DOI: 10.1002/ejoc.200600082

Domino Michael/Retro-Michael/Mukaiyama-Aldol Reactions of 1,3-Bis-Silyl Enol Ethers with 3-Acyl- and 3-Formylbenzopyrylium Triflates – Synthesis of Functionalised 2,4′-Dihydroxybenzophenones

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Keywords: Benzophenones / Cyclisations / Chromones / Domino reactions / Silyl enol ethers

The reaction of 1,3-bis-silyl enol ethers with 3-acyl- and 3-formylbenzopyrylium triflates, which can be generated in situ from 3-acyl- and 3-formylchromones, affords a great variety of functionalised 2,4′-dihydroxybenzophenones and 4-(2-hydroxybenzoyl)salicylates. These products are formed by a domino Michael/retro-Michael/Mukaiyama-aldol reaction. This methodology is successfully applied to the synthesis of novel UV-A/B and UV-B filters. Three 4-(2-hydroxybenzoyl)salicylic acids show a good in vitro activity in a selectin bioassay.
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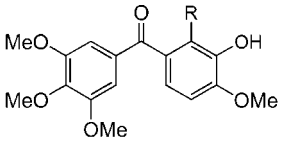
Introduction

Functionalised benzophenones have found various medicinal and technical applications. They occur in a variety of natural products and represent important core structures for the development of pharmaceuticals.[1] For example, the benzophenone phenstatin has been reported to be an antitubulin agent.[2] Microtubules are an important target for anticancer therapy. Recently, Hsieh and co-workers reported the synthesis of cytotoxic 2-hydroxy- and 2-aminobenzophenones as potent antitubulin agents.[3a,3b]



Phenstatin (R = H)
Antitubulin agents (R = OH, NH_2)

Benzophenones are widely used as photosensitizers and represent one of the most important substance classes in photochemistry.[4] 2-Hydroxybenzophenones are also widely used as sun-protecting materials.[5] Long exposure to sunlight may cause photoallergic and cytotoxic reactions and skin cancer; the latter is induced by photochemical reactions of the DNA (e.g. [2+2] cycloadditions of thymin). The most dangerous irradiation of sunlight lies in the range 320–290 nm, although higher wavelengths also contribute significantly to the negative effects of sunlight. Optimal sun-protecting materials should have a broad and strong absorption of UV-A (400–320 nm) and UV-B irradiation (320–280 nm). Other important parameters of sun-protecting materials include photostability, thermostability, chemical stability (particularly against water) and a moderate lipophilicity. In fact, a high water-solubility decreases the protection in water; in contrast, a too high lipophilicity results in rapid absorption of the material by the skin and thus reduced protection. Sun-protecting materials often contain a mixture of UV-A and UV-B filters.[5] Salicylates (e.g. ethylhexyl salicylate) and dibenzoylmethanes (e.g. 4-butyl-4′-methoxydibenzoylmethane) are widely used UV-B and UV-A filters, respectively. Alternatively, UV-A/B filters, which combine a UV-A and UV-B filter in one molecule, are also frequently employed. Functionalised benzophenones, such as benzophenone-3 (oxybenzone), are widely used UV-A/B filters.[5] However, due to allergic reactions brought about by the photosensitizing effects of oxybenzone, the development of new UV-A/B filters is of considerable interest.

Classic syntheses of benzophenones mainly rely on reactions of aryllithium or -magnesium reagents with aldehydes and subsequent oxidation of the alcohol thus formed;[3a] Friedel–Crafts acylations have also been used.[6] For the synthesis of *functionalised* benzophenones (e.g. containing a hydroxy, halide or ester group), however, these methods give unsatisfactory results due to competing side-reactions.

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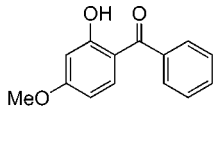
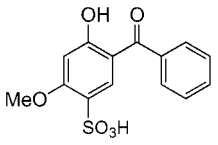


Benzophenone-3
(Oxybenzone)
λ_{max1} = 325 nm
λ_{max2} = 288 nm



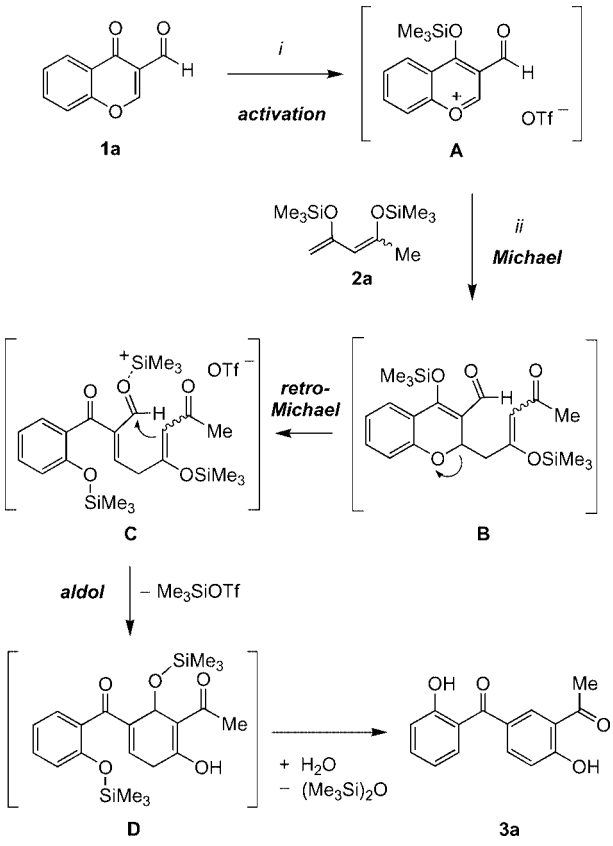
Benzophenone-4
λ_{max1} = 323 nm
λ_{max2} = 285 nm

The development of alternative methods is therefore of considerable interest.[7] Recently, we reported[8] a new approach to 4-(2-hydroxybenzoyl)salicylates by domino Michael/retro-Michael/Mukaiyama-aldol reactions of 3-formylchromones[9–11] with 1,3-bis-silyl enol ethers.[12,13] Herein, we report full details of these studies. The preparative scope has been considerably extended with regard to our preliminary communication,[8]and the method has been applied to the synthesis of novel selectin antagonists and UV-A/B filters.

Results and Discussion

Mechanism

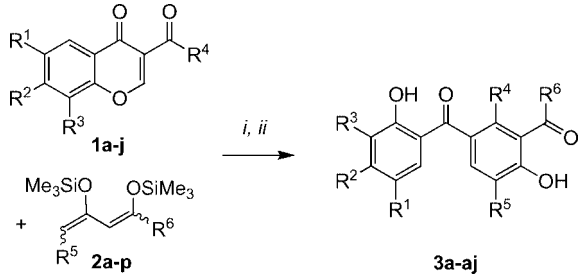
The reaction of 3-formylchromone (**1a**) with 1,3-bis-silyl enol ether **2a**, which is readily available from acetylacetone,[13b] affords 2,4′-dihydroxybenzophenone (**3a**). The presence of TMSOTf (0.3 equiv.) proved to be an important parameter during the optimisation of the reaction; the use of stoichiometric amounts of the Lewis acid, however, did not result in an increase of the yield. The reaction proved to be robust against minor changes of the reaction time and temperature. However, the use of no or other Lewis acids proved to be unsuccessful (decomposition). The formation of **3a** can be explained by a domino Michael/retro-Michael/Mukaiyama-aldol reaction (Scheme 1). The reaction of 3-formylchromone with TMSOTf afforded the benzopyrylium triflate **A**.[14,15] The reaction of **A** with the terminal carbon atom of **2a** gives intermediate **B**, which undergoes a retro-Michael reaction to give the polyketide **C**. An intramolecular aldol reaction gives intermediate **D**, which is transformed into **3a** by elimination of siloxane.



Scheme 1. Mechanism of the formation of **3a**: i) Me_3SiOTf (0.3 equiv.), 20 °C, 10 min; ii) 1. **2a** (1.3 equiv.), CH_2Cl_2, 0 → 20 °C, 12 h; 2. HCl (10%).

Synthesis of 2,4′-Dihydroxybenzophenones

The cyclisation of 3-formylchromone (**1a**) with 1,3-bis-silyl enol ether **2b**, which was prepared from benzoylacetone, afforded 2,4′-dihydroxybenzophenone **3b** (Scheme 2, Table 1). The 4-(2-hydroxybenzoyl)salicylates **3c**,**d** were prepared by reaction of the β-keto ester derived from 1,3-bis-silyl enol ethers **2c**,**d** with **1a**. The alkyl-substituted 4-(2-hydroxybenzoyl)salicylates **3e**–**m** were prepared by cyclisation of **1a** with 1,3-bis-silyl enol ethers containing an alkyl group located at carbon atom C-4. The cyclisation of 1,3-bis-silyl enol ethers with functionalised 3-formylchromones afforded the alkyl-, nitro-, chloro- and bromo-substituted 4-(2-hydroxybenzoyl)salicylates **3n**–**ae**. The reaction of **1a** with 1,3-bis-silyl enol ethers containing a terminal methoxy and benzyloxy functionality proved to be unsuccessful. The cyclisation of 3-acetylchromone with 1,3-bis-silyl enol ethers gave the methyl-substituted 4-(2-hydroxybenzoyl)salicylates **3ah**–**aj**. The yields vary in the range 36–82%. The presence of functional groups located at the chromone moiety and the use of substituted 1,3-bis-silyl enol ethers had no major influence on the yields of the reactions. In some reactions, a small amount of starting material could be recovered. However, the yields could not be improved by variation of the stoichiometry of the starting materials. The formation of side-products could not be detected.



Scheme 2. Synthesis of **3a**–**aj**: i) Me_3SiOTf (0.3 equiv.) 20 °C, 10 min; ii) 1. **2a**–**p** (1.3 equiv.), CH_2Cl_2, 0 → 20 °C, 12 h; 2. HCl (10%).

The structure of the products was established by spectroscopic methods. The ^1H NMR spectra show the presence of two low-field signals assigned to the intramolecular O–

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Table 1. Products and yields.

1	2	3	R^1	R^2	R^3	R^4	R^5	R^6	Yield of **3** [%][a]
a	**a**	**a**	H	H	H	H	H	Me	43
a	**b**	**b**	H	H	H	H	H	Ph	61
a	**c**	**c**	H	H	H	H	H	OEt	51
a	**d**	**d**	H	H	H	H	H	OR[b]	51
a	**e**	**e**	H	H	H	H	Me	OMe	56
a	**f**	**f**	H	H	H	H	Et	OEt	53
a	**g**	**g**	H	H	H	H	*n*Pr	OEt	51
a	**h**	**h**	H	H	H	H	Allyl	OEt	42
a	**i**	**i**	H	H	H	H	*n*Bu	OEt	62
a	**j**	**j**	H	H	H	H	*n*Oct	OEt	43
a	**k**	**k**	H	H	H	H	*n*Non	OEt	61
a	**l**	**l**	H	H	H	H	*n*Dec	OEt	58
a	**m**	**m**	H	H	H	H	Bn	OEt	48
b	**c**	**n**	Me	H	H	H	H	OEt	57
c	**b**	**o**	*i*Pr	H	H	H	H	Ph	58
d	**c**	**p**	Cl	H	H	H	H	OEt	46
d	**f**	**q**	Cl	H	H	H	Et	OEt	55
d	**g**	**r**	Cl	H	H	H	*n*Pr	OEt	46
e	**f**	**s**	NO_2	H	H	H	Et	OEt	63
f	**c**	**t**	Cl	Me	H	H	H	OEt	56
f	**f**	**u**	Cl	Me	H	H	Et	OEt	51
g	**f**	**v**	Me	H	Me	H	Et	OEt	46
g	**h**	**w**	Me	H	Me	H	Allyl	OEt	47
h	**a**	**x**	Cl	H	Cl	H	H	Me	52
h	**c**	**y**	Cl	H	Cl	H	H	OEt	82
h	**f**	**z**	Cl	H	Cl	H	Et	OEt	42
h	**g**	**aa**	Cl	H	Cl	H	*n*Pr	OEt	52
h	**h**	**ab**	Cl	H	Cl	H	Allyl	OEt	57
h	**i**	**ac**	Cl	H	Cl	H	*n*Bu	OEt	53
h	**j**	**ad**	Cl	H	Cl	H	*n*Oct	OEt	56
i	**f**	**ae**	Br	H	Br	H	Et	OEt	54
a	**n**	**af**	H	H	H	H	OMe	OMe	0
a	**o**	**ag**	H	H	H	H	OBn	OEt	0
j	**c**	**ah**	H	H	H	Me	H	OEt	42
j	**f**	**ai**	H	H	H	Me	Et	OEt	48
j	**p**	**aj**	H	H	H	Me	*n*Hex	OEt	36

[a] Isolated yields. [b] R = $(CH_2)_2OCH_3$.

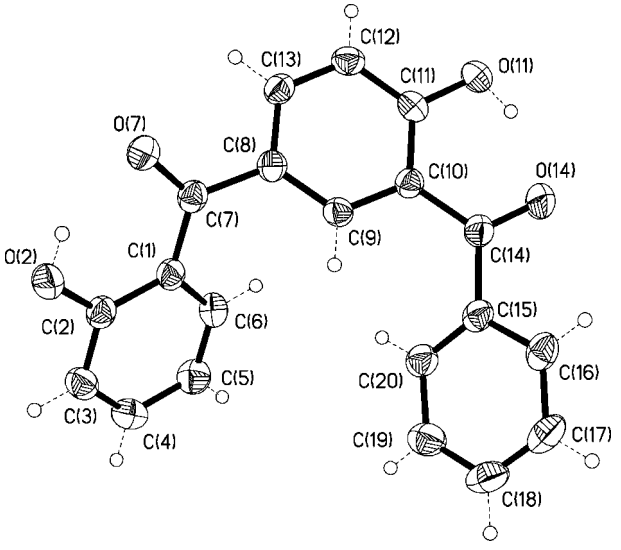
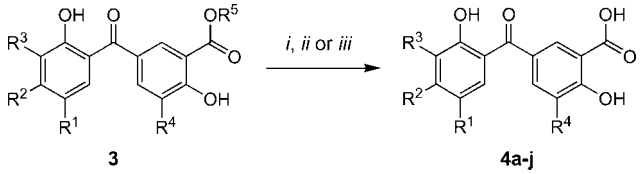


Figure 1. ORTEP plot of **3b**.

H···O hydrogen bonds. The structure of 2,4′-dihydroxybenzophenone **3b** was independently confirmed by an X-ray crystal structure analysis (Figure 1).[16] Two hydrogen bonds are present in the solid state.

Biological Evaluation

In addition to filtering UV-A/B irradiation, benzophenones including a salicylic substructure, like **4a**–**j**, are interesting compounds for medical applications against inflammatory disorders. They belong to a promising compound class for modulating the lectin domain of selectins. E-, P- and L-selectin play an important role in the early stages of inflammatory processes that occur in chronic asthma, chronic obstructive pulmonary disease (COPD), psoriasis, dermatitis, rheumatoid arthritis or Crohn's disease.[17] The 4-(2-hydroxybenzoyl)salicylic acids **4a**–**j** were prepared by hydrolysis of the corresponding esters in order to increase their water solubility (Scheme 3, Table 2). The acids **4b**–**e** and **4g**–**j** were tested for their activity as selectin antagonists. With slight modifications, the ELISA-type assay was performed according to the method of Weitz-Schmidt.[18] Sialyl Lewis^x and tyrosine sulfate modified polymer instead of Sialyl Lewis^a were used as the synthetic selectin ligand. In addition to E-selectin, P- and L-selectin have also been used for binding. The concentration of the substrates in the bioassays was 100 μM. The 4-(2-hydroxybenzoyl)salicylic acids **4e**, **4i** and **4j** showed a good in vitro activity in our selectin bioassay (Table 3). The best activity was observed for **4j**. The non-peptidic and non-glycosidic nature of **4e**,**i**,**j** and their low molecular weight represent interesting structural features that are different from those of most of the known selectin antagonists.



Scheme 3. Synthesis of **4a**–**j**: i) 1. aqueous KOH (10%, 13.0 equiv.), DMSO, 20 °C, 12 h; 2. aqueous HCl (1 M); ii) 1. aqueous KOH (2 M, 4.0 equiv.), 20 °C, 36 h; 2. aqueous HCl (10%); iii) 1. BBr_3 (4.0 equiv.), CH_2Cl_2, 0 → 20 °C, 12 h; 2. aqueous HCl (10%).

Table 2. Products and yields.

3	4	R^1	R^2	R^3	R^4	R^5	Method[a]	Yield of **4** [%][b]
c	**a**	H	H	H	H	Et	*i*	88[c]
e	**b**	H	H	H	Me	Me	*ii*	100
h	**c**	H	H	H	Allyl	Et	*ii*	100
i	**d**	H	H	H	*n*Bu	Et	*ii*	100
m	**e**	H	H	H	Bn	Et	*ii*	100
t	**f**	Cl	Me	H	H	Et	*iii*	82[c]
u	**g**	Cl	Me	H	Et	Et	*ii*	100
v	**h**	Me	H	Me	Et	Et	*ii*	100
w	**i**	Me	H	Me	Allyl	Et	*ii*	100
ac	**j**	Cl	H	Cl	*n*Bu	Et	*ii*	100

[a] See legend of Scheme 3. [b] Conversion. [c] Isolated yield.

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Table 3. In vitro activity in selectin bioassays.

4	E-selectin[a]	P-selectin[a]	L-selectin[a]
e	10	77	48
i	–	78	58
j	16	94	89

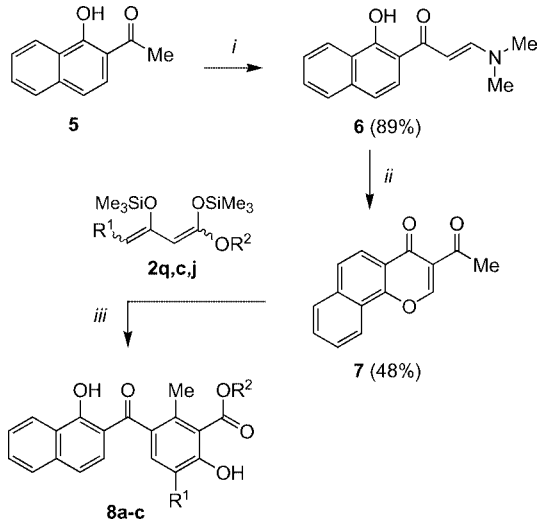
[a]% Inhibition.

Synthesis of 2,4′-Dihydroxynaphthophenones

The reaction of 2-acetylnaphth-1-ol (**5**) with diethoxy-*N*,*N*-dimethylmethanamine afforded **6**, which was transformed into 3-acetyl-4*H*-benzo[*h*]chromen-4-one (**7**). The cyclisation of **7** with 1,3-bis-silyl enol ethers afforded the 2,4′-dihydroxynaphthophenones **8a**–**c** (Scheme 4, Table 4). The structure of **8a** was independently confirmed by an X-ray crystal structure analysis (Figure 2).[16] As expected, two intramolecular hydrogen bonds O–H···O are present.

UV Absorption

Optimal UV-A/B filters require a broad and strong absorption in the UV-A and UV-B region. Oxybenzone exhibits its absorptions at λ_{max} = 325 and 288 nm and is a widely used UV-A/B filter. However, the UV-B absorption of oxybenzone is relatively weak and therefore it has to be used together with a strong UV-B filter.[5] Allergic reactions of the skin have been reported for oxybenzone due to its photosensitizing properties.[19] Therefore, sun-protecting materials containing oxybenzone must be adequately labelled within the European Union. To develop a new UV-A/B filter, we have studied the UV absorptions of a great variety of 2,4′-dihydroxybenzophenones (Table 5). The best results were observed for benzophenones **3a**, **3g**, **3j** and **3k**, all of which exhibit strong absorptions in the range of λ_{max} = 318–323 and 285–291 nm; **3m** and **3n** show strong absorptions at λ_{max} = 348 and 289 nm, respectively. The lipophilicity of these promising UV-A/B filters varies depending on the alkyl groups. Tuning of the lipophilicity should be also possible by varying the ester group. The 2,4′-dihydroxynaphthophenone **8a** exhibits strong absorptions at λ_{max} = 298 and 287 nm and is thus a promising UV-B filter.



Scheme 4. Synthesis of **8a**–**c**: i) **5** (1.0 equiv.), diethoxy-*N*,*N*-dimethylmethanamine (1.0 equiv.), 20 °C, 12 h; ii) Ac_2O (4 equiv.), pyridine, MeCN, 6 h, reflux, then 12 h, 20 °C; iii) 1. Me_3SiOTf (0.3 equiv.), 0 °C, 10 min, **2c**,**j**,**q** (1.3 equiv.), CH_2Cl_2, 20 °C, 12 h; 2) HCl (10%).

Table 4. Products and yields.

2	8	R^1	R^2	% (**8**)[a]
q	**a**	H	Me	40
c	**b**	H	Et	36
j	**c**	*n*Oct	Et	33

[a] Isolated yields.

In conclusion, we have reported the synthesis of a variety of functionalised 4-(2-hydroxybenzoyl)salicylates by a domino Michael/retro-Michael/Mukaiyama-aldol reaction of 1,3-bis-silyl enol ethers with 3-acyl- and 3-formylbenzopyrylium triflates. The methodology has been successfully applied to the synthesis of novel UV absorbers and selectin antagonists.

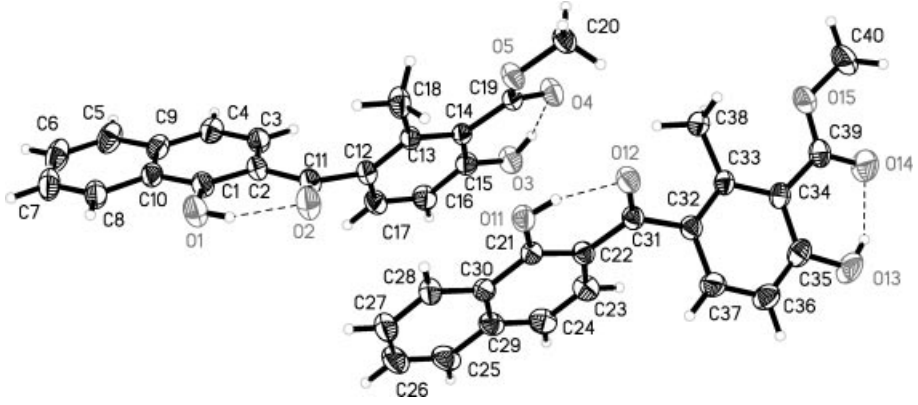


Figure 2. ORTEP plot of **8a**. Selected bond lengths [Å] and angles [°]: C(1)–O(1) 1.3375(16), C(2)–C(11) 1.4668(16), C(11)–O(2) 1.2437(18), C(11)–C(12) 1.4975(18), C(12)–C(17) 1.3990(19), C(14)–C(15) 1.4153(16), C(14)–C(19) 1.4825(15), C(15)–O(3) 1.3518(16), C(19)–O(4) 1.2279(15), C(19)–O(5) 1.3238(14), C(39)–O(14) 1.2267(16), C(39)–O(15) 1.3179(18), C(40)–O(15) 1.4457(18), O(1)–H(1) 0.8400, O(3)–H(3A) 0.8400, O(11)–H(11) 0.8400, O(13)–H(13) 0.8400; O(1)–C(1)–C(2) 122.57(11), O(1)–C(1)–C(10) 116.56(11), C(2)–C(1)–C(10) 120.87(12).

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Table 5. UV absorptions.

Compd.	λ_{max} (lg ε) [nm] in CH_3CN
3a	323 (3.93), 285 (4.02), 250 (4.30)
3b	336 (3.95), 261 (4.35)
3d	283 (4.02), 263 (3.98), 235 (4.23), 214 (4.43)
3e	317 (3.92), 287 (3.99), 238 (4.31), 220 (4.33)
3f	316 (3.90), 290 (3.95), 243 (4.21)
3g	319 (3.91), 291 (3.95), 240 (4.24), 214 (4.46)
3h	317 (3.88), 288 (3.94), 243 (4.20)
3i	320 (3.89), 291 (3.91), 240 (4.24), 215 (4.44)
3j	318 (3.89), 292 (3.92), 244 (4.20)
3k	320 (3.94), 291 (3.97), 241 (4.28), 215 (4.50)
3l	322 (3.85), 292 (3.87), 242 (4.20), 215 (4.41)
3m	348 (4.28), 283 (4.04), 266 (4.07), 236 (3.73)
3n	348 (4.28), 283 (4.04), 266 (4.07), 236 (3.73)
3o	338 (3.53), 263 (3.95), 226 (4.11)
3p	344 (3.73), 286 (3.97), 238 (4.20)
3q	343 (3.77), 297 (3.84), 219 (4.45)
3r	345 (3.78), 297 (3.86), 239 (4.25), 219 (4.48)
3t	344 (3.76), 285 (4.04), 269 (4.02), 223 (4.39), 207 (4.43)
3u	284 (3.40), 247 (4.22)
3v	304 (3.70), 250 (4.09)
3w	355 (3.70), 290 (3.98), 271 (3.98), 242 (4.19), 216 (4.38)
3x	289 (3.90), 248 (4.27), 230 (4.16)
3y	347 (3.69), 291 (4.01), 232 (4.27)
3z	307 (3.90), 245 (4.24)
3aa	346 (3.78), 307 (3.96), 219 (4.51)
3ab	348 (3.75), 304 (3.85), 219 (4.46)
3ac	346 (3.76), 308 (3.86), 220 (4.44)
3ad	306 (3.87), 243 (4.22)
3ae	307 (3.89), 245 (4.26)
3ah	325 (3.80), 254 (4.10), 213 (4.50)
3ai	324 (3.85), 255 (4.21), 215 (4.48)
3aj	324 (3.90), 255 (4.20), 213 (4.50)
4a	283 (3.99), 263 (3.98), 233 (4.19), 212 (4.44)
4f	286 (4.02), 269 (4.01), 222 (4.39), 207 (4.44)
8a	298 (4.19), 287 (4.13), 259 (4.66), 217 (4.67)
8b	298 (4.03), 287 (3.96), 259 (4.42), 215 (4.49)
8c	298 (3.79), 287 (3.69), 259 (4.28), 219 (4.31)

Experimental Section

General Comments: All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data were obtained by electron ionisation (EI = 70 eV), chemical ionisation (CI, H_2O) or electrospray ionisation (ESI). Silica gel (60–200 mesh) was used for preparative scale chromatography. The melting points are corrected.

General Procedure 1 (Synthesis of Benzophenones): Me_3SiOTf (0.3 equiv.) was added to the 3-formylchromone **1** (1.0 equiv.) at 20 °C. After stirring for 10 min, CH_2Cl_2 (8 mL) was added, the solution was cooled to 0 °C and the 1,3-bis-silyl enol ether (1.3 equiv.) was added. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic and aqueous layers were separated and the latter was extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 10:1 → 3:1).

1-[(2-Hydroxybenzoyl)-2-hydroxyphenyl]ethan-1-one (3a): Starting with **1a** (200 mg 1.15 mmol), Me_3SiOTf (77 mg, 0.34 mmol) and 1,3-bis-silyl enol ether **2a** (365 mg, 1.49 mmol), **3a** was isolated as a colourless solid (127 mg, 43%), m.p. 129 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, CH_3), 6.91 (m, 1 H, Ar), 7.08 (d, *J* = 8.7 Hz, 1 H, Ar), 7.10 (dd, *J* = 8.4, *J* = 0.8 Hz, 1 H, Ar), 7.53 (m, 1 H, Ar), 7.58 (dd, *J* = 8.0, *J* = 1.5 Hz, 1 H, Ar), 7.86 (dd, *J* = 8.7, *J* = 2.2 Hz, 1 H, Ar), 8.20 (d, *J* = 2.1 Hz, 1 H, Ar), 11.78 (s, 1 H, OH), 12.68 (s, 1 H, OH) ppm. ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ = 26.8 (CH_3), 118.5, 118.7, 118.8 (CH), 119.0, 119.3, 128.8 (C), 132.7, 133.2, 136.3, 137.4 (CH), 163.0, 165.5 (C–OH), 198.9, 204.5 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3081 (m), 2973 (m), 2925 (m), 1644 (s), 1626 (s), 1588 (s), 1482 (m), 1440 (m), 1423 (m), 1363 (s), 1295 (s), 1241 (s), 1221 (s), 1161 (m), 975 (m), 914 (w), 864 (w), 834 (s), 761 (s), 633 cm^{-1} (m). UV/Vis (CH_3CN): λ_{max} (lg ε) = 425 (3.16), 403 (3.17), 323 (3.93), 285 (4.02), 250 nm (4.30). MS (EI, 70 eV): *m*/*z* (%) 256 (70) [M^+], 241 (14), 213 (9), 163 (17), 136 (6), 121 (100), 92 (14), 66 (22). $C_{15}H_{12}O_4$ (256.26): calcd. C 70.33, H 4.72; found C 70.04, H 4.89.

General Procedure 2 (Synthesis of Benzophenones 3ah–aj): Me_3SiOTf (0.3 equiv.) was added to 3-acetyl-4*H*-chromen-4-one **1j** (1.0 equiv.) at 20 °C. After stirring for 10 min, CH_2Cl_2 (15 mL) was added, the solution cooled down to 0 °C and the 1,3-bis-silyl enol ether **2c**, **2f** or **2p** (1.3 equiv.) was added. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 20:1 → 1:1) to give the methyl-substituted benzophenones **3ah**–**aj**.

Ethyl 5-(2-Hydroxybenzoyl)-6-methylsalicylate (3ah): Starting with 3-acetyl-4*H*-chromen-4-one **1j** (178 mg, 0.95 mmol), Me_3SiOTf (63 mg, 0.29 mmol) and 1,3-bis-silyl enol ether **2c** (365 mg, 1.33 mmol), **3ah** was isolated as a colourless solid (120 mg, 42%), m.p. 109 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.47 (s, 3 H, CH_3), 4.47 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.8 (m, 1 H, Ar), 6.94 (d, *J* = 8.6 Hz, 1 H, Ar), 7.05 (dd, *J* = 8.4, *J* = 1.0 Hz, 1 H, Ar), 7.26 (m, 2 H, Ar), 7.50 (m, 1 H, Ar), 11.44 (s, 1 H, OH), 12.20 (s, 1 H, OH) ppm. ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ = 14.1 (CH_3), 20.6 (OCH_2CH_3), 62.2 (OCH_2CH_3), 113.5 (C), 115.5, 118.3, 118.9 (CH), 120.9 (C), 131.4, 133.1, 133.5, 136.9 (CH), 139.1 (C), 163.2, 163.6 (C–OH), 171.3, 203.9 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3073 (m), 3028 (m), 2987 (m), 2944 (m), 2913 (m), 1664 (s), 1628 (s), 1590 (s), 1476 (s), 1450 (m), 1399 (m), 1376 (s), 1335 (s), 1310 (s), 1289 (m), 1248 (s), 1205 (s), 1145 (m), 1114 (w), 1029 (w), 1000 (w), 936 (w), 842 (w), 807 (m), 765 (s), 645 cm^{-1} (w). UV/Vis (CH_3CN): λ_{max} (lg ε) = 325 nm (3.8), 254 (4.1), 213 (4.5). MS (EI, 70 eV): *m*/*z* (%) = 300 (100) [M^+], 285 (38), 253 (81), 237 (36), 161 (26), 134 (52), 121 (73), 93 (20), 66 (24), 43 (16). $C_{17}H_{16}O_5$ (300.32): calcd. C 67.99 H 5.37; found C 67.85, H 5.35.

5-(2-Hydroxybenzoyl)salicylic Acid (4a): Salicylic acid (**3c**; 1.17 mmol, 336 mg) was added to an aqueous solution of KOH (381 mg in 190 mL of water). After stirring for 4 h at 80 °C the solution was poured into an aqueous solution of hydrochloric acid (1 M). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 3:1 → 1:5) to give **4a** as a colourless solid (266 mg, 88%), m.p. 171 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.12 (br. s, 1 H, COOH), 6.94 (m, 2 H, Ar), 7.06 (d, *J* = 8.7 Hz, 1 H, Ar), 7.31 (dd, *J* = 7.6, *J* = 1.7 Hz, 1 H, Ar), 7.41 (m, 1 H, Ar), 7.89 (dd, *J* = 8.7, *J* = 2.3 Hz, 1 H, Ar), 8.15 (d, *J* = 2.3 Hz, 1 H, Ar), 10.18 (s, 1 H, Ar–OH), 12.60 (br. s, 1 H, Ar–OH) ppm. ^{13}C NMR

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(DEPT, [D$_6$]DMSO, 75.5 MHz): δ = 113.2 (C), 116.5, 117.5, 119.1 (CH), 125.3, 128.6 (C), 129.8, 132.6, 133.0, 136.1 (CH), 156.0, 164.8 (C–OH), 171.2, 194.7 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3410 (m), 3113 (m), 3081 (m), 2930 (m), 2665 (m), 2605 (m), 1685 (s), 1628 (s), 1591 (s), 1487 (s), 1447 (s), 1341(s), 1305 (s), 1249 (s), 1231 (s), 1205 (s), 1161 (m), 1083(m), 979 (w), 847 (m), 796 (m), 758 (s), 695 (m), 667 (m), 631 cm^{-1} (m). UV/Vis (CH_3CN): λ_{max} (lg ε) = 283 (3.99), 263 (3.98), 233 (4.19), 212 nm (4.44). MS (EI, 70 eV): *m*/*z* (%) 258 (3) [M$^+$], 213 (2), 165 (2), 149 (2), 121 (6), 108 (17), 91 (4), 58 (4). HRMS (FT-ICR) calcd. for $C_{14}H_{11}O_5$ ([M + 1]$^+$): 259.06010; found 259.06005.

General Procedure 3 (Synthesis of Salicylic Acids 4b–e/g–j): The salicylic ester (45 μmol) was dissolved in DMSO (0.5 mL) and an aqueous solution of KOH (585 μmol, 0.3 mL) was added at 20 °C. After stirring for 12 h an aqueous solution of hydrochloric acid (1 M, 600 μL) was added. The solvent was removed in vacuo to afford a solid. The solid was suspended in a small amount of water (twice) using an ultrasound bath to wash out KCl. The suspension was centrifuged and the aqueous layer was decanted and the remaining crude samples dried in a Speedvac apparatus to obtain the salicylic acid as a white solid with complete conversion. No further purification was necessary.

5-(2-Hydroxybenzoyl)-3-methylsalicylic Acid (4b): Starting with **3e**, **4b** was isolated as a colourless solid. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.20 (s, 3 H, CH_3), 3.89 (br. s, 1 H, COOH), 6.92 (t, *J* = 7.6 Hz, 1 H, Ar), 6.98 (d, *J* = 8.0 Hz, 1 H, Ar), 7.29 (dd, *J* = 7.6, *J* = 1.5 Hz, 1 H, Ar), 7.39 (td, *J* = 8.0, *J* = 1.5 Hz, 1 H, Ar), 7.81 (br. s, 1 H, Ar), 7.99 (br. s, 1 H, Ar), 10.21 (br. s, 1 H, OH), 12.27 (br. s, 1 H, OH) ppm. MS (ESI, negative mode): *m*/*z* 271.2 [M – H].

5-(5-Chloro-2-hydroxy-4-methylbenzoyl)salicylic Acid (4f): BBr_3 (1.20 mmol, 301 mg, 0.11 mL) was added to a CH_2Cl_2 solution (5 mL) of **3t** (0.26 mmol, 86 mg) at 0 °C. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 3:1 → 1:5) to give **4f** as a colourless solid (65 mg, 82%), m.p. 210 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.32 (s, 3 H, CH_3), 3.48 (br. s, 2 H, Ar–OH, COOH), 6.93 (s, 1 H, Ar), 7.05 (d, *J* = 8.7 Hz, 1 H, Ar), 7.31 (s, 1 H, Ar), 7.88 (dd, *J* = 8.7, *J* = 2.3 Hz, 1 H, Ar), 8.13 (d, *J* = 2.3 Hz, 1 H, Ar), 10.27 (s, 1 H, Ar–OH) ppm. ^{13}C NMR (DEPT, 75.5 MHz, [D$_6$]DMSO): δ = 19.9 (CH_3), 117.6 (CH), 118.9 (C), 118.9 (CH), 123.2, 125.0, 128.3 (C), 129.4, 133.1, 136.1 (CH), 139.9 (C), 154.5, 165.1 (C–OH), 171.1, 192.8 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3412 (m), 3070 (m), 2988 (m), 2929 (m), 1698 (s), 1931 (s), 1584 (s), 1479 (m), 1424 (m), 1354 (s), 1339 (s), 1304 (m), 1258 (s), 1215 (s), 1176 (s), 1082 (w), 843 (w), 793 (m), 752 cm^{-1} (w). UV/Vis (CH_3CN): λ_{max} (lg ε) = 343 (3.81), 286 (4.02), 269 (4.01), 222 (4.39), 207 nm (4.44). MS (EI, 70 eV): *m*/*z* (%) 306 (15) [M$^+$], 288 (2), 168 (23), 147 (5), 121 (3), 77 (5), 45 (4). HRMS (FT-ICR) calcd. for $C_{15}H_{12}ClO_5$ [M + 1]$^+$: 307.03678; found 307.03726.

3-Dimethylamino-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one (6): Diethoxy-*N*,*N*-dimethylmethanamine (5.15 g, 35 mmol) was added to a THF solution (8 mL) of 1-(1′-hydroxynaphthalen-2′-yl)ethanone (**5**; 6.48 g, 35 mmol) and the mixture was stirred for 12 h at 20 °C to give a precipitate. This precipitate was filtered off and washed with water to give 3-dimethylamino-1-(1′-hydroxynaphthalen-2′-yl)prop-2-en-1-one (**6**) as a yellow solid (7.51 g, 89%), m.p. 172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99 (s, 3 H, NCH_3), 3.19 (s, 3 H, NCH_3), 5.83 [d, *J* = 12.2 Hz, 1 H, C(O)C*H*=C], 7.20 (d, *J* = 8.8 Hz, 1 H, Ar), 7.26–7.58 (br. m, 2 H, Ar), 7.66 (d, *J* = 8.9 Hz, 1 H, Ar), 7.72 (d, *J* = 7.6 Hz, 1 H, Ar), 7.93 [d, *J* = 12.2 Hz, 1 H, C=C*H*N(CH_3)$_2$], 8.44 (dd, *J* = 8.2, *J* = 0.6 Hz, 1 H, Ar), 15.85 (s, 1 H, OH) ppm. ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ = 41.2 [N(CH_3)$_2$], 90.3 (CH), 113.2 (C), 117.1, 123.9, 124.1, 125.2 (CH), 125.9 (C), 127.2, 128.7 (CH), 136.5 (C), 154.5 [CH(N)], 162.6 (C–OH), 191.4 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3064 (w), 2926 (w), 2880 (w), 2808 (w), 1914 (w), 1626 (s), 1555 (s), 1500 (s), 1465 (s), 1416 (s), 1388 (m), 1365 (s), 1333 (m), 1278 (s), 1245 (s), 1116 (m), 1199 (m), 1151 (m), 1110 (s), 1073 (m), 1020 (w), 981 (w), 939 (m), 863 (w), 794 (m), 772 (s), 603 cm^{-1} (w). UV/Vis (CH_3CN): λ_{max} (lg ε) = 385 (4.46), 373 (4.47), 350 (4.35), 276 (4.11), 266 (4.11), 241 (4.28), 218 nm (4.40). MS (EI, 70 eV): *m*/*z* (%) 241 (44) [M$^+$], 223 (2), 197 (19), 170 (5), 141 (3), 127 (3), 114 (22), 72 (100), 56 (21), 42 (18). $C_{15}H_{15}NO_2$: calcd. C 74.66 H 6.26, N 5.80; found C 74.72, H 5.73, N 5.77.

3-Acetyl-4*H*-benzo[*h*]chromen-4-one (7): Pyridine (50 mL) and acetic anhydride (4.08 g, 40 mmol) were added to an acetonitrile solution (300 mL) of **6** (2.41 g, 10 mmol) at 20 °C. After stirring for 6 h under reflux, followed by stirring for 12 h at 20 °C, most of the solvent (250 mL) was removed in vacuo and an aqueous solution of hydrochloric acid (10%) was added. After adding CH_2Cl_2 (40 mL) the layers were separated and the aqueous solution was extracted with CH_2Cl_2 (8 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, the filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 5:1) to give 4*H*-benzo[*h*]chromen-4-one as a colourless solid (431 mg, 22%) and 3-acetyl-4*H*-benzo[*h*]chromen-4-one (**7**) as a yellow solid (1.13 g, 48%), m.p. 175 °C.

7: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (s, 3 H, CH_3), 7.68–7.78 (m, 2 H, Ar), 7.84 (d, *J* = 8.7 Hz, 1 H, Ar), 7.96 (m, 1 H, Ar), 8.21 (d, *J* = 8.8 Hz, 1 H, Ar), 8.49 (m, 1 H, Ar), 8.76 (s, 1 H, CH) ppm. ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ = 31.6 (CH_3), 120.7 (C), 120.8 (CH), 121.9 (C), 122.2 (ArCH), 123.6, 123.9 (C), 126.4, 127.6, 128.2, 129.8 (ArCH), 136.1 (C), 160.5 (CH), 175.2, 196.8 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3110 (w), 3076 (m), 3012 (w), 2926 (w), 2362 (w), 1689 (s), 1643 (s), 1595 (m), 1552 (s), 1465 (m), 1443 (m), 1394 (s), 1362 (s), 1311 (s), 1264 (m), 1212 (m), 1154 (w), 1101 (s), 1024 (m), 972 (w), 889 (w), 795 (m), 769 (s), 648 cm^{-1} (m). UV/Vis (CH_3CN): λ_{max} (lg ε) = 339 (3.69), 325 (3.69), 301 (3.81), 246 (4.55), 239 (4.52), 222 (4.42), 212 nm (4.38). MS (EI, 70 eV): *m*/*z* (%) 238 (95) [M$^+$], 223 (100), 196 (44), 171 (74), 139 (40), 126 (40), 113 (55), 88 (9), 64 (11), 53 (21), 43 (23). $C_{15}H_{10}O_3$: calcd. C 75.62 H 4.23; found C 75.13, H 4.15.

General Procedure 4 (Synthesis of Naphthophenones 8a–c): Me_3SiOTf (0.3 equiv.) was added to 3-acetyl-4*H*-benzo[*h*]chromen-4-one (**7**; 1.0 equiv.) at 20 °C. Following general procedure 2, the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 20:1 → 5:1) to give the methyl-substituted benzophenones **8a**–**c**.

Methyl 3-[(1-Hydroxynaphthalen-2-yl)carbonyl]-2-methylsalicylate (8a): Starting with **7** (238 mg, 1 mmol), Me_3SiOTf (67 mg, 1.3 mmol) and 1,3-bis-silyl enol ether **2q** (338 mg, 1.3 mmol), naphthophenone **8a** was obtained as a yellow solid (131 mg, 40%), m.p. 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 6.97 (d, *J* = 8.8 Hz, 1 H, Ar), 7.15–7.19 (m, 2 H, Ar), 7.35 (d, *J* = 8.6 Hz, 1 H, Ar), 7.56 (m, 1 H, Ar), 7.66 (m, 1 H, Ar), 7.74 (dd, *J* = 8.2, *J* = 0.7 Hz, 1 H, Ar), 8.52 (d, *J* = 8.1 Hz, 1 H, Ar), 11.38 (s, 1 H, OH), 14.04 (s, 1 H, OH) ppm. ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ = 20.6 (CH_3), 52.6 (OCH_3), 113.3, 113.8 (C), 115.6, 118.4, 124.5 (CH), 125.2 (C), 126.1, 126.9, 127.5,

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130.6 (CH), 131.7 (C), 133.3 (CH), 137.6, 138.9 (C), 163.6, 163.8 (C–OH), 171.8, 203.5 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3056 (m), 3046 (m), 2957 (m), 1656 (s), 1628 (s), 1601 (s), 1503 (m), 1459 (s), 1417 (m), 1385 (s), 1335 (s), 1275 (s), 1251 (s), 1209 (s), 1145 (m), 1032 (m), 983 (m), 809 (s), 766 (m), 669 cm^{-1} (w). UV/Vis (CH_3CN): λ_{max} (lg ε) = 378 (3.94), 308 (4.08), 298 (4.19), 287 (4.13), 259 (4.66), 217 nm (4.67). MS (EI, 70 eV): *m/z* (%) 336 (14) [M^+], 289 (7), 247 (2), 231 (1), 189 (2), 170 (100), 134 (11), 113 (17), 77 (54), 51 (2). $C_{20}H_{16}O_5$: calcd. C 71.42 H 4.79; found C 70.96, H 4.44.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and spectroscopic data.

Acknowledgments

We are grateful to Dr. M. Noltemeier for carrying out a crystal structure analysis and to Simon Backhaus for experimental contributions. Financial support by the Deutsche Forschungsgemeinschaft, Revotar Biopharmaceuticals AG, the state of Brandenburg (Ministry of Economics), the European Union and by the state of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt "Neue Wirkstoffe und Screeningverfahren") is gratefully acknowledged. The content of this publication is the sole responsibility of the authors.

[1] For salicylic esters and salicylic glycosides (e.g. salicortin), see for example: *Römpp Lexikon Naturstoffe* (Eds.: W. Steglich, B. Fugmann, S. Lang-Fugmann), Thieme, Stuttgart: **1997**.
[2] G. R. Pettit, B. Toki, D. L. Herald, P. Verdier-Pinard, M. R. Boyd, E. Hamel, R. K. Pettit, *J. Med. Chem.* **1998**, *41*, 1688.
[3] a) J.-P. Liou, J.-Y. Chang, C.-W. Chang, C.-Y. Chang, N. Mahindroo, F.-M. Kuo, H.-P. Hsieh, *J. Med. Chem.* **2004**, *47*, 2897; b) J.-P. Liou, C.-W. Chang, J. S. Song, Y. S. Yang, C. F. Yeh, H. Y. Tseng, Y. K. Lo, C.-L. Chang, C.-M. Chang, H.-P. Hsieh, *J. Med. Chem.* **2002**, *45*, 2556.
[4] X. Cai, M. Sakamoto, M. Fujitsuka, T. Majima, *Chem. Eur. J.* **2005**, *11*, 6471, and references cited therein.
[5] H. Langhals, K. Fuchs, *Chem. Unserer Zeit* **2004**, *38*, 98, and references cited therein.
[6] E. Buchta, H. Egger, *Chem. Ber.* **1957**, *90*, 2760.
[7] For the SmI_2-mediated reaction of benzaldehydes with benzyl halides and subsequent oxidation, see: J.-S. Shiue, M.-H. Lin, J.-M. Fang, *J. Org. Chem.* **1997**, *62*, 4643.
[8] P. Langer, B. Appel, *Tetrahedron Lett.* **2003**, *44*, 7921.
[9] For reviews of 3-formylchromone, see: a) G. P. Ellis, *Heterocyclic Compounds* (Ed.: A. Weisberger), **1977**, *35*, 921; b) C. K. Ghosh, C. Ghosh, *Indian J. Chem., Sect. B* **1997**, *36*, 968.
[10] For reactions of 3-formylchromones, see: a) A. Nohara, T. Umetani, Y. Sanno, *Tetrahedron* **1974**, *30*, 3553; b) W. D. Jones, W. L. Albrecht, *J. Org. Chem.* **1976**, *41*, 706; for cyclisations of 3-formylchromone with amidines, see: c) W. Löwe, *Synthesis* **1976**, 274 and d) U. Petersen, H. Heitzer, *Justus Liebigs Ann. Chem.* **1976**, 1663; with enamines: e) D. Heber, *Synthesis* **1978**, 691; with hydrazines: f) F. Eiden, H. Haverland, *Arch. Pharm. (Weinheim Ger.)* **1968**, *301*, 819 and g) C. K. Ghosh, K. K. Mukhopadhyay, *J. Indian Chem. Soc.* **1978**, *55*, 386; with $H_2NOH{\cdot}HCl$: h) R. P. Hsung, C. A. Zificsak, L.-L. Wei, L. R. Zehnder, F. Park, M. Kim, T.-T. T. Tran, *J. Org. Chem.* **1999**, *64*, 8736; with *o*-phenylenediamine: i) C. K. Ghosh, S. Khan, *Synthesis* **1980**, 701. For conversions into pyrroles and thiophenes, see: j) A. O. Fitton, J. R. Frost, H. Suschitzky, P. G. Hougton, *Synthesis* **1977**, 133; for reactions with ketene acetals: k) T. W. Wallace, I. Wardell, K.-D. Li, P. Leeming, A. D. Redhouse, S. R. Challand, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2293; with dienes: l) A. Sandulache, A. M. S. Silva, J. A. S. Cavaleiro, *Tetrahedron* **2002**, *58*, 105.
[11] For reactions of 3-formylchromone with C-nucleophiles, see: a) C. K. Ghosh, S. Khan, *Synthesis* **1981**, 903; b) G. Hass, J. L. Stanton, A. von Sprecher, P. Wenk, *J. Heterocycl. Chem.* **1981**, *18*, 607; c) J. Prousek, *Collect. Czech. Chem. Commun.* **1991**, 1361; d) C. K. Ghosh, C. Bandyopadhyay, S. Biswas, A. K. Chakravarty, *Indian J. Chem., Sect. B* **1990**, *29*, 814; e) C. Bandyopadhyay, K. R. Sur, R. Patra, *J. Chem. Res. Synop.* **1998**, *12*, 802.
[12] For a review of 1,3-bis-silyl enol ethers, see: P. Langer, *Synthesis* **2002**, 441.
[13] a) T.-H. Chan, P. Brownbridge, *J. Chem. Soc., Chem. Commun.* **1979**, 578; b) G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830.
[14] For the activation of chromones towards conjugate addition by the formation of silylated benzopyrylium triflates, see: a) Y.-G. Lee, K. Ishimaru, H. Iwasaki, K. Ohkata, K. Akiba, *J. Org. Chem.* **1991**, *56*, 2058. For thiobenzopyrylium triflates, see: b) U. Beifuss, M. Tietze, H. Gehm, *Synlett* **1996**, 182.
[15] For reactions of benzopyrylium triflates from our laboratory, see: a) P. Langer, N. N. R. Saleh, I. Freifeld, *Chem. Commun.* **2002**, 168; b) P. Langer, B. Appel, *Tetrahedron Lett.* **2003**, *44*, 5133; c) U. Albrecht, M. Lalk, P. Langer, *Bioorg. Med. Chem.* **2005**, *13*, 1531; d) S. Rotzoll, B. Appel, P. Langer, *Tetrahedron Lett.* **2005**, *46*, 4057.
[16] CCDC-286226 (for **3b**) and -286227 (for **8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[17] a) K. Ley, *Trends Mol. Med.* **2003**, *9*, 263; b) M. Sperandio, B. Lange-Sperandio, O. Linderkamp, A. Leo, *Vasc. Dis. Prev.* **2004**, *1*, 185.
[18] G. Weitz-Schmidt, D. Stokmaier, G. Scheel, N. E. Nifant'ev, A. B. Tuzikov, N. V. Bovin, *Anal. Biochem.* **1996**, *238*, 184.
[19] T. Delatour, T. Douke, C. D'Ham, J. Cadet, *J. Photochem. Photobiol., B* **1998**, *44*, 191.

Received: February 1, 2006
Published Online: June 7, 2006

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