Tetrahedron 67 (2011) 7703–7707

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A straightforward conversion of aurones to 2-benzoylbenzofurans: transformation of one class of natural products into another

Samir Yahiaoui, Marine Peuchmaur, Ahcène Boumendjel *

Université de Grenoble/CNRS, UMR 5063, Département de Pharmacochimie Moléculaire, BP 53, 38041 Grenoble Cedex 9, France

ARTICLE INFO

Article history:
Received 5 July 2011
Received in revised form 29 July 2011
Accepted 3 August 2011
Available online 10 August 2011

Keywords:
Aurones
2-Benzoylbenzo[*b*]furans
Conversion
Natural products

ABSTRACT

The naturally occurring aurones (2-benzylidene-3(2*H*)-benzofuran-3-ones) can be easily converted to another class of natural products 2-benzoylbenzo[*b*]furans, via an effective reduction, acid-mediated rearrangement, and oxidation cascade. This easy conversion was conducted without purification of intermediates. This straightforward conversion may be considered as a possible biosynthesis pathway of 2-benzoylbenzo[*b*]furans in plants.

1. Introduction

2-Benzoylbenzo[*b*]furans and aurones (2-benzylidene-3-(2*H*)-benzofuran-3-ones) (Fig. 1) are two naturally occurring classes of compounds, bearing the same carbon skeleton (C_6–C_3–C_6). 2-Benzoylbenzo[*b*]furans have been isolated from different traditional medicine plants[1] and they were the subject of various investigations related to their therapeutic potential.[2] In some circumstances, they were used as intermediates for the synthesis of biological active compounds, such as aromatase inhibitors.[3]

Aurones are frequently isolated from flowers of different plant species, where they are responsible for their gold-yellow color.[4] Recently, the occurrence of aurones in marine sponges was reported.[5] The therapeutic potential of aurones was frequently highlighted in various therapeutical domains, such as cancer, melanoma-related diseases, diabetes, and in cosmetic.[6] 2-Benzoylbenzo[*b*]furans and aurones are regioisomers but so far, these two classes of compounds have never been isolated from the same plant source.

The biogenesis of aurones occurs via cyclization of chalcones, catalyzed by an enzyme, namely aureusidin synthase.[4b,7] However, the biogenesis of 2-benzoylbenzo[*b*]furans is still unknown.

Given the close structural relation between 2-benzoylbenzo[*b*]furans and aurones, it would therefore be very useful to have a reliable, mild, and facile method for the conversion of aurones into 2-benzoylbenzo[*b*]furans. Herein, we report a convenient method for the preparation of 2-benzoylbenzo[*b*]furans via reduction of aurones, rearrangement of the resulting allylic alcohol, and oxidation of the later.

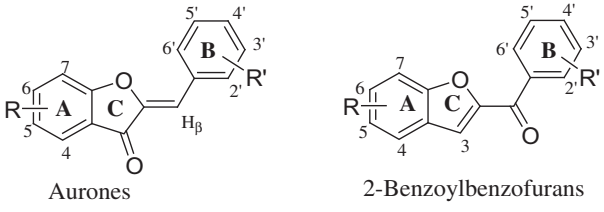


Fig. 1. Structures of aurones (2-benzylidenebenzofuran-3-ones) and 2-benzoylbenzo[*b*]furans.

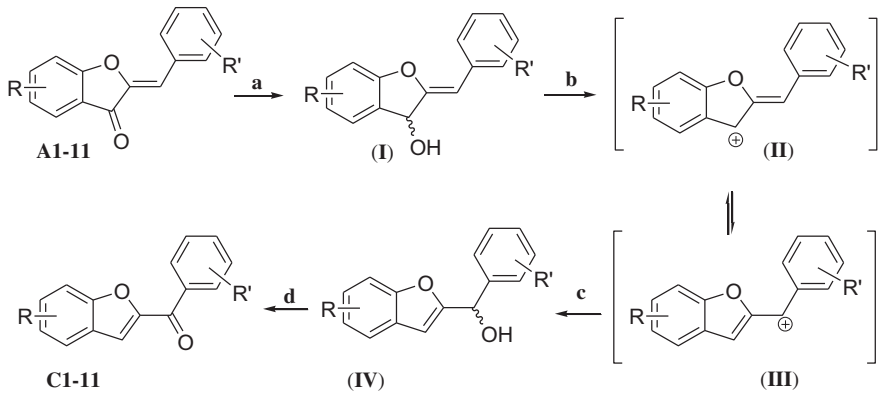
2. Results and discussion

The conversion pathway is described in Scheme 1. The investigated aurones were prepared according to previously reported method[8] and obtained as exclusively *Z*-isomers, corresponding to the configuration of naturally occurring aurones.

The reduction of aurones was performed with sodium borohydride in methanol at room temperature to give the corresponding allylic alcohols (2,3-dihydrobenzofuran-3-ols) (**I**). The obtained alcohols require careful handling, due to their sensitivity to excessive temperature and acidic conditions (see Experimental section). The isomerization step was carried out at room temperature in

* Corresponding author. Tel.: +33 4 76 63 53 11; fax: +33 4 76 63 52 98; e-mail address: Ahcene.Boumendjel@ujf-grenoble.fr (A. Boumendjel).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.08.011



Scheme 1. (a) $NaBH_4$, CH_3OH, rt; (b) CH_3CN/H_2O, aqueous HCl, rt; (c) H_2O, (d) MnO_2, CH_2Cl_2, molecular sieves, rt.

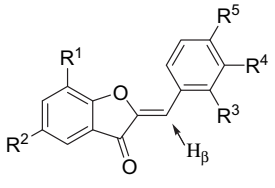
a mixture of water and acetonitrile and in the presence of catalytic amount of aqueous HCl. The reaction was monitored by TLC, which shows that the formed compound (**IV**) was slightly less polar than the starting materiel (**I**) (see Supplementary data). To better handle the resulting product, water is added and the reaction mixture was extracted with dichloromethane and subjected to the final step without evaporating the solvent. The mechanism involves probably a carbocation formation (**II**) then rearrangement of the later to the extracyclic methine carbon (**III**), which would be stabilized by the B-aryl group. The organic solution of the rearranged alcohol was directly used for the oxidation step with 10 equiv of MnO_2 in dry conditions. This three steps conversion was applied to a panel of aurones (**A1**-**11**) (Table 1). The benzoylbenzo[*b*]furans analogs (**C1**-**11**) were obtained with excellent yields (76–86%). The influence of the B-ring substitution pattern on the conversion process was investigated. It appears that, mono-substituted aurones at position 4′ with electron-donating groups as well with electro-withdrawing groups give total conversion (compounds: **C1**, **C2**, and **C3**, Table 1). Additionally, *para*, *ortho*, and *meta* methoxy derivatives were synthesized in order to determine the impact of the substituents position on the B ring (compounds: **C4**, **C5**, and **C6**, Table 1). The results showed that, there is no influence of the position on the obtained yields. Concerning the A ring substitution, our investigation showed that, the conversion is stimulated by the presence of substituent at the 5 or 7 positions. However, despite the use of drastic conditions ($LiAlH_4$, $LiAlH_4/AlCl_3$ at room temperature and in refluxed THF) the reduction of 4- and/or 6-substituted aurones was not fruitful. The reduction was either impossible or leading to a multitude of degradation compounds, and consequently not convertible to targeted benzoylbenzo[*b*]furans.

The structures of the resulting compounds were unambiguously determined by ^1H NMR and confirmed by HMBC experiments. In most cases, the ^1H NMR showed a clear difference of the chemical shifts of protons of aurones and 2-benzoylbenzofurans. The most important difference concerns the chemical shift of the methine proton. In aurones, the methine proton (H_β) appears at ~6.9 ppm, whereas in 2-benzoylbenzofurans, the H_3-proton was observed around 7.5 ppm (Table 1).

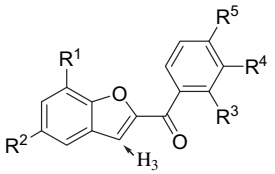
The HMBC experiment conducted on 2-benzoylbenzo[*b*]furans showed a direct correlation between the carbonyl-carbon and the *ortho*-protons of the B-phenyl ring. This type of correlation is missing among aurones (Fig. 2).

It is worth to prove whether this procedure simply isomerizes *Z* to *E*-aurones rather than formation of 2-benzoylbenzofurans (Scheme 2). To investigate this possibility, we synthesized an *E*-aurone (*E*-isomer of aurone A1 in Table 1) according to

Table 1
Scope and yields of the conversion of aurones to benzoylbenzo[*b*]furans and the chemical shifts difference of their methine protons



Aurones (A1-11)



2-Benzoylbenzo[*b*]furans (C1-11)

Compounds	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)	δ H_3 (ppm) (**C1**–**C11**)	δ H_β (ppm) (**A1**–**A11**)
C1	H	H	H	H	OMe	81	7.53	6.89
C2	H	H	H	H	CO_2Me	79	7.60	6.88
C3	H	H	H	H	F	76	7.56	6.86
C4	OMe	H	H	H	OMe	83	7.53	6.90
C5	OMe	H	H	OMe	H	82	7.54	6.89
C6	OMe	H	OMe	H	H	80	7.31	7.52
C7	OMe	H	H	H	Cl	86	7.57	6.85
C8	H	OMe	F	H	F	81	7.47	7.14
C9	H	OMe	H	H	OMe	80	7.47	6.92
C10	OMe	H	H	OMe	OMe	77	7.59	6.95
C11	OMe	H	OMe	OMe	OMe	79	7.38	7.39

[a] Yield of three steps.

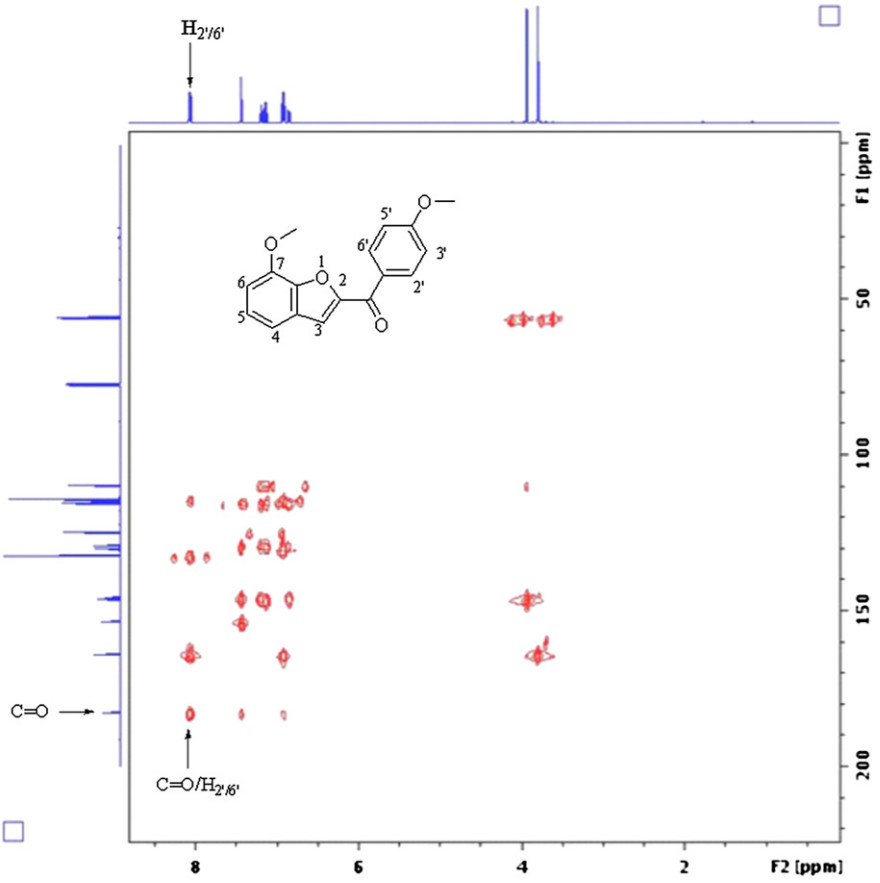
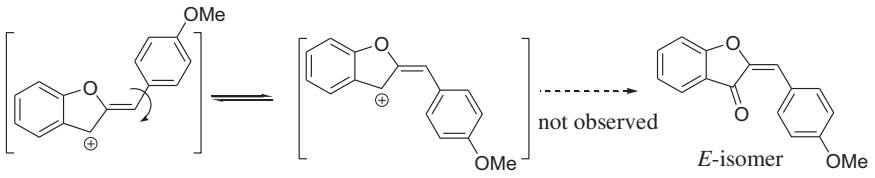


Fig. 2. The correlation between 2′,6′ protons with the C=O of 2-benzoylbenzo[*b*]furans, evidenced by HMBC experiment.



Scheme 2. Possible isomerization of the intracyclic carbocation.

a photochemical approach reported by Venkateswarlu et al.[9] and compared its ^{1}H and ^{13}C NMR with the obtained 2-benzoylbenzo[*b*]furans. The NMR data was quite different, thus ruling out the possibility of simple isomerization.

3. Conclusion

The reported transformation sequence can have multiple applications and interest. First, the sequence may be exploited for the preparation of bioactive 2-benzoylbenzo[*b*]furans starting from aurones. Second, since the biosynthesis of 2-benzoylbenzo[*b*]furans has never been reported, this conversion could be examined as a potential biogenesis pathway of naturally occurring benzofurans. The later assessment is supported by the fact that the conversion process (reduction, rearrangement, and oxidation) could be easily achieved by plant enzymes. Finally, the reported NMR data makes clear discrimination between aurones and 2-benzoylbenzo[*b*]furans, which is of valuable help for the phytochemists community, working on the isolation and structure elucidation of aurones and 2-benzoylbenzo[*b*]furans.

4. Experimental section

4.1. General information and materials

^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz at ambient temperature on a Bruker Avance-400 instrument. The chemical shifts (δ) for ^{1}H NMR and ^{13}C NMR are reported in parts per million. ESI mass spectra and elemental analyses were performed at the analysis facilities of the department of chemistry of the University of Grenoble. Aurones were obtained following literature methods.[8] Sodium borohydride and manganese oxide were purchased from Sigma–Aldrich and used as received. The other reagents and solvents were obtained from commercial sources and used as received.

4.2. General experimental procedure

4.2.1. The reduction procedure. To a solution of 100 mg of an aurone in methanol (15 mL) was added $NaBH_4$ (4 equiv). The mixture was stirred at room temperature for 10–40 min (see Supplementary

data). After reaction completion (as monitored by TLC, cyclohexane/EtOAc 7:3), water was added. After stirring for few seconds, a suspension was formed. The reduced aurone (2,3-dihydrobenzofuran-3-ols) was filtered off and washed with water to obtain a white solid. According to the TLC, the resulting solid was pure, thus, it was used as obtained for the next step.

4.2.2. The rearrangement procedure. In a dry flask, the reduced aurone was dissolved in acetonitrile (10 mL), then a solution of aqueous HCl (10 mL H_2O+0.1 mL of HCl 10%) was added. The reaction mixture was allowed to stir for 10 min to 4 h (see Supplementary data) at room temperature. The reaction was monitored by TLC (cyclohexane/EtOAc 7:3), most of cases, the product of isomerization was slightly less polar than the reduced aurone. TLC with several migrations was needed if the resulting product possesses nearly the same retention factor (R_f) as the reduced aurone. By the end of the reaction, water was added and the mixture was extracted with dicholoromethane (three times), then, the organic layer was dried over $MgSO_4$ and filtered off. The obtained dichloromethane solution was directly used for the oxidation step.

4.2.3. The oxidation procedure. The previous dichloromethane solution was treated with molecular sieves (powder) and the mixture was stirred at room temperature for 5 min, then, 10 equiv of MnO_2 were added and stirring was continued at room temperature for 25 min–3 h 45 min. After reaction completion (monitored by TLC, cyclohexane/EtOAc 7:3), the resulting mixture was filtered off through Celite, then the filtrate was washed with water and the dichloromethane solution was dried over $MgSO_4$ and filtered off. The solvent was removed under reduced pressure to give pure 2-aroylbenzofuran without purification.

4.3. Characterization

4.3.1. 2-(p-Methoxybenzoyl)benzofuran ***C1***. Known;[10] yellow powder; mp 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12 (d, J=8.9 Hz, 2H), 7.74 (br d, J=7.8 Hz, 1H), 7.63 (dd, J=8.5 and 0.8 Hz, 1H), 7.53 (d, J=0.9 Hz, 1H), 7.50 (td, J=7.8 and 1.2 Hz, 1H), 7.34 (td, J=7.6 and 0.9 Hz, 1H), 7.03 (d, J=8.9 Hz, 2H), 3.92 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 183.8, 164.5, 156.8, 153.6, 132.9, 130.8, 129.0, 128.0, 124.8, 124.1, 116.5, 114.8, 113.4, 56.5. MS (ESI) 253 $(M+H)^+$.

4.3.2. 2-(p-Methyesterbenzoyl)benzofuran ***C2***. Unknown; white powder; mp 171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.25 (d, J=8.5 Hz, 2H), 8.14 (d, J=8.5 Hz, 2H), 7.79 (br d, J=7.9 Hz, 1H), 7.70 (br d, J=8.5 Hz, 1H), 7.60 (d, J=0.8 Hz, 1H), 7.57 (td, J=7.8 and 1.2 Hz, 1H), 7.40 (td, J=7.5 and 0.8 Hz, 1H), 4.03 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 183.7, 166.3, 156.2, 152.0, 140.8, 133.7, 129.8, 129.4, 128.8, 126.9, 124.2, 123.5, 117.1, 112.7, 52.6. MS (ESI) 303 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{12}O_4$: C 72.85%; H 4.32%. Found: C 72.51%; H 4.42%.

4.3.3. 2-(p-Fluorobenzoyl)benzofuran ***C3***. Known;[11] yellow-pale crystal; mp 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14 (dd, J=8.9 and 5.5 Hz, 2H), 7.75 (d, J=7.9 Hz, 1H), 7.65 (br d, J=7.5 Hz, 1H), 7.56 (br s, 1H), 7.52 (td, J=7.4 and 1.2 Hz, 1H), 7.35 (br td, J=7.5 and 0.7 Hz, 1H), 7.23 (t, J=8.6 Hz, 2H). ^{13}C (100 MHz, $CDCl_3$): 183.7, 166.6 (J_{C-F}=255.1 Hz), 156.9, 153.1, 134.3 (J_{C-F}=2.4 Hz), 133.1 (J_{C-F}=9.2 Hz), 129.4, 127.9, 125.0, 124.3, 117.3, 116.7 (J_{C-F}=21.8 Hz), 113.5. MS (ESI) 263 $(M+Na)^+$. Anal. Calcd for $C_{15}H_9O_2F$: C 75.00%; H 3.78%. Found: C 75.36%; H 4.13%.

4.3.4. 7-Methoxy-2-(p-methoxybenzoyl)benzofuran ***C4***. Known;[12] yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16 (d, J=8.9 Hz, 2H), 7.53 (s, 1H), 7.29 (dd, J=7.9 and 1.1 Hz, 1H), 7.23 (t, J=7.8 Hz, 1H), 7.02(d, J=8.9 Hz, 2H), 6.95 (dd, J=7.8 and 1.0 Hz, 1H), 4.03 (s, 3H), 3.90 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 183.3, 164.5, 154.1, 147.0, 146.4, 133.1, 130.7, 129.6, 125.5, 116.3, 115.8, 114.8, 110.2, 57.0, 56.5. MS (ESI) 283 $(M+H)^+$.

4.3.5. 7-Methoxy-2-(m-methoxybenzoyl)benzofuran ***C5***. Known;[12] yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68 (dt, J=7.6 and 1.2 Hz, 1H), 7.58 (dd, J=2.5 and 1.6 Hz, 1H), 7.54 (s, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.30 (dd, J=8.0 and 1.2 Hz, 1H), 7.24 (t, J=7.9 Hz, 1H), 7.18 (ddd, J=8.4; 2.7 and 0.9 Hz, 1H), 6.97 (dd, J=7.7 and 1.1 Hz, 1H), 4.03 (s, 3H), 3.89 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 184.7, 160.6, 153.4, 147.1, 146.7, 139.3, 130.5, 129.5, 125.6, 123.1, 120.4, 117.5, 115.9, 114.8, 110.5, 57.1, 56.4. MS (ESI) 283 $(M+H)^+$.

4.3.6. 7-Methoxy-2-(o-methoxybenzoyl)benzofuran ***C6***. Unknown; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (d, J=7.5 Hz, 1H), 7.49 (td, J=7.2 and 1.8 Hz, 1H), 7.31 (s, 1H), 7.24 (dd, J=7.9 and 1.5 Hz, 1H), 7.21 (t, J=7.9 Hz, 1H), 7.07–7.05 (m, 1H), 7.03–7.01 (m, 1H), 6.94 (dd, J=7.5 and 1.5 Hz, 1H), 4.01 (s, 3H), 3.80 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 185.5, 158.7, 154.2, 147.1, 146.7, 133.5, 130.7, 129.7, 128.8, 125.4, 121.3, 117.2, 116.0, 112.7, 110.7, 57.1, 56.8. MS (ESI) 283 $(M+H)^+$.

4.3.7. 7-Methoxy-2-(p-chlorobenzoyl)benzofuran ***C7***. Known;[13] yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (d, J=8.7 Hz, 2H), 7.57 (s, 1H), 7.52 (d, J=8.7 Hz, 2H), 7.31 (dd, J=7.9 and 1.2 Hz, 1H), 7.25 (t, J=7.8 Hz, 1H), 6.97 (dd, J=7.7 and 1.2 Hz, 1H), 4.03 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 183.5, 153.4, 147.0, 146.7, 140.4, 136.2, 132.0, 129.8, 129.4, 125.7, 117.3, 115.9, 110.6, 57.0. MS (ESI) 287 $(M+H)^+$. Anal. Calcd for $C_{16}H_{11}O_3Cl$: C 67.03%; H 3.87%. Found: C 66.67%; H 3.96%.

4.3.8. 5-Methoxy-2-(2,4-difluorobenzoyl)benzofuran ***C8***. Unknown; yellow powder; mp 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (m, 1H), 7.54 (d, J=9.0 Hz, 1H), 7.47 (br s, 1H), 7.18 (dd, J=9.0 and 2.6 Hz, 1H), 7.14 (d, J=2.5 Hz, 1H), 7.10–7.06 (m, 1H), 7.04–6.98 (m, 1H), 3.90 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 180.4, 165.2 (dd, J_{C-F}=255.5 and 12.0 Hz), 161.1 (dd, J_{C-F}=257.3 and 12.4 Hz), 156.8, 152.8, 151.5, 132.3 (dd, J_{C-F}=10.4 and 4.1 Hz), 127.5, 122.8 (dd, J_{C-F}=14.1 and 3.7 Hz), 119.3, 116.7 (d, J_{C-F}=2.2 Hz), 113.3, 111.9 (dd, J_{C-F}=21.6 and 3.7 Hz), 105.0 (t, J_{C-F}=25.5 Hz), 103.9, 55.9. MS (ESI) 289 $(M+H)^+$. Anal. Calcd for $C_{16}H_{10}O_3F_2$: C 66.67%; H 3.50%. Found: C 66.82%; H 3.87%.

4.3.9. 5-Methoxy-2-(p-methoxybenzoyl)benzofuran ***C9***. Unknown; yellow powder; mp 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11 (d, J=8.9 Hz, 2H), 7.52 (br d, J=9.7 Hz, 1H), 7.47 (d, J=1.0 Hz, 1H), 7.11 (s, 1H), 7.10 (dd, J=7.7 and 2.7 Hz, 1H), 7.02 (d, J=8.9 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 183.6, 164.5, 157.5, 154.4, 151.9, 132.9, 130.8, 128.5, 119.0, 116.5, 114.8, 114.1, 104.8, 56.8, 56.5. MS (ESI) 283 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}O_4$: C 72.33%; H 5.00%. Found: C 72.08%; H 5.17%.

4.3.10. 7-Methoxy-2-(3,4-dimethoxybenzoyl)benzofuran ***C10***. Known;[14] beige powder; mp 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (dd, J=8.4 and 2.1 Hz, 1H), 7.73 (d, J=2.0 Hz, 1H), 7.59 (s, 1H), 7.34 (dd, J=7.9 and 1.0 Hz, 1H), 7.28 (t, J=7.9 Hz, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.99 (dd, J=7.8 and 0.9 Hz, 1H), 4.07 (s, 3H), 4.02 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 182.3, 153.4, 153.2, 149.1, 146.1, 145.5, 129.8, 128.7, 124.8, 124.6, 115.4, 114.9, 112.0, 110.2, 109.3, 56.2, 56.1, 56.0. MS (ESI) 313 $(M+H)^+$.

4.3.11. 7-Methoxy-2-(2,3,4-trimethoxybenzoyl)benzofuran ***C11***. Unknown; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 (s, 1H), 7.31 (d, J=8.6 Hz, 1H), 7.26 (dd, J=8.1 and 1.3 Hz, 1H), 7.21 (t, J=7.9 Hz, 1H), 6.94 (dd, J=7.7 and 1.2 Hz, 1H), 6.75 (d, J=8.6 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H). ^{13}C (100 MHz,

$CDCl_3$): 184.4, 157.6, 154.3, 154.0, 147.0, 146.6, 143.1, 129.7, 126.5, 126.2, 125.4, 116.6, 116.0, 110.4, 107.6, 63.1, 61.9, 57.1, 57.0. MS (ESI) 343 $(M+H)^+$.

Supplementary data

The table of reactions times, the R_f of intermediates, and the NMR copies (^1H and ^{13}C) of all compounds (aurones and 2-benzoylbenzo[*b*]furans). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.011.

References and notes

1. (a) Hänsel, R.; Rimpler, H.; Schwarz, R. *Tetrahedron Lett.* **1965**, *21*, 1545–1548; (b) Hu, Z.-F.; Chen, L.-L.; Qi, J.; Wang, Y.-H.; Zhang, H.; Yu, B.-Y. *Fitoterapia* **2011**, *82*, 190–192.
2. (a) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796–4805; (b) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Naruto, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 455–458.
3. Saberi, M. R.; Vinh, T. K.; Yee, S. W.; Griffiths, B. J.; Evans, P. J.; Simons, C. *J. Med. Chem.* **2006**, *49*, 1016–1022.
4. (a) Andersen, Ø. M.; Markham, K. R. *Flavonoids. Chemistry, Biochemistry and Applications*; CRC: Boca Raton, 2006; (b) Ono, E.; Fukuchi-Mizutani, M.; Nakamura, N.; Fukui, Y.; Yonekura-Sakakibara, K.; Yamaguchi, M.; Nakayama, T.; Tanaka, T.; Kusumi, T.; Tanaka, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 11075–11080.
5. Atta-ur-Rahman; Choudhary, M. I.; Hayat, S.; Khan, A. M.; Ahmed, A. *Chem. Pharm. Bull.* **2001**, *49*, 105–107.
6. (a) Boumendjel, A. *Curr. Med. Chem.* **2003**, *10*, 2621–2630; (b) Okombi, S.; Rival, D.; Bonnet, S.; Mariotte, A.-M.; Perrier, E.; Boumendjel, A. *J. Med. Chem.* **2006**, *49*, 329–333; (c) Bandgar, B. P.; Patil, S. A.; Korbad, B. L.; Biradar, S. C.; Nile, S. N.; Khobragade, C. N. *Eur. J. Med. Chem.* **2010**, *45*, 3223–3227; (d) Maya, Y.; Ono, M.; Watanabe, H.; Haratake, M.; Saji, H.; Nakayama, M. *Bioconjugate Chem.* **2009**, *20*, 95–101; (e) Ono, M.; Maya, Y.; Haratake, M.; Ito, K.; Mori, H.; Nakayama, M. *Biochem. Biophys. Res. Commun.* **2007**, *361*, 116–121; (f) Sim, H. M.; Lee, C. Y.; Ee, P. L.; Go, M. L. *Eur. J. Pharm. Sci.* **2008**, *35*, 293–306.
7. (a) Nishihara, M.; Nakatsuka, T. *Biotechnol. Lett.* **2011**, *33*, 433–441; (b) Sanchez-Gonzalez, M.; Rosazza, J. P. *J. Agric. Food Chem.* **2006**, *54*, 4646–4650; (c) Ono, E.; Hatayama, M.; Isono, Y.; Sato, T.; Watanabe, R.; Yonekura-Sakakibara, K.; Fukuchi-Mizutani, M.; Tanaka, Y.; Kusumi, T.; Nishino, T.; Nakayama, T. *Plant J.* **2006**, *45*, 133–143; (d) Nakayama, T. *J. Biosci. Bioeng.* **2002**, *94*, 487–491; (e) Nakayama, T.; Yonekura-Sakakibara, K.; Sato, T.; Kikuchi, S.; Fukui, Y.; Fukuchi-Mizutani, M.; Ueda, T.; Nakao, M.; Tanaka, Y.; Kusumi, T.; Nishino, T. *Science* **2000**, *290*, 1163–1166.
8. (a) Beney, C.; Mariotte, A.-M.; Boumendjel, A. *Heterocycles* **2001**, *55*, 967–972; (b) Wallez, V.; Durieux-Poissonnier, S.; Chavatte, P.; Boutin, J. A.; Audinot, V.; Nicolas, J.-P.; Bennejean, C.; Delagrange, P.; Renard, P.; Lesieur, D. *J. Med. Chem.* **2002**, *45*, 2788–2800.
9. Venkateswarlu, S.; Panchagnula, G. K.; Gottumukkala, A. L.; Subbaraju, G. V. *Tetrahedron* **2007**, *63*, 6909–6914.
10. Shang, Y.; Cuie, W.; Xinwei, H.; Kai, J.; Min, Z.; Shuyan, Y.; Jiaping, W. *Tetrahedron* **2010**, *66*, 9629–9633.
11. Vinh, T. K.; Yee, S. W.; Kirby, A. J.; Nicholls, P. J.; Simons, C. *Anticancer Drug Des.* **2001**, *16*, 217–225.
12. Azevedo, M. S.; Alves, A. P. L.; Alves, G. B. C.; Cardoso, J. N.; Lopes, R. S. C.; Lopes, C. C. *Quim. Nova* **2006**, *29*, 1259–1265.
13. Pestellini, V.; Giolitti, A.; Pasqui, F.; Abelli, L.; Cutrufo, C.; De Salvia, G.; Evangelista, S.; Meli, A. *Eur. J. Med. Chem.* **1988**, *23*, 203–206.
14. Richtzenhain, H.; Alfredsson, B. *Chem. Ber.* **1956**, *89*, 378–385.