Tetrahedron 68 (2012) 4107–4111

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Chemical synthesis of funicone analogs☆

Emiliano Manzo*, Maria Letizia Ciavatta

Consiglio Nazionale delle Ricerche, Istituto di Chimica Biomolecolare, Via Campi Flegrei 34, 80078-I Napoli, Italy

ARTICLE INFO

Article history:
Received 30 January 2012
Received in revised form 15 March 2012
Accepted 2 April 2012
Available online 9 April 2012

Keywords:
Rapicone
Deoxyfunicone
Funicone analogs
Chemical synthesis

ABSTRACT

Deoxyfunicone, rapicone and their 5,6-epoxy-derivatives are γ-pyrone compounds with cytostatic and antiproliferative properties. Here we describe a synthesis of these compounds by carbonylative Stille coupling between kojic acid derivatives and functionalized iodo aryl compounds. The main advantages of this patent pending synthetic strategy lie in the simplicity and clean conversion of products, and in the possibility to obtain a high number of analogs by minor changes of the synthetic synthons.

1. Introduction

As part of our continuing research of bioactive secondary metabolites from natural sources, fungal compounds have attracted our attention for their interesting biological activities.[1]

In this regard the γ-pyrone motif is present in a large number of bioactive natural products of polyketide origin.[2] Funicone (**1**)[3] and structurally-related compounds form a characteristic subclass that is characterized by a keto bridge between a substituted γ-pyrone ring and α-resorcyclic acid (Fig. 1). The family embraces a number of derivatives showing promising biomedical potential as fungicides, antiviral and antitumor candidates.[2e-4] Funicone (**1**) was first isolated from *Penicillium funiculosum*[3] but structural analogs have been reported from many other terrestrial fungi.

In view of the pharmaceutical development of this family of polyketides, we have elaborated a short and versatile synthesis of funicone analogs from commercially available compounds (patent pending). To illustrate the potential of the synthetic strategy, here we report preparation of deoxyfunicone[2a,5] (**2**), a HIV-1-integrase inhibitor,[5,6] and rapicone[7] (**3**), a phytopatogenic fungi antagonist, which differ only for the alkyl substituents at C-2 of the pyrone ring, as well as the synthesis of fungal 5,6-epoxy-derivatives.[8]

To the best of our knowledge, this is the first report on synthesis of members of the funicone family.

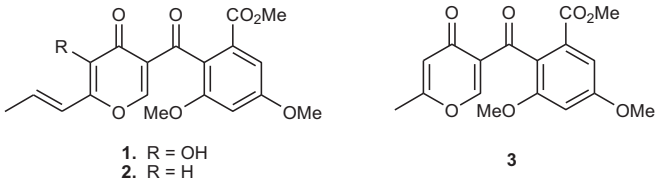


Fig. 1. Funicone (**1**) and structurally-related deoxyfunicone (**2**) and rapicone (**3**).

2. Results and discussion

Chemical preparations of γ-pyrone compounds have been previously reported, and traditionally rely on a biomimetic approach based on cyclization of triketide precursor (Fig. 2).[9]

Recently, Kamino and co-workers[10] introduced a general method to prepare 5-substituted γ-pyrone compounds from 5-stannane derivatives of the commercially available kojic acid by Stille carbonylative coupling with iodo benzene.[11] The methodology is highly versatile and replacement of the last reagent with functionalized iodo aryl derivatives gives theoretically access to the funicone skeleton of **2** and **3** in one step (Fig. 3).

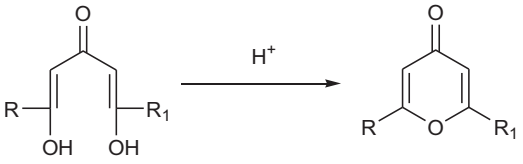


Fig. 2. General synthetic procedures for γ-pyrones preparation.

☆ Patent pending; application no. PCT/IB2011/054262.

* Corresponding author. Tel.: +39 081 8675310; fax: +39 081 8041770; e-mail addresses: emanzo@icb.cnr.it, emanzo@icmib.na.cnr.it (E. Manzo).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.04.010

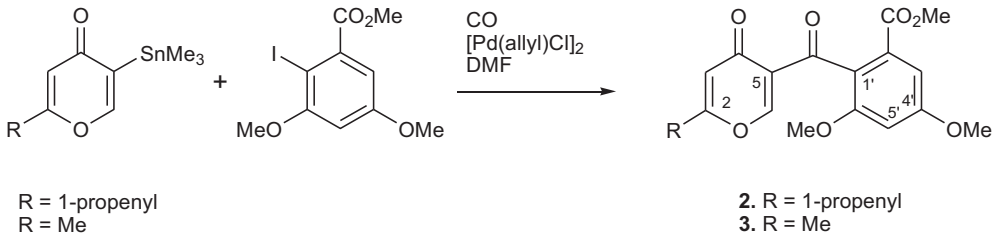


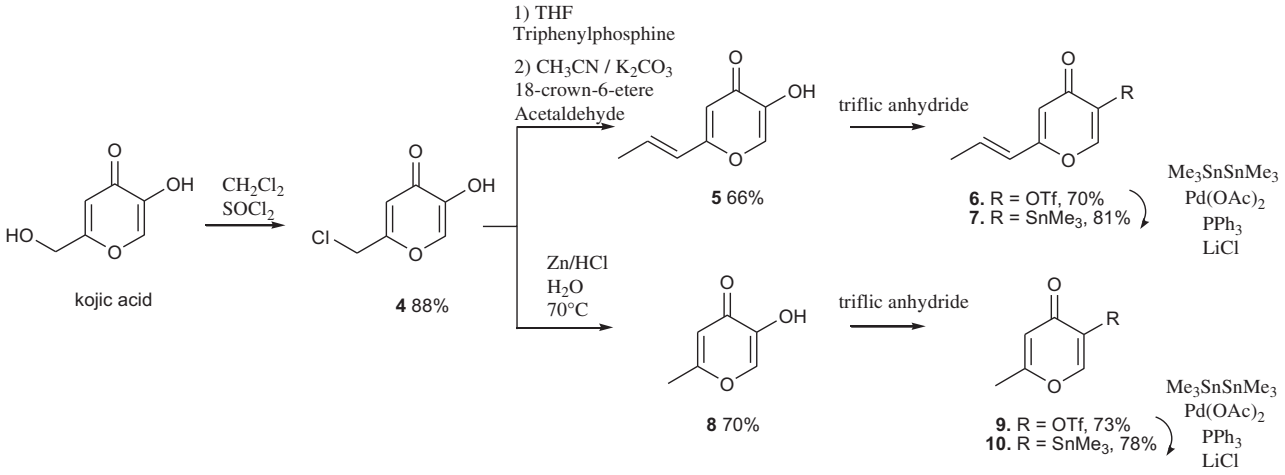
Fig. 3. Synthesis of deoxyfunicone (**2**) and rapicone (**3**) by Kamino's procedure.

For the preparation of the stannane precursors (Scheme 1), kojic acid was chlorinated by thionyl chloride in dichloromethane to give **4**. Triphenylphosphorylation of this product followed by Wittig reaction with acetaldehyde led to *trans* 1-propenyl derivative **5** from which the stannane precursor **7** was obtained by a simple sequence of transformations including activation of enolic function with triflic anhydride and substitution with hexamethylditin in presence of palladium(II) acetate, triphenylphosphine and lithium chloride.[11,12] The stannane **10** was obtained in the same way after preparation of the methyl derivative **8** by zinc reduction[13] of the chloro intermediate **4**.

Furthermore, in agreement with the literature,[15–17] the partial deactivation of the aromatic reagent also favored the competitive reaction of homocoupling of the stannane intermediates (Fig. 6).

Finally, oxidation of deoxyfunicone (**2**) and rapicone (**3**) with hydrogen peroxide in presence of lithium diisopropylamide and trimethylborate (Scheme 2),[18] gave 5,6-epoxy-deoxyfunicone (**12**)[8] and 5,6-epoxy-rapicone (**13**), respectively.

In this manner, all a series of funicone-related compounds, starting from the precursor **14**, various types of aldehydes and differently functionalized iodo aryl derivatives, could be prepared (Fig. 7).



Scheme 1. Preparation of stannane precursors for the synthesis of deoxyfunicone (**2**) and rapicone (**3**).

More simply, the iodo benzo-intermediate **11** was prepared by iodination of the commercially available methyl-3,5-dimethoxybenzoate with silver trifluoroacetate and iodine (Fig. 4).[14] As expected, coupling of **11** with the stannanes **7** and **10** under Kamino's conditions gave deoxyfunicone (**2**) and rapicone (**3**) with 33% and 35% yields, respectively.

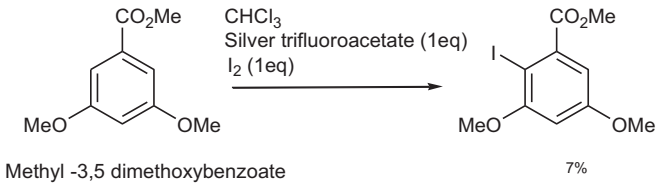


Fig. 4. Preparation of iodo benzo-precursor.

The coupling was less efficient than we could expect on the basis of Kamino's report,[10] which is likely due to the two electron-donating methoxy groups on the aromatic ring that counteract the electron-withdrawing effect of the ester moiety.[15] In confirmation of this, the coupling yield increased to 73% with unfunctionalized aryl iodide (Fig. 5).

3. Conclusion

In summary, access to natural and unusual compounds of the funicone family was achieved by a versatile and simple chemical procedure involving Stille carbonylative coupling[11] between kojic acid derivatives stannane- and iodo-precursors in carbon monoxide atmosphere with allylpalladium(II) chloride dimer as catalyst.[10] The synthetic procedure is of general application and gives access to a large variety of funicone-related compounds of biomedical interest simply starting from modified precursors. With this aim carbon-3 oxidation of deoxyfunicone (**2**) and rapicone (**3**) is in progress opening the way to the preparation of all another series of funicone analogs.

4. Experimental section

4.1. General experimental procedures

1D and 2D NMR spectra were recorded on a Bruker Avance-400 and on a Bruker DRX-600 equipped with TXI CryoProbe™ in $CDCl_3$, CD_2Cl_2 and DMSO-d_6 (δ values are reported referred to $CHCl_3$, CH_2Cl_2 and DMSO protons at 7.25, 5.32, and 2.49 ppm, respectively) and ^{13}C

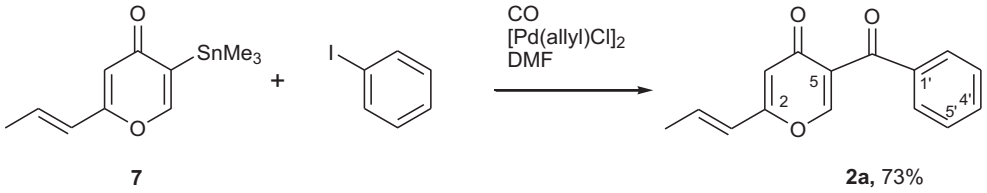


Fig. 5. Coupling reaction between the stannane intermediate **7** and unfunctionalized aryl iodide.

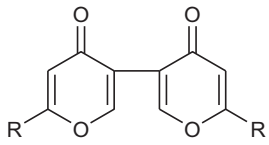
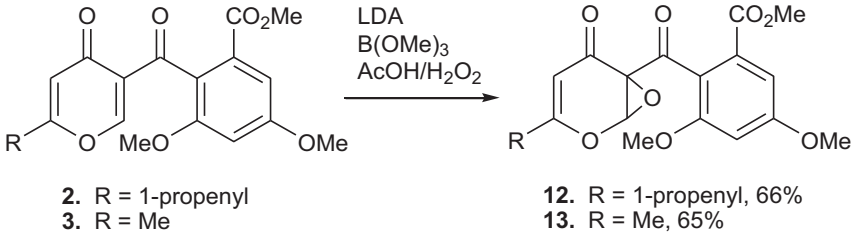


Fig. 6. γ-pyrone dimers producted by homocoupling of the stannane intermediates.

4.33 (2H, s, H_2-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.3 (C, C4), 162.9 (C, C2), 146.2 (C, C5), 138.1 (CH, C6), 112.3 (CH, C3), 41.1 (CH_2, C7); HRESIMS: *m*/*z* calcd for $C_6H_5^{35}ClNaO_3$: 182.9825; found: 182.9833.

*4.2.2. Compound **5**.* Compound **4** (0.450 g, 0.003 mol) was dissolved in 7 mL of anhydrous THF and triphenylphosphine (1.570 g, 0.006 mol) was added; after stirring for four days at 67 °C, the precipitate was filtered obtaining triphenylphosphonium chloride, dissolved in 12 mL of acetonitrile and potassium carbonate (0.410 g,



Scheme 2. Preparation of 5,6-epoxy-deoxyfunicone (**12**) and 5,6-epoxy-rapicone (**13**).

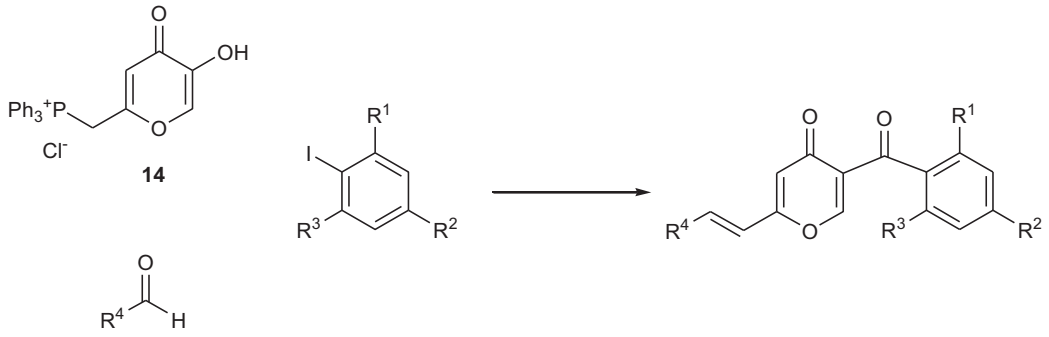


Fig. 7. General synthetic scheme for funicone-related derivatives.

NMR were recorded on a Bruker DPX-300 (75.0 MHz) and Bruker DRX-600 (150 MHz) (δ_C values are reported to $CHCl_3$, CH_2Cl_2 and DMSO carbon at 77.0, 53.8 and 39.5 ppm, respectively); IR spectra were recorded on Biorad FTS 155 spectrometer; HRESIMS were carried out on a Micromass Q-TOF micro; TLC plates (KieselGel 60 F_{254}) were from Merck (Darmstadt, Germany), silica gel powder (Kieselgel 60 0.063–0.200 mm) was from Merck (Darmstadt, Germany).

Kojic acid, methyl-3,5-dimethoxybenzoate, all the solvents and reagents were purchased by Sigma–Aldrich.

4.2. Synthetic procedures

*4.2.1. Compound **4**.* Kojic acid (1.000 g, 0.007 mol) was dissolved in 10 mL of anhydrous dichloromethane and thionyl chloride (1.070 g, 1.3 equiv) was added; after stirring overnight at room temperature, the reaction mixture was evaporated and purified by silica gel chromatography using a gradient of $CHCl_3/CH_3OH$ to give **4** (0.986 g, 88%) as a pale yellow oil; R_f ($CHCl_3/CH_3OH$ 9:1)=0.51; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.89 (1H, s, H-6), 6.57 (1H, br s, H-3), 0.003 mol); dicyclohexyl-18-crown-6 (10 mg, 0.027 mmol) and acetaldehyde (0.400 g, 0.009 mol) were added; after stirring overnight at room temperature, the reaction mixture was purified by silica gel chromatography using a gradient of $CHCl_3/CH_3OH$ to give **5** (0.282 g, 66%) as a white solid; R_f ($CHCl_3/CH_3OH$, 9:1)=0.67; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.00 (1H, s, H-6), 6.68 (1H, dq, *J*=15.2, 6.9 Hz, H-8), 6.27 (1H, s, H-3), 6.08 (1H, br d, *J*=15.2 Hz, H-7), 1.92 (3H, d, *J*=6.9 Hz, H_3-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.2 (C, C4), 163.0 (C, C2), 148.7 (CH), 138.1 (CH), 122.1 (CH), 113.5 (CH), 19.1 (CH_3, C9); HRESIMS: *m*/*z* calcd for $C_8H_8NaO_3$: 175.0371; found: 182.0362.

*4.2.3. Compound **6**.* Compound **5** (0.282 g, 0.0019 mol) was dissolved in 4 mL of pyridine and triflic anhydride (1.128 g, 0.0040 mol) was added slowly under argon atmosphere; after stirring overnight at room temperature, the mixture was evaporated and purified by silica gel chromatography using a gradient of $CHCl_3/CH_3OH$ to give **6** (0.378 g, 70%) as a pale yellow oil; R_f (Light petroleum ether/ethyl-acetate 3:7)=0.83; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (1H, s, H-6), 6.70 (1H, dq, *J*=15.2, 6.9 Hz, H-8), 6.30 (1H, s, H-3), 6.10 (1H, br d,

J=15.2 Hz, H-7), 1.97 (3H, d, J=6.9 Hz, H_3-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.1 (C, C4), 162.7 (C, C2), 148.5 (CH), 138.0 (CH), 120.7 (CH), 113.1(CH), 18.5 (CH_3, C9); HRESIMS: m/z calcd for $C_9H_7F_3NaO_5S$: 306.9864; found: 306.9855.

4.2.4. Compound ***7***. Compound **6** (0.045 g, 0.158 mmol) was dissolved in 2 mL of anhydrous DMF and palladium(II) acetate (0.2 mg, 3% mol), hexamethylditin (0.049 g, 0.152 mmol), triphenylphosphine (0.2 mg, 3% mol) and lithium chloride (0.033 g, 0.79 mmol) were added; after stirring for 21 h at room temperature, the mixture was portioned between aqueous buffer (pH=7) and diethyl ether; the organic phase was purified by silica gel chromatography using a gradient of light petroleum ether and ethyl acetate obtaining **7** (0.038 g, 81%) as a white solid; R_f (Light petroleum ether/ethylacetate 3:7)= 0.90; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41 (1H, s, H-6), 6.59 (1H, dq, J=15.2, 6.9 Hz, H-8), 6.02 (1H, s, H-3), 6.02 (1H, d, J=15.2 Hz, H-7), 1.92 (3H, d, J=6.9 Hz, H_3-9), 0.30 (9H, s, MeSn); ^{13}C NMR (100 MHz, $CDCl_3$): δ=182.7 (C, C4), 165.9 (C, C2), 157.1 (CH, C6), 145.6 (C, C5), 134.9 (CH, C8), 125.1 (CH, C7), 112.6 (C, C3), 19.6 (CH_3, C9), -9.6 ($SnCH_3$); HRESIMS: m/z calcd for $C_{11}H_{16}NaO_2Sn$: 323.0070; found: 323.0082.

4.2.5. Compound ***8***. Compound **4** (0.450 g, 0.003 mol) was added to 6 mL of distilled water and heated to 50 °C with stirring; zinc dust (0.384 g, 0.006 mol) was added followed by the dropwise addition of concentrated hydrochloric acid (3.7 mL) over 1 h with vigorous stirring maintaining the temperature at 75 °C; the reaction mixture was stirred for other 3 h at 70 °C. The excess of zinc was eliminated by hot filtration and the filtrate was extracted with CH_2Cl_2 obtaining obtaining **8** (0.264 g, 70%) as a white solid; R_f ($CHCl_3$/CH_3OH, 9:1)= 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (1H, s, H-6), 6.19 (1H, s, H-3), 2.21 (3H, s, H_3-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.3 (C, C4), 166.4 (C, C2), 145.3 (C, C5), 137.9 (CH, C3), 111.3 (CH, C6), 20.0 (CH_3, C7); HRESIMS: m/z calcd for $C_6H_6NaO_3$: 149.0215; found: 149.0220.

4.2.6. Compound ***9***. Compound **8** (0.264 g, 0.0021 mol) was dissolved in 4 mL of pyridine and triflic anhydride (2.900 g, 0.0084 mol) was added slowly under argon atmosphere; after stirring overnight at room temperature, the mixture was evaporated and purified by silica gel chromatography using a gradient of $CHCl_3$/CH_3OH to give **9** (0.393 g, 73%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)=0.70; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (1H, s, H-6), 6.34 (1H, s, H-3), 2.34 (3H, s, H_3-7); HRESIMS: m/z calcd for $C_7H_5F_3NaO_5S$: 280.9707; found: 280.9713.

4.2.7. Compound ***10***. Compound **9** (0.393 g, 1.5 mmol) was dissolved in 2 mL of anhydrous DMF and palladium(II) acetate (1.9 mg, 3% mol), hexamethylditin (0.466 g, 1.44 mmol), triphenylphosphine (1.9 mg, 3% mol) and lithium chloride (0.314 g, 7.5 mmol) were added; after stirring for 21 h at room temperature, the mixture was portioned between aqueous buffer (pH=7) and diethyl ether; the organic phase was purified by silica gel chromatography using a gradient of light petroleum ether and ethyl acetate obtaining **10** (0.309 g, 78%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)=0.71; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37 (1H, s, H-6), 6.00 (1H, s, H-3), 2.17 (3H, s, H_3-7), 0.24 (9H, s, MeSn); ^{13}C NMR (100 MHz, $CDCl_3$): δ=182.7 (C, C4), 165.9 (C, C2), 157.1 (CH, C6), 126.6 (C, C5), 113.7 (CH, C3), 20.6 (CH_3, C7), -9.5 ($SnCH_3$); HRESIMS: m/z calcd for $C_9H_{14}NaO_2Sn$: 296.9913; found: 296.9907.

4.2.8. Compound ***11***. Methyl-3,5-dimethoxybenzoate (2.000 g, 0.0103 mol) was dissolved in 50 mL of chloroform; iodine (1.330 g, 0.0103 mol) and silver trifluoroacetate (1.71 g, 0.0103 mol) were added; after stirring for 5 h at room temperature, the mixture was purified by silica gel chromatography using a gradient of light petroleum ether and diethyl ether getting **11** (2.500 g, 77%) as a pale yellow oil; R_f(Light petroleum ether/diethyl ether 1:1)=0.60; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.74 (1H, d, J=2.3 Hz, H-3′), 6.45 (1H, d, J=2.3 Hz, H-5′), 3.88 (3H, s, OMe), 3.80 (3H, s, OMe), 3.76 (3H, s, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.2 (C), 161.9 (C), 159.9 (C), 139.2 (C), 107.8 (CH), 101.7 (CH), 57.0 (OCH_3), 56.7 (OCH_3), 52.8 (OCH_3); HRESIMS: m/z calcd for $C_{10}H_{11}NaIO_4$: 344.9600; found: 344.9607.

4.2.9. Compound ***2***. Compound **7** (0.030 g, 0.1 mmol) was dissolved in 2 mL of anhydrous DMF in monoxide carbon atmosphere; compound **11** (0.161 g, 0.5 mmol), allylpalladium(II) chloride dimer (2.7 mg, 0.015 mmol) were added; after stirring one day at room temperature, the mixture was portioned between water and ethyl acetate and the organic phase was purified by silica gel chromatography using a gradient of *n*-hexane and ethyl acetate obtaining **2** (0.012 g, 33%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)=0.12; IR (liquid film) ν_{max} 2934, 2849, 1714, 1683, 1637, 1606, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.52 (1H, s, H-6), 7.08 (1H, d, J=1.9 Hz, H-3′), 6.68 (1H, dq, J=15.2, 6.9 Hz, H-8), 6.64 (1H, d, J=1.9 Hz, H-5′), 6.09 (1H, s, H-3), 6.07 (1H, d, J=15.2 Hz, H-7), 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 3.73 (3H, s, OMe), 1.94 (3H, d, J=6.9 Hz, H_3-9). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.5 (C, C10), 175.7 (C, C4), 166.1 (C, C7′), 161.1 (C, C2), 160.4 (C, C4′), 160.4 (CH, C6), 157.3 (C, C6′), 136.2 (CH, C8), 129.9 (C, C2′), 126.4 (C, C1′), 126.0 (C, C5), 122.8 (CH, C7), 115.1 (CH, C3), 105.1 (CH, C3′), 103.0 (CH, C5′), 56.0 (CH_3, C9′), 55.5 (CH_3, C10′), 52.2 (CH_3, C8′), 18.6 (CH_3, C9); HRESIMS: m/z calcd for $C_{19}H_{18}NaO_7$: 381.0950; found: 381.00943.

4.2.10. Compound ***3***. Compound **10** (0.030 g, 0.1 mmol) was dissolved in 2 mL of anhydrous DMF in monoxide carbon atmosphere; compound **11** (0.161 g, 0.5 mmol), allylpalladium(II) chloride dimer (2.7 mg, 0.015 mmol) were added; after stirring one day at room temperature, the mixture was portioned between water and ethyl acetate and the organic phase was purified by silica gel chromatography using a gradient of *n*-hexane and ethyl acetate obtaining **3** (0.013 g, 35%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)=0.12; IR (liquid film) ν_{max} 2931, 2839, 1718, 1679, 1653, 1602, 1556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.50 (1H, s, H-6), 7.07 (1H, d, J=2.0 Hz, H-3′), 6.63 (1H, d, J=2.0 Hz, H-5′), 6.12 (1H, s, H-3), 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 3.72 (3H, s, OMe), 2.27 (3H, s, H_3-7). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.6 (C,C8), 175.4 (C, C4), 166.6 (C, C7′), 165.0 (C, C2), 160.8 (C, C4′), 160.8 (CH, C6), 157.1 (C, C6′), 129.9 (C, C2′), 126.2 (C, C1′), 126.1 (C, C5), 117.2 (CH, C3), 105.1 (CH, C3′), 103.0 (CH, C5′), 55.9 (CH_3, C9′), 55.5 (CH_3, C10′), 52.3 (CH_3, C8′), 19.2 (CH_3, C7); HRESIMS: m/z calcd for $C_{17}H_{16}NaO_7$: 355.0794; found: 355.0802.

4.2.11. Compound ***2a***. Compound **7** (0.010 g, 0.03 mmol) was dissolved in 1 mL of anhydrous DMF in monoxide carbon atmosphere; aryl iodide (0.031 g, 0.15 mmol), allylpalladium(II) chloride dimer (1 mg, 0.005 mmol) were added; after stirring one day at room temperature, the mixture was portioned between water and ethyl acetate and the organic phase was purified by silica gel chromatography using a gradient of *n*-hexane and ethyl acetate obtaining **2a** (0.005 g, 73%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)=0.12; IR (liquid film) ν_{max} 2923, 2841, 1663, 1617, 1610, 1414 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (1H, s, H-6), 7.86 (2H, d, J=7.5 Hz, H-2′, H-6′), 7.58 (1H, t, J=7.5 Hz, H-4′), 7.46 (1H, dd, J=7.5, 7.5 Hz, H-3′, H-5′), 6.67 (1H, dq, J=15.2, 6.9 Hz, H-8), 6.09 (1H, s, H-3), 6.07 (1H, d, J=15.2 Hz, H-7), 1.95 (3H, d, J=6.9 Hz, H_3-9); HRESIMS: m/z calcd for $C_{15}H_{12}NaO_3$: 263.0684; found: 263.0690.

4.2.12. Compound ***12***. Three different solutions were prepared:

Solution S1: Lithium diisopropylamide (5 mg) dissolved in 1.5 mL of anhydrous THF at −78 °C.

Solution S2: Compound **2** (15 mg (0.042 mmol)) dissolved in 1 mL of anhydrous THF.

Solution S3: Trimethylborate (5 μL) dissolved in 0.5 mL of anhydrous THF.

S2 was added to S1 at −78 °C; after stirring for 30 min, S3 was added slowly; the temperature was increased to room temperature and 4 μL of acetic acid and 5 μL of hydrogen peroxide (30%) were added; after portioning between water and ethyl acetate, the organic phase was purified by silica gel chromatography using a gradient of *n*-hexane and ethyl acetate obtaining **12** (10 mg, 66%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)=0.50; IR (liquid film) ν_{max} 2922, 2829, 1718, 1682, 1630, 1602, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.87 (1H, d, J=2.0 Hz, H-3′), 6.68 (1H, dq, J=15.2, 6.1 Hz, H-8), 6.54 (1H, d, J=2.0 Hz, H-5′), 5.94 (1H, br d, J=15.2 Hz, H-7), 5.61 (1H, s, H-6), 5.48 (1H, s, H-3), 3.86 (6H, s, OMe), 3.76 (3H, s, OMe), 1.91 (3H, d, J=6.1 Hz, H_3-9). ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.3 (C, C10), 185.4 (C, C4), 167.5 (C, C7′), 163.0 (C, C4′), 161.2 (C, C2), 158.8 (C, C6′), 137.8 (CH, C8), 134.3 (C, C2′), 124.1 (CH, C7), 119.7 (C, C1′), 106.1 (CH, C3′), 104.3 (CH, C3), 101.4 (CH, C5′), 81.6 (CH, C6), 62.6 (C, C5), 56.0 (CH_3, C9′), 55.8 (CH_3, C10′), 52.9 (CH_3, C8′), 18.4 (CH_3, C9); HRESIMS: *m*/*z* calcd for $C_{19}H_{18}O_8Na$: 397.0899; found: 397.0907.

*4.2.13. Compound **13**.* Three different solutions were prepared:

Solution S1: Lithium diisopropylamide (5 mg) dissolved in 1.5 mL of anhydrous THF at −78 °C.

Solution S2: Compound **3** (15 mg (0.042 mmol)) dissolved in 1 mL of anhydrous THF.

Solution S3: Trimethylborate (5 μL) dissolved in 0.5 mL of anhydrous THF.

S2 was added to S1 at −78 °C; after stirring for 30 min, S3 was added slowly; the temperature was increased to room temperature and 4 μL of acetic acid and 5 μL of hydrogen peroxide (30%) were added; after portioning between water and ethyl acetate, the organic phase was purified by silica gel chromatography using a gradient of *n*-hexane and ethyl acetate obtaining **13** (10 mg, 65%) as a pale yellow oil; R_f (Light petroleum ether/ethylacetate 3:7)= 0.47; IR (liquid film) ν_{max} 2918, 2840, 1716, 1685, 1628, 1604, 1555 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ=6.84 (1H, d, J=2.0 Hz, H-3′), 6.58 (1H, d, J=2.0 Hz, H-5′), 5.53 (1H, s, H-6), 5.48 (1H, s, H-3), 3.88 (3H, s, OMe), 3.84 (3H, s, OMe), 3.78 (3H, s, OMe), 2.08 (3H, s, H_3-7). ^{13}C NMR (100 MHz, CD_2Cl_2): δ=190.5 (C, C8), 185.2 (C, C4), 168.2 (C, C7), 167.4 (C, C2), 163.9 (C, C4′), 159.8 (C, C6′), 135.2 (CH, C2′), 119.3 (C, C1′), 106.8 (CH, C3′), 105.1 (CH, C3), 101.3 (CH, C5′), 81.9 (CH, C6), 62.9 (C, C5), 56.5 (CH_3, C9′), 56.3 (CH_3, C10′), 53.4 (CH_3, C8′), 20.6 (CH_3, C7); HRESIMS: *m*/*z* calcd for $C_{17}H_{16}O_8Na$: 371.0743; found: 371.0752.

Acknowledgements

Authors thank Mr. A. Esposito for NMR spectra, Mr. C. Iodice for spectrophotometric measurements and Mr. M. Zampa for mass spectra analysis.

Supplementary data

Full experimental procedures and spectral data of all synthetic compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.04.010.

References and notes

1. (a) Nicoletti, R.; Manzo, E.; Ciavatta, M. L. *Int. J. Mol. Sci.* **2009**, *10*, 1430–1444; (b) Nicoletti, R.; Ciavatta, M. L.; Buommino, E.; Tufano, M. A. *Int. J. Biomed. Pharm. Sci.* **2008**, 1–23; (c) Ciavatta, M. L.; Lopez-Gresa, M. P.; Gavagnin, M.; Nicoletti, R.; Manzo, E.; Mollo, E.; Guo, Y.-W.; Cimino, G. *Tetrahedron* **2008**, *64*, 5365–5369; (d) Nicoletti, R.; Lopez-Gresa, M. P.; Manzo, E.; Carella, A.; Ciavatta, M. L. *Mycopathologia* **2007**, *163*, 295–301.
2. (a) Sassa, T.; Nukina, M.; Suzuki, Y. *Agric. Biol. Chem.* **1991**, *55*, 2415–2416; (b) Wang, C.-Y.; Wang, B.-G.; Brauers, G.; Guan, H.-S.; Proksch, P.; Ebel, R. *J. Nat. Prod.* **2002**, *65*, 772–775; (c) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371–5374; (d) Proksa, B. *Chem. Pap.* **2010**, *64*, 696–714; (e) Mizushina, Y.; Motoshima, H.; Yamaguchi, Y.; Takeuchi, T.; Hirano, K.; Sugawara, F.; Yoshida, H. *Mar. Drugs* **2009**, *7*, 624–639; (f) Boukouvalas, J.; Wang, J. X. *Org. Lett.* **2008**, *10*, 3397–3399.
3. Merlini, L.; Nasini, G.; Selva, A. *Tetrahedron* **1970**, *26*, 2739–2749.
4. (a) Stammati, A.; Nicoletti, R.; De Stefano, S.; Zampaglioni, F.; Zucco, F. *Altern. Lab. Anim.* **2002**, *30*, 69–75; (b) Nicoletti, R.; Buommino, E.; De Filippis, A.; Lopez-Greza, M. P.; Manzo, E.; Carella, A.; Petrazzuolo, M.; Tufano, M. A. *World J. Microbiol. Biotechnol.* **2008**, *24*, 189–195.
5. Singh, S. B.; Jayasuriya, H.; Dewey, R.; Polishook, J. D.; Dombrowski, A. W.; Zink, D. L.; Guan, Z.; Collado, J.; Platas, G.; Pelaez, F.; Felock, P. J.; Hazuda, D. J. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 721–731.
6. Singh, S. B.; Pelaez, F.; Hazuda, D. J.; Lingham, R. B. *Drugs Future* **2005**, *30*, 277–299.
7. Nozawa, K.; Nakajima, S.; Kawai, K. I.; Udagawa, S. I. *Phytochemistry* **1992**, *31*, 4177–4179.
8. Komai, S.; Hosoe, T.; Itabashi, T.; Nozawa, K.; Okada, K.; de Campos Takaki, G. M.; Chikamori, M.; Yaguchi, T.; Fukushima, K.; Miyaji, M.; Kawai, K. *Mycotoxins* **2001**, *54*, 15–19.
9. (a) Li, C.-S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565–3568; (b) Tyvorskii, V. I.; Bobrov, D. N.; Kulinkovich, O. G.; Kimpe, N. D.; Tehrani, K. A. *Tetrahedron* **1998**, *54*, 2819–2826; (c) Zawacki, F. J.; Crimmins, M. T. *Tetrahedron Lett.* **1996**, *37*, 6499–6502; (d) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619–5620; (e) Koreeda, M.; Akagi, H. *Tetrahedron Lett.* **1980**, *21*, 1197–1200; (f) Miller, A. K.; Trauner, D. *Synlett* **2006**, 2295–2316.
10. Kamino, T.; Kuramochi, K.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 7349–7351.
11. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
12. Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K. S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277–279.
13. Liu, Z. D.; Piyamongkol, S.; Liu, D. Y.; Khodr, H. H.; Lu, S. L.; Hider, R. C. *Bioorg. Med. Chem.* **2001**, *9*, 563–573.
14. Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553–2563.
15. (a) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572–2574; (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.
16. Jeanneret, V.; Meerpoel, L.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 543–546.
17. (a) See, E. G.; Dubois, E.; Beau, J. M. *J. Am. Chem. Soc., Chem. Commun.* **1990**, 1191–1192; (b) See, E. G.; Dubois, E.; Beau, J. M. *Tetrahedron Lett.* **1990**, *31*, 5165–5168; (c) Nicolau, K. C.; Sato, M.; Miller, N. D.; Gunzner, L.; Renaud, J.; Unsterseller, E. *Angew. Chem., Int. Ed.* **1996**, *35*, 889–891.
18. Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Varma, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 799–808.