; Ukawa, K.; Kuzuna, S.; Nohara, A. *Chem. Pharm. Bull.* **1986**, *34*, 1108–1117.
17. (a) Ghosh, C. K.; Khan, S. *Synthesis* **1981**, 903; (b) Bandyopadhyay, C.; Sur, K. R.; Patra, R. *J. Chem. Res., Synop.* **1998**, 802–803.
18. (a) Langer, P.; Saleh, N. N. R.; Freifeld, I. *Chem. Commun.* **2002**, 168–169; (b) Appel, B.; Saleh, N. N. R.; Langer, P. *Chem.—Eur. J.* **2006**, *12*, 1221–1236; (c) Ullah, E.; Appel, B.; Fischer, C.; Langer, P. *Tetrahedron* **2006**, *62*, 9694–9700.
19. (a) Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, *44*, 7921–7923; (b) Nguyen, V. T. H.; Appel, B.; Langer, P. *Tetrahedron* **2006**, *62*, 7674–7686; (c) Lubbe, M.; Appel, B.; Flemming, A.; Fischer, C.; Langer, P. *Tetrahedron* **2006**, *62*, 11755–11759; (d) Yawer, A. M.; Hussain, I.; Fischer, C.; Görls, H.; Langer, P. *Tetrahedron* **2008**, *64*, 894–900.
20. Holtz, E.; Albrecht, U.; Langer, P. *Tetrahedron* **2007**, *63*, 3293–3301.
21. (a) Liou, J.-P.; Chang, J.-Y.; Chang, C.-W.; Chang, C.-Y.; Mahindroo, N.; Kuo, F.-M.; Hsieh, H.-P. *J. Med. Chem.* **2004**, *47*, 2897–2905; (b) Liou, J.-P.; Chang, C.-W.;

Song, J. S.; Yang, Y. S.; Yeh, C. F.; Tseng, H. Y.; Lo, Y. K.; Chang, C.-L.; Chang, C.-M.; Hsieh, H.-P. *J. Med. Chem.* **2002**, *45*, 2556–2562; (c) Pettit, G. R.; Toki, B.; Herald, D. L.; Verdier-Pinard, P.; Boyd, M. R.; Hamel, E.; Pettit, R. K. *J. Med. Chem.* **1998**, *41*, 1688–1695.
22. (a) Müller, K.; Leukel, P.; Ziereis, K.; Gawlik, I. *J. Med. Chem.* **1994**, *37*, 1660–1669; (b) Carter, G. T.; Nietsche, J. A.; Goodman, J. J.; Torrey, M. J.; Dunne, T. S.; Siegel, M. M.; Borders, D. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1271–1273; (c) Kaneda, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiot.* **1981**, *34*, 1366–1368.
23. Cai, X.; Sakamoto, M.; Fujitsuka, M.; Majima, T. *Chem.—Eur. J.* **2005**, *11*, 6471–6477 and references cited therein.
24. Langhals, H.; Fuchs, K. *Chem. Unserer Zeit* **2004**, *38*, 98–112 and references cited therein.
25. Buchta, E.; Egger, H. *Chem. Ber.* **1957**, *90*, 2760–2763.
26. Shiue, J. S.; Lin, M. H.; Fang, J. M. *J. Org. Chem.* **1997**, *62*, 4643–4649.
27. Sidwell, W. T. L.; Fritz, H.; Tamm, C. *Helv. Chim. Acta* **1971**, *54*, 207–215.
28. Tamm, C. *Arzneim. Forsch.* **1972**, *22*, 1776–1784.
29. Raistrick, H.; Stickings, C. E.; Thomas, R. *Biochem. J.* **1953**, *55*, 421–433.
30. Pero, R. W.; Harvan, D.; Blois, M. C. *Tetrahedron Lett.* **1973**, *14*, 945–948.
31. Schmidt, J. M.; Tremblay, G. B.; Pagé, M.; Mercure, J.; Feher, M.; Dunn-Dufault, R.; Peter, M. G.; Redden, P. R. *J. Med. Chem.* **2003**, *46*, 1289–1292.
32. Pandey, J.; Jha, A. K.; Hajela, K. *Bioorg. Med. Chem.* **2004**, *12*, 2239–2249.
33. Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870–1873.
34. Bringmann, G.; Reuscher, H. *Tetrahedron Lett.* **1989**, *30*, 5249–5252.
35. (a) Alo, B. I.; Kandil, A.; Patil, P. A.; Scharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763–3768; (b) Nguyen, V. T. H.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 1013–1015; (c) Zhou, Q. J.; Worm, K.; Dolle, R. E. *J. Org. Chem.* **2004**, *691*, 5147–5149.
36. Gammill, R. B. *J. Org. Chem.* **1979**, *22*, 3988–3990.
37. The multiplicities and chemical shifts of the aromatic protons have been confirmed after simulation with program SpinWorks, version 2.5, available from ftp://davinci.chem.umanitoba.ca.
38. Complete crystallographic data for compounds **4c** and **5d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 694985 and CCDC 694986. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (int. code): +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk).