Tetrahedron 64 (2008) 8930–8937

Contents lists available at ScienceDirect

Tetrahedron

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

# Synthesis of vulpinic and pulvinic acids from tetronic acid

Yann Bourdreux, Ewen Bodio, Catherine Willis, Célia Billaud, Thierry Le Gall *, Charles Mioskowski [1]

*CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, Bât. 547, 91191, Gif-sur-Yvette, France*

ARTICLE INFO

*Article history:*
Received 22 April 2008
Received in revised form 11 June 2008
Accepted 16 June 2008
Available online 20 June 2008

*Keywords:*
Natural products
Pulvinic acid
Vulpinic acid
Tetronic acid
Suzuki–Miyaura cross-coupling

ABSTRACT

A common precursor, tetronic acid, was used in the synthesis of several vulpinic acids and pulvinic acids, which are pigments found in several lichens and mushrooms. The key features of this method are a two-step alkylidenation of benzyl tetronate and a Suzuki–Miyaura cross-coupling. The synthesis of several natural products, vulpinic acid, pinastric acid, xerocomic acid is described.



## 1. Introduction

Pulvinic acids (**1**) and vulpinic acids (**2**, methyl esters of pulvinic acids) are yellow and orange pigments found in lichens and in mushrooms, which display various biological activities.[1] Vulpinic acid has been reported to display antimicrobial activity against Gram-positive organisms.[2] It displayed anti-inflammatory activity in rats,[3] but also caused hyperventilation in rats,[3] cats, and guinea pigs.[4] Lichens containing vulpinic acid were employed in northern Europe to poison wolves. The antiviral, antimicrobial, and antitumor activities of pinastric acid were recently reported.[5] Xerocomic acid was reported as an inhibitor of HIV-1 integrase.[6]

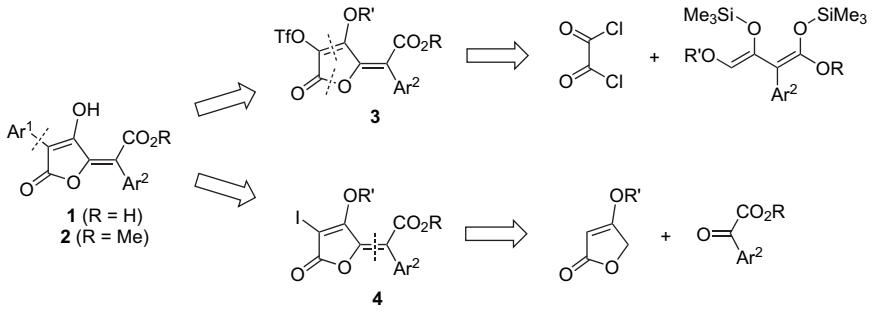
Studies in our laboratory have shown that several pulvinic derivatives have interesting antioxidant properties,[7,8] and we thus became interested in the synthesis of these compounds or their analogs in a convergent, efficient fashion. Structurally, a pulvinic acid is constituted by a β-hydroxylated α,β-unsaturated butyrolactone, which is substituted by an α-aryl group, and by a γ-methylidene bonded to a hydroxycarbonyl group and to an aryl group.

Efficient processes have been reported for the access to symmetrical pulvinic acids (in which the two aryl groups are identical). A classical example involves the reaction of 2 equiv of arylacetonitrile anion with dialkyl oxalate,[9,3] which is followed by a cyclization to a bis(lactone), and by the selective opening of one lactone ring that affords the pulvinic acid. The bis(lactone) can also be prepared by oxidation of a terphenylquinone.[10] We recently reported another process that makes use of the reaction of at least 2 equiv of silyl ketene acetal with oxalyl chloride,[11] followed by a base-mediated cyclization to the corresponding pulvinic acid methyl ester. The access to non-symmetrical pulvinic acids cannot be performed under such straightforward ways. The hydrolytic cleavage of a non-symmetrical bis(lactone) leads to a mixture of regioisomers.[12] Various regioselective approaches have then been reported.[13] The key reactions in these approaches are Dieckmann cyclizations of enol esters,[13a] alkylidenations of methyl 4-arylltetronates,[13b] Reformatsky-type reactions with arylmethoxymaleic anhydrides,[13c,d] reactions of lithium enolates of arylacetic esters with 4-alkylidene-1,3-dioxolan-4-ones,[13e] Wadsworth–Emmons olefinations involving 2-aryl-4-methoxy-2(5*H*)-furanone phosphonates, and α-oxoarylacetates.[13f]

A palladium-mediated cross-coupling is particularly useful to create a linkage between an aryl group and a double bond, it was thus quite appropriate for the introduction of the aryl group bonded on the lactone ring. This strategy, which made use of a triflate such as **3**, has been employed by us[14] as well as by Langer et al.[15] for the preparation of several pulvinic acids (Scheme 1). It was recently applied to the synthesis of norbadione A, a mushroom pigment related to the pulvinic acids.[16] The access to this triflate relied on the Langer cyclocondensation of a bis(trimethylsilyloxy)-diene on oxalyl chloride.[17] We have then devised another approach, which makes also use of a Suzuki–Miyaura cross-coupling[18] as key reaction, but which involves an iodide such as **4**, which would

* Corresponding author. Tel.: +39 1 6908 7105; fax: +39 1 6908 7991.
*E-mail address:* thierry.legall@cea.fr (T. Le Gall).
[1] Deceased on June 2007.

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.06.058



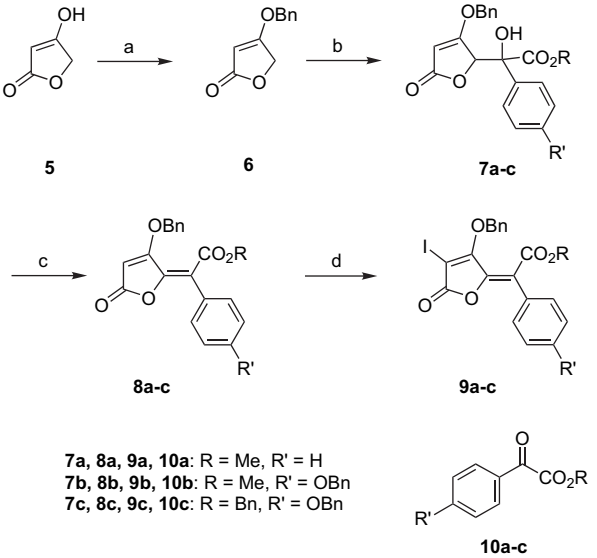

**Scheme 1.**

be prepared via a two-step alkylidenation and an halogenation from a protected form of tetronic acid.[19]

Herein, we report in detail the preparation of vulpinic and pulvinic acids from tetronic acid following this general approach.[20] Three iodides in which the exocyclic double bond is substituted by a phenyl, a *p*-methoxyphenyl or a *p*-benzyloxyphenyl group have been prepared and employed as intermediates. Several final compounds are natural products. Hence, a formal synthesis of pulvinic acid and the total synthesis of vulpinic acid, pinastric acid, and xerocomic acid are described.

## 2. Results and discussion

The preparation of the three iodides **9a–c** started with the conversion of tetronic acid to 4-benzyloxy-2(5*H*)-furanone **6** (Scheme 2, Table 1). Two methods were used for this purpose. Either a Mitsunobu reaction with benzyl alcohol[21] or an alkylation with benzyl bromide in the presence of potassium carbonate led to the expected compound, the latter method being more convenient for large scale preparations. The reaction of the anion generated by the treatment of **6** with butyllithium at −78 °C in THF with α-oxoarylacetates **10a–c** then led to alcohols **7a–c**, which were obtained as mixtures of diastereomers. The yield of alcohol **7c** was notably lower, perhaps because of the increased steric crowding in that case. The diastereomers could be partially separated by silica gel column chromatography. However, this was not necessary,




**Scheme 2.** Synthesis of iodides **9a–c**. Reagents and conditions: (a) $K_2CO_3$, BnBr, DMF, room temp, 12 h, 75% or BnOH, $Ph_3P$, DEAD, room temp, 12 h, 85%; (b) (i) *n*-BuLi, THF, −78 °C, 20 min, (ii) Ketoester **10**, −78 °C to room temp, 12 h; (c) $(CF_3CO)_2O$, DMAP (cat.), $Et_3N$, $CH_2Cl_2$, 4 h, 0 °C; (d) $I_2$, CAN, $CH_3CN$, 40 °C, 4.5 h.

**Table 1**
Synthesis of compounds **7a–c**, **8a–c**, and **9a–c**

| Entry | R | R′ | Yield (%) | | |
|---|---|---|---|---|---|
| 1 | Me | H | **7a** (67) | **8a** (88) | **9a** (78) |
| 2 | Me | OBn | **7b** (62) | **8b** (91) | **9b** (73) |
| 3 | Bn | OBn | **7c** (36) | **8c** (100) | **9c** (65) |

since the deshydratation conditions employed were efficient from both isomers. Thus, using trifluoroacetic anhydride in the presence of triethylamine and a catalytic amount of DMAP in methylene chloride,[22] alcohols **7a–c** were converted efficiently to alkenes **8a–c**. These compounds were obtained mainly as *E*-stereomers, containing 5–10% of the *Z*-stereomers, which proved to be difficult to separate. The *E*-configuration of the major isomers was eventually established by comparison of the spectroscopic properties of the final products synthesized from them with known compounds.

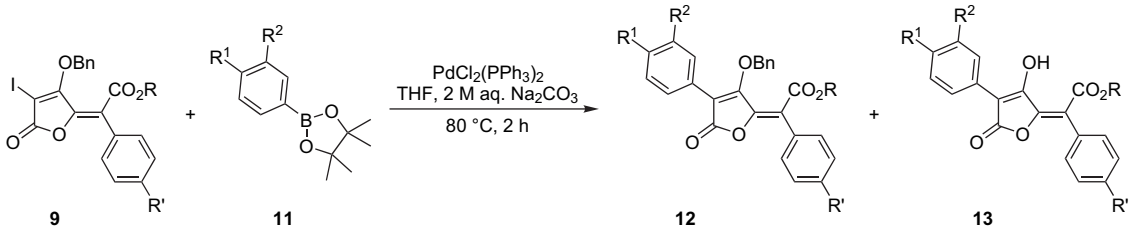
Alkenes **8a–c** were converted to the corresponding iodides **9a–c** in 65–78% yield by treatment with iodine and ammonium cerium(IV) nitrate in acetonitrile.[23] The reaction leading to **9a** was performed at 40 °C. Preparation of compounds **9b** and **9c** at this temperature led to some degradation of the products. These compounds were eventually prepared at room temperature. Iodides **9a–c** were thus obtained in four steps from tetronic acid.

The Suzuki–Miyaura cross-coupling of iodides **9a–c** with several arylboronates **11a–e** was then performed in a THF/2 M aqueous $Na_2CO_3$ refluxing mixture, using $Pd(PPh_3)_2Cl_2$ as catalyst,[24] as described in the Scheme 3. These conditions were previously used for the couplings involving triflates[14] and were also found satisfactory in the present case.

The results of the couplings are summarized in Table 2. The expected adducts **12a–j** were obtained in 55–93% yield after chromatographic purification. In two cases, compounds **13** resulting from a cleavage of the benzyl enol ether function were also obtained (entries 1 and 4). The debenzylation probably occurred after the cross-coupling reaction. We had also observed such debenzylation on some occasions in couplings involving triflates.[14b] In compounds **12**, the *Z*-isomer occurred in 6–12%.

The hydrogenolysis of the benzyl protecting groups of several adducts **12a–c**,**i**,**j** obtained by the cross-coupling reactions was then performed by treatment under hydrogen (1 atm) over palladium on charcoal (Scheme 4, Table 3).

The reaction of compound **12a** in methylene chloride led to the corresponding adduct, vulpinic acid **13a** (entry 1). After 48 h, the reaction was still incomplete. Chromatographic separation afforded **13a**, isolated in 44% yield as pure *E*-isomer, and starting material **12a**, recovered in 16% yield. The remaining minor *Z*-isomer was easily removed by chromatography. The spectroscopic data of **13a** are in good agreement with those reported for vulpinic acid in the literature.[10b,c,13e,15a] This also constitutes a formal synthesis of pulvinic acid, which can be obtained by saponification of the ester function of vulpinic acid.[11] For the hydrogenolysis of compounds

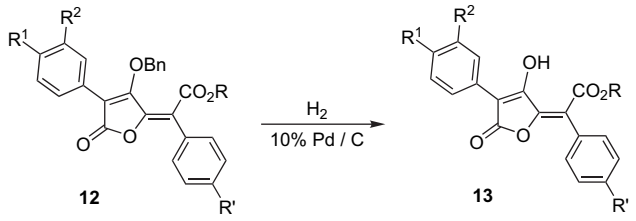



**Scheme 3.** Synthesis of compounds **12**.

**Table 2**
Suzuki–Miyaura cross-couplings of iodides **9** with boronates **11**

| Entry | Iodide | Boronate | R | R′ | $R^1$ | $R^2$ | Product | *E*/*Z* ratio in **12**[a] | Yield of **12** (%) | Yield of **13** (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **9a** | **11a** | Me | H | H | H | **12a** | 94/6 | 55 | 16 |
| 2 | **9a** | **11b** | Me | H | OMe | H | **12b** | 91/9 | 77 | — |
| 3 | **9a** | **11c** | Me | H | H | OH | **12c** | 91/9 | 93 | — |
| 4 | **9a** | **11d** | Me | H | Cl | H | **12d** | 88/12 | 62 | 31 |
| 5 | **9b** | **11a** | Me | OBn | H | H | **12e** | 89/11 | 79 | — |
| 6 | **9b** | **11b** | Me | OBn | OMe | H | **12f** | 95/5 | 69 | — |
| 7 | **9b** | **11d** | Me | OBn | Cl | H | **12g** | 90/10 | 60 | — |
| 8 | **9c** | **11a** | Bn | OBn | H | H | **12h** | 95/5 | 71 | — |
| 9 | **9c** | **11b** | Bn | OBn | OMe | H | **12i** | 95/5 | 71 | — |
| 10 | **9c** | **11e** | Bn | OBn | OBn | OBn | **12j** | 93/7 | 70 | — |

[a] Determined by integration of characteristic signals in the $^1$H NMR spectra.




**12a, 13a**: R = Me, R′ = $R^1$ = $R^2$ = H
**12b, 13b**: R = Me, $R^1$ = OMe, R′ = $R^2$ = H
**12c, 13c**: R = Me, R′ = $R^1$ = H, $R^2$ = OH
**12j**: R = Bn, R′ = $R^1$ = $R^2$ = OBn
**13j**: R = H, R′ = $R^1$ = $R^2$ = OH

**Scheme 4.** Hydrogenolysis of compounds **12**.

**Table 3**
Hydrogenolysis of compounds **12a–c,i,j**

| Entry | Compound **12** | Product **13** | Yield (%) |
|---|---|---|---|
| 1 | **12a**[a] | **13a** | 44[b] |
| 2 | **12b**[c] | **13b** | 71 |
| 3 | **12c**[c] | **13c** | 68 |
| 4 | **12i**[c] | **13i** | 82 |
| 5 | **12j**[c] | **13j** | 68 |

[a] Reaction in $CH_2Cl_2$, 48 h.
[b] The starting material was recovered in 16% yield.
[c] Reaction in DMF, containing concentrated HCl, 2.5 h.

**12a**,**b**,**i**,**j**, the conditions previously described by Ramage et al.[13e] for the deprotection of benzylated pulvinic esters were applied. The reactions, performed in DMF in the presence of hydrochloric acid, were completed after 2.5 h. After chromatographic purification, the products **13b**,**c**,**i**,**j** were obtained as pure *E*-isomers in 68–82% yield. The spectroscopic data of **13b** are in good agreement with those reported for pinastric acid.[10c,15b] The spectroscopic data of **13j** are in good agreement with those reported for xerocomic acid.[13e,15b]

## 3. Conclusion

In summary, we have reported a flexible approach for the synthesis of vulpinic acids and pulvinic acids, in a few steps from tetronic acid. The key feature is a Suzuki–Miyaura cross-coupling involving iodides **9a–c**. The total syntheses of three natural products, vulpinic acid, pinastric acid, and xerocomic acid and a formal synthesis of pulvinic acid were accomplished using this method.

## 4. Experimental section

### 4.1. General information

THF was freshly distilled from sodium benzophenone ketyl. Dichloromethane was freshly distilled over $P_2O_5$. Reactions were performed under an argon atmosphere. TLC: Silica Gel $60F_{254}$ plates with detection by UV light and by an ethanol solution of phosphomolybdic acid. Column chromatography: 40–63 μm silica gel. Melting points were uncorrected. NMR: 400.133 and 100.624 MHz for $^1$H and $^{13}$C, respectively, or 300.13 and 75.47 MHz for $^1$H and $^{13}$C, respectively. Except when noted otherwise, for mixtures of stereomers, only the NMR chemical shifts values pertaining to the major (*E*)-stereomer are indicated. Chemical shifts ($\delta$) are in parts per million (s=singlet, d=doublet, t=triplet, m=multiplet, and br=broad), coupling constants (*J*) are in hertz.

### 4.2. 4-Benzyloxy-5*H*-furan-2-one (6)

Potassium carbonate (13.8 g, 100 mmol) was added to a solution of tetronic acid (5 g, 50 mmol) in DMF (100 mL). After stirring for 45 min at room temperature, benzyl bromide (6.54 mL, 50 mmol) was added. After stirring for 15 h at room temperature, DMF was removed under vacuum; ethyl acetate was added to the residue obtained. The organic phase was extracted with water, and then with saturated aqueous $NH_4Cl$ solution. The combined aqueous phases were extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. Ethyl acetate and diethyl ether were successively added to

the viscous oil obtained, leading to the formation of a precipitate. Filtration of the suspension afforded compound **6** as a white solid (7.1 g, 75%).

Mp=88–90 °C (lit.[25] 90 °C, lit.[26] 103–104 °C); TLC: $R_f$=0.70 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3113, 2945, 2885, 1746, 1668, 1621, 1319, 1236, 1149, 1043, 956, 880, 817, 755, 702 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.44–7.25 (m, 5H, Ar–*H*), 5.19 (s, 1H, =$CHCO_2$), 5.07 (s, 2H, O$CH_2$Ph), 4.67 (s, 2H, $CH_2$OCO); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=179.0, 173.4, 133.8, 129.1, 128.9, 128.3, 89.8, 74.6, 67.9; Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.52; H, 5.18.

### 4.3. Methyl (4-benzyloxyphenyl)oxoacetate (10b)[27]

A solution of *n*-butyllithium (10.3 mL, 1.6 M in hexanes, 16.4 mmol, 1.2 equiv) was added dropwise to a solution of 4-benzyloxy-1-bromobenzene (3.7 g, 13.7 mmol, 1 equiv) in THF (75 mL) cooled at −78 °C. The white slurry obtained was stirred for 1 h at −78 °C, then it was transferred via cannula to a solution of dimethyl oxalate (4.85 g, 41.1 mmol, 3 equiv) in THF (75 mL) cooled at −78 °C. The solution obtained was stirred for 1.5 h at −78 °C, and then allowed to warm to room temperature. A saturated aqueous $NH_4Cl$ solution (150 mL) was added. The aqueous layer was extracted with ethyl acetate (3×150 mL). The combined organic layers were washed successively with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (pentane/$Et_2O$, 95:5 to 80:20 gradient) afforded ketoester **10b** as a clear oil (950 mg, 30%).

TLC: $R_f$=0.65 (8:2 pentane/AcOEt); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$=7.78 (d, 2H, *J*=8.0 Hz, Ar–*H*), 7.46–7.33 (m, 5H, Ar–*H*), 7.02 (d, 2H, *J*=8.0 Hz, Ar–*H*), 5.16 (s, 2H, ArO$CH_2$Ph), 3.96 (s, 3H, $CH_3$).

### 4.4. Benzyl (4-benzyloxyphenyl)oxoacetate (10c)[28]

A solution of *n*-butyllithium (0.75 mL, 1.6 M in hexanes, 1.2 mmol, 1.2 equiv) was added dropwise to a solution of 4-benzyloxy-1-bromobenzene (263 mg, 1 mmol, 1 equiv) in THF (5 mL) cooled at −78 °C. The white slurry obtained was stirred for 30 min at −78 °C, then it was transferred via cannula to a solution of dibenzyl oxalate (324 mg, 1.2 mmol, 1.2 equiv) in THF (5 mL) cooled at −78 °C. The solution obtained was stirred for 2 h at −78 °C, then 2 h at 0 °C. A saturated aqueous $NH_4Cl$ solution (20 mL) was added. The aqueous layer was extracted with ethyl acetate (3×40 mL). The combined organic layers were washed successively with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (pentane/$Et_2O$, 95:5 to 90:10 gradient) afforded ketoester **10c** as a white solid (105 mg, 30%).

Mp=73–74 °C (lit.[28] 75.0–76.5 °C); TLC: $R_f$=0.50 (9:1 pentane/$Et_2O$); IR (KBr pellet) $\nu_{max}$=3061, 2910, 2868, 1729, 1687, 1600, 1508, 1455, 1379, 1302, 1261, 1208, 1171, 988, 840, 748, 697 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$=8.00 (d, 2H, *J*=8.8 Hz, Ar–*H*), 7.50–7.35 (m, 10H, Ar–*H*), 7.03 (d, 2H, *J*=8.8 Hz, Ar–*H*), 5.43 (s, 2H, $CO_2CH_2$Ph), 5.16 (s, 2H, ArO$CH_2$Ph); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=184.4, 164.1, 164.0, 135.7, 134.6, 132.4, 128.6, 128.4, 128.2, 127.4, 125.6, 115.0, 70.2, 67.5; MS (ESI-TOF) *m*/*z* 347 (100, $[M+H]^+$); Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.52; H, 5.18.

### 4.5. Typical procedure for the preparation of alcohols 7a–c

A solution of benzyl tetronate **6** (2.5 g, 13.2 mmol) in THF (60 mL) was added dropwise to a solution of *n*-butyllithium (9 mL, 1.6 M in hexanes, 14.55 mmol) in THF (30 mL) cooled at −78 °C. The yellow solution obtained was stirred at −78 °C for 20 min, and then a solution of methyl benzoylformate (1.9 mL, 13.5 mmol) in THF (20 mL) was added dropwise. The reaction mixture was maintained at −78 °C for 25 min, and then allowed to warm to room temperature. A saturated aqueous $NH_4Cl$ solution (45 mL) was added and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (7:3, then 6:4 pentane/AcOEt) afforded alcohol **7a**.

#### 4.5.1. Methyl (3-benzyloxy-5-oxo-2,5-dihydrofuran-2-yl)hydroxyphenylacetate (*7a*)

*Less polar diastereomer*. White solid. Mp=140–144 °C; TLC: $R_f$=0.35 (6:4 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3309, 3130, 2957, 1769, 1724, 1636, 1452, 1352, 1261, 1060, 996 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$=7.72 (m, 2H, Ar–*H*), 7.46–7.28 (m, 4H, Ar–*H*), 7.20 (d, 2H, *J*=7.3 Hz, Ar–*H*), 6.71 (d, 2H, *J*=7.3 Hz, Ar–*H*), 5.66 (s, 1H, OH), 5.16 (s, 1H, =*CH*COO), 4.82 (d, 1H, *J*=11.6 Hz, O$CH_2$Ph), 4.75 (d, 1H, *J*=11.6 Hz, O$CH_2$Ph), 4.18 (s, 1H, CHOCO), 3.84 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$=177.2, 171.9, 135.6, 133.4, 128.3, 128.1, 128.0, 126.4, 125.9, 91.2, 81.7, 77.5, 73.5, 53.9 (several aromatic CH signals overlap); MS (ESI-TOF) *m*/*z* 355 (100, $[M+H]^+$), 377 (20, $[M+Na]^+$).

*More polar diastereomer*. Slightly yellow solid. Mp=137–138 °C; TLC: $R_f$=0.25 (6:4 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3467, 3100, 2954, 1754, 1633, 1496, 1451, 1347, 1263, 1145 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$=7.63 (m, 2H, Ar–*H*), 7.39–7.26 (m, 8H, Ar–*H*), 5.67 (s, 1H, OH), 5.20 (s, 1H, =*CH*COO), 4.96 (d, 1H, *J*=11.0 Hz, O$CH_2$Ph), 4.91 (d, 1H, *J*=11.0 Hz, O$CH_2$Ph), 4.24 (s, 1H, CHOCO), 3.45 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$=177.1, 172.0, 171.6, 137.4, 133.5, 128.9, 128.5, 128.3, 125.8, 91.5, 81.5, 77.1, 74.8, 53.1 (several aromatic CH signals overlap); MS (ESI-TOF) *m*/*z* 355 (100, $[M+H]^+$), 377 (11, $[M+Na]^+$).

#### 4.5.2. Methyl (3-benzyloxy-5-oxo-2,5-dihydrofuran-2-yl)(4-benzyloxyphenyl)hydroxyacetate (*7b*)

White solid (mixture of two diastereomers; isomer ratio: 60/40). Mp=153–154 °C; TLC: $R_f$=0.3 (6:4 pentane/AcOEt). *Major diastereomer*. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.55 (d, *J*=8.8 Hz, 2H, Ar–*H*), 7.50–6.90 (m, 10H, Ar–*H*), 6.94 (d, 2H, *J*=8.8 Hz, Ar–*H*), 5.61 (s, 1H, CHOCO), 5.26 (s, 1H, =$CHCO_2$), 5.06 (s, 4H, O$CH_2$Ph), 5.01 (s, 2H, O$CH_2$Ph), 3.78 (s, 1H, OH), 3.54 (s, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=177.0, 172.0, 171.8, 158.9, 136.7, 135.6, 133.5, 129.2, 128.8, 128.6, 128.2, 128.0, 127.4, 127.3, 114.7, 91.6, 81.5, 76.8, 74.9, 69.9, 53.3. *Minor diastereomer*. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.62 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.50–6.90 (m, 10H, Ar–*H*), 6.81 (d, 2H, *J*=8.4 Hz, Ar–*H*), 5.62 (s, 1H, CHOCO), 5.17 (s, 1H, =$CHCO_2$), 5.03 (s, 2H, O$CH_2$Ph), 4.86 (d, 1H, *J*=11.8 Hz, O$CH_2$Ph), 4.80 (d, 1H, *J*=11.8 Hz, O$CH_2$Ph), 4.02 (s, 1H, OH), 3.87 (s, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=177.3, 172.2, 172.0, 159.0, 136.7, 135.6, 133.6, 129.6, 128.6, 128.4, 128.3, 128.0, 127.4, 126.7, 114.5, 91.3, 81.7, 77.4, 73.7, 69.9, 54.0.

#### 4.5.3. Benzyl (3-benzyloxy-5-oxo-2,5-dihydrofuran-2-yl)(4-benzyloxyphenyl)hydroxyacetate (*7c*)

*Less polar diastereomer*. White solid. Mp=142–144 °C. TLC: $R_f$=0.65 (6:4 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3463, 3097, 3035, 1759, 1721, 1635, 1510, 1347, 1247, 1158, 695 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.60 (d, 2H, *J*=8.5 Hz, Ar–*H*), 7.50–7.20 (m, 13H, Ar–*H*), 6.92 (d, 2H, *J*=8.5 Hz, Ar–*H*), 6.81 (m, 2H, Ar–*H*), 5.62 (s, 1H, CHOCO), 5.30 (d, 1H, *J*=12.2 Hz, O$CH_2$Ph), 5.23 (d, 1H, *J*=12.2 Hz, O$CH_2$Ph), 5.17 (s, 1H, =$CHCO_2$), 5.02 (s, 2H, O$CH_2$Ph), 4.83 (d, 1H, *J*=12.2 Hz, O$CH_2$Ph), 4.76 (d, 1H, *J*=12.2 Hz, O$CH_2$Ph), 4.12 (s, 1H, OH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=177.3, 172.0, 171.6, 159.0, 136.7, 134.4, 133.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.4, 126.7, 144.4, 91.4, 81.7, 77.4, 73.7, 69.9, 69.0 (several aromatic CH signals overlap); MS (ESI-TOF) *m*/*z* 559 (100, $[M+Na]^+$). *More polar diastereomer*. White solid. Mp=122–123 °C. TLC: $R_f$=0.4 (6:4 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3507, 3036, 2887, 1779, 1758, 1727, 1633, 1509, 1348, 1295, 1237, 1142, 948, 799, 764, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$=7.55 (m, 2H, Ar–*H*), 7.46–7.24 (m, 13H, Ar–*H*), 7.05 (m, 2H, Ar–*H*), 6.95 (m, 2H, Ar–*H*), 5.62 (s, 1H, CHOCO), 5.22 (s, 1H, =$CHCO_2$), 5.05 (s, 2H, O$CH_2$Ph), 4.97 (d, 2H, *J*=11.0 Hz,

OC$H_2$Ph), 4.91 (d, 1H, $J$=11.0 Hz, OC$H_2$Ph), 4.84 (d, 1H, $J$=12.2 Hz, OC$H_2$Ph), 3.96 (s, 1H, OH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=176.9, 171.7, 171.5, 158.9, 136.7, 134.2, 133.6, 129.6, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.4, 127.3, 114.7, 91.7, 81.4, 76.8, 74.8, 69.9, 68.5 (several aromatic CH signals overlap); MS (ESI-TOF) $m/z$ 559 (100, $[M+Na]^+$).

### 4.6. Typical procedure for the preparation of alkenes 8a–c

Triethylamine (5.19 mL, 37.29 mmol, 6 equiv) and DMAP (a spatula tip) were added to a solution of alcohol **7a** (2.2 g, 6.215 mmol, 1 equiv) in methylene chloride (45 mL) cooled at 0 °C. A solution of trifluoroacetic anhydride (2.64 mL, 18.64 mmol, 3 equiv) in methylene chloride (30 mL) was then added dropwise over 90 min. The solution was allowed to warm to room temperature under stirring for 14 h. A saturated aqueous $NaHCO_3$ solution (50 mL) and water (50 mL) were successively added. The aqueous layer was extracted with ether (3×75 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Addition of diethyl ether to the residue obtained led to the formation of a precipitate. Filtration afforded alkene **8a** as a white solid (1.84 g, 88%).

#### *4.6.1. Methyl (3-benzyloxy-5-oxo-5H-furan-2-ylidene)phenylacetate (**8a**)*

White solid (*E*/*Z* isomer ratio: 95/5). Mp=122–124 °C; TLC: $R_f$=0.65 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3109, 2953, 1758, 1731, 1601, 1350, 1302, 1206, 1087, 1036, 959, 880 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.63 (dd, 2H, $J$=8.0, 1.8 Hz, Ar–*H*), 7.44–7.33 (m, 8H, Ar–*H*), 5.43 (s, 1H, =C*H*COO), 5.09 (s, 2H, OC$H_2$Ph), 3.44 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.5, 167.3, 166.4, 141.0, 133.3, 130.7, 129.4, 129.3, 129.1, 128.9, 128.7, 128.5, 116.5, 90.8, 75.1, 52.4; MS (ESI-TOF) $m/z$ 337 (100, $[M+H]^+$); Anal. Calcd for $C_{11}H_{10}O_3$: C, 71.42; H, 4.79. Found: C, 71.01; H, 4.88.

#### *4.6.2. Methyl (3-benzyloxy-5-oxo-5H-furan-2-ylidene)(4-benzyloxyphenyl)acetate (**8b**)*

White solid (*E*/*Z* isomer ratio: 95/5). Mp=159 °C; TLC: $R_f$=0.6 (6:4 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3109, 1776, 1723, 1604, 1512, 1455, 1432, 1404, 1381, 1353, 1316, 1259, 1205, 1183, 1149, 1090, 1043, 971, 880, 739, 696, 673, 632 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.59 (dd, 2H, $J$=8.0, 1.8 Hz, Ar–*H*), 7.45–7.25 (m, 10H, Ar–*H*), 6.98 (dd, 2H, $J$=8.0, 1.8 Hz, Ar–*H*), 5.40 (s. 1H, OC$H_2$Ph), 5.09 (s, 4H, OC$H_2$Ph), 3.45 (s, 3H, $CO_2CH_3$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{27}H_{22}NaO_6$ $[M+Na]^+$ 465.1314, found: 465.1310.

#### *4.6.3. Benzyl (3-benzyloxy-5-oxo-5H-furan-2-ylidene)(4-benzyloxyphenyl)acetate (**7c**)*

Slightly yellow solid (*E*/*Z* isomer ratio: 80/20). Mp=142–143 °C; TLC: $R_f$=0.75 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3034, 1764, 1724, 1598, 1510, 1457, 1349, 1308, 1280, 1257, 1223, 1202, 1182, 1040, 954, 891 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$=7.59 (m, 2H, Ar–*H*), 7.43–7.24 (m, 13H, Ar–*H*), 7.13 (m, 2H, Ar–*H*), 6.93 (m, 2H, Ar–*H*), 5.33 (s, 1H, $CHCO_2$), 5.04 (s, 2H, OC$H_2$Ph), 4.96 (s, 2H, OC$H_2$Ph), 4.86 (s, 2H, OC$H_2$Ph); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$=168.6, 167.6, 166.0, 159.6, 139.6, 136.4, 134.7, 133.5, 130.8, 128.8, 128.5, 128.4, 128.3, 128.0, 127.4, 123.5, 116.3, 115.1, 90.3, 74.8, 70.0, 67.6 (several aromatic CH signals overlap); MS (ESI-TOF) $m/z$ 519 (100, $[M+H]^+$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{33}H_{26}NaO_6$ $[M+Na]^+$ 541.1614, found: 541.1627.

### 4.7. Typical procedure for the preparation of iodides 9a–c

Iodine (1.81 g, 7.14 mmol, 3 equiv) and cerium(IV) ammonium nitrate (3.92 g, 7.14 mmol, 3 equiv) were added to a solution of **8a** (800 mg, 2.38 mmol, 1 equiv) in acetonitrile (70 mL). The reaction mixture was heated at 40 °C for 4.5 h. After cooling to room temperature, a saturated aqueous $Na_2S_2O_3$ solution (40 mL) was added. The aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed successively with a saturated aqueous $Na_2S_2O_3$ solution (35 mL), brine (35 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (pentane/AcOEt, 95:5 to 8:2 gradient) afforded iodide **9a** as a slightly yellow solid (858 mg, 78%).

#### *4.7.1. Methyl (3-benzyloxy-4-iodo-5-oxo-5H-furan-2-ylidene)phenylacetate (**9a**)*

Yellow solid (*E*/*Z* isomer ratio: 93/7). Mp=137 °C; TLC: $R_f$=0.70 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3035, 2944, 1775, 1729, 1590, 1299, 1271, 1215, 1132, 1044, 947 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.58 (m, 2H, Ar–*H*), 7.48–7.32 (m, 8H, Ar–*H*), 5.75 (s, 2H, OC$H_2$Ph), 3.17 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=166.8–166.0–165.9, 142.2, 133.5, 130.2, 129.5–129.3–129.0–128.9–128.6, 116.5, 75.1, 50.2, 51.9; MS (ESI-TOF) $m/z$ 463 (100, $[M+H]^+$); Anal. Calcd for $C_{11}H_{10}O_3$: C, 51.97; H, 3.27; I, 27.45. Found: C, 51.83; H, 3.31; I, 27.15.

#### *4.7.2. Methyl (3-benzyloxy-4-iodo-5-oxo-5H-furan-2-ylidene)(4-benzyloxyphenyl)acetate (**9b**)*

Yellow solid (*E*/*Z* isomer ratio: 89/11). Mp=158–159 °C; TLC: $R_f$=0.50 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3066, 3033, 2924, 2853, 1765, 1719, 1589, 1508, 1453, 1382, 1310, 1282, 1245, 1217, 1177, 1128, 1046, 946, 911, 835, 743, 696, 674, 640, 609, 523 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.51 (d, 2H, $J$=8.9 Hz, Ar–*H*), 7.45–7.25 (m, 10H, Ar–*H*), 6.97 (d, 2H, $J$=8.9 Hz, Ar–*H*), 5.76 (s, 2H, OC$H_2$Ph), 5.42 (s, 2H, OC$H_2$Ph), 3.19 (s, 3H, $CO_2CH_3$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{27}H_{21}INaO_6$ $[M+Na]^+$ 591.0281, found: 591.0267.

#### *4.7.3. Benzyl (3-benzyloxy-4-iodo-5-oxo-5H-furan-2-ylidene)(4-benzyloxyphenyl)acetate (**9c**)*

Yellow solid (*E*/*Z* isomer ratio: 80/20). Mp=130–131 °C; TLC: $R_f$=0.60 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3054, 3033, 2932, 2871, 1772, 1738, 1511, 1500, 1453, 1382, 1304, 1280, 1254, 1213, 1182, 1049, 949, 913, 831, 755, 741, 696, 610 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$=7.52 (d, 2H, $J$=9.2 Hz, Ar–*H*), 7.47–7.33 (m, 11H, Ar–*H*), 7.27 (m, 2H, Ar–*H*), 7.08 (m, 2H, Ar–*H*), 6.92 (d, 2H, $J$=9.2 Hz, Ar–*H*), 5.71 (s, 2H, $C_4$–OC$H_2$Ph), 5.07 (s, 2H, OC$H_2$Ph), 4.57 (s, 2H, OC$H_2$Ph); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=167.1, 166.2, 165.6, 159.8, 141.1, 136.3, 134.7, 133.9, 130.9, 129.4, 129.0, 128.8, 128.6, 128.4, 128.32, 128.27, 128.1, 127.4, 123.0, 116.6, 115.1, 74.9, 70.0, 67.3, 51.5 (two non-identified aromatic CH signals overlap); HRMS (ESI-TOF) ($m/z$): calcd for $C_{33}H_{25}INaO_6$ $[M+Na]^+$ 667.0594, found: 667.0597.

### 4.8. Typical procedure for the Suzuki–Miyaura reaction

All the solvents were degassed. To a solution of iodide **9a** (50 mg, 0.108 mmol) in THF (5.5 mL) were added $Pd(PPh_3)_2Cl_2$ (4 mg, 5.4 μmol, 5 mol %), a solution of 4-methoxyphenylboronic acid pinacol ester (37.9 mg, 0.162 mmol, 1.5 equiv) in THF (2 mL), and 2 M aqueous $Na_2CO_3$ (2.4 mL). The reaction mixture was refluxed for 2 h under argon. After cooling to room temperature, water (5.5 mL) and saturated aqueous $NH_4Cl$ (2 mL) were added. The aqueous layer was extracted with $CH_2Cl_2$ (3×5 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. Silica gel chromatography (9:1 to 6:4 pentane/AcOEt) afforded **12b** (*E*/*Z* isomer ratio: 91/9) as a yellow solid (37 mg, 77%).

#### *4.8.1. Methyl (3-benzyloxy-5-oxo-4-phenyl-5H-furan-2-ylidene)phenylacetate (**12a**)*

Yellow solid (*E*/*Z* isomer ratio: 94/6). Mp=151 °C; TLC: $R_f$=0.7 (8:2 pentane/AcOEt); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.67 (dd, 2H,

$J$=8.0, 1.8 Hz, Ar–*H*), 7.56–7.31 (m, 11H, Ar–*H*), 7.23 (m, 2H, Ar–*H*), 4.97 (s, 2H, OC*H*$_2$Ph), 3.36 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=166.6 (2C), 161.3, 141.3 (s, $C_5$), 134.1, 131.1, 130.2, 129.9, 129.2, 129.0, 128.7, 128.5, 128.4, 116.5, 108.3, 75.4, 52.3; MS (ESI-TOF) $m/z$ 435 (100, $[M+Na]^+$).

#### 4.8.2. Methyl [3-benzyloxy-4-(4-methoxyphenyl)-5-oxo-5H-furan-2-ylidene]phenylacetate (**12b**)

Yellow solid (*E*/*Z* isomer ratio: 91/9). Mp=138–139 °C; TLC: $R_f$=0.6 (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=3031, 2953, 2843, 1776, 1726, 1630, 1602, 1514, 1433, 1292, 1258, 1163, 1045, 941, 833, 759, 698 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.67 (d, $J$=8.7 Hz, 2H, Ar–*H*), 7.49 (d, $J$=8.7 Hz, 2H, Ar–*H*), 7.42–7.24 (m, 8H, Ar–*H*), 6.98 (d, $J$=8.7 Hz, 2H, Ar–*H*), 4.97 (s, 2H, OC*H*$_2$Ph), 3.85 (s, 3H, ArOC*H*$_3$), 3.39 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.1, 166.8, 160.7, 160.2, 141.6, 134.4, 131.4, 131.2, 129.2, 129.0, 128.7, 128.7, 128.6, 120.7, 116.2, 114.1, 108.7, 75.1, 55.4, 52.4 (two non-identified aromatic CH signals overlap); HRMS (ESI-TOF) ($m/z$): calcd for $C_{27}H_{22}NaO_6$ $[M+Na]^+$ 465.1314, found: 465.1323.

#### 4.8.3. Methyl [3-benzyloxy-4-(3-hydroxyphenyl)-5-oxo-5H-furan-2-ylidene]phenylacetate (**12c**)

Yellow solid (*E*/*Z* isomer ratio: 91/9). IR (KBr pellet) $\nu_{max}$=3389, 2951, 1763, 1727, 1707, 1633, 1594, 1496, 1441, 1346, 1328, 1304, 1245, 1217, 1048, 988, 868, 763, 693, 676, 609 cm$^{-1}$. *Major (E)-isomer*. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.67 (d, 2H, $J$=8.0 Hz, Ar–*H*), 7.50–7.20 (m, 9H, Ar–*H*), 7.08 (d, 1H, $J$=7.6 Hz, Ar–*H*), 6.96 (br s, 1H, Ar–*H*), 6.89 (dd, 1H, $J$=8.0, 2.5 Hz, Ar–*H*), 5.30 (br s, 1H, OH), 4.99 (s, 2H, OC*H*$_2$Ph), 3.37 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.9, 166.9, 161.4, 156.9, 141.3, 134.1, 131.1, 130.2–129.2–129–128.7–128.5–128.4, 129.9, 116.5, 108.3, 75.6, 52.3; HRMS (ESI-TOF) ($m/z$): calcd for $C_{26}H_{20}NaO_6$ $[M+Na]^+$ 451.1158, found: 451.1155.

#### 4.8.4. Methyl [3-benzyloxy-4-(4-chlorophenyl)-5-oxo-5H-furan-2-ylidene]phenylacetate (**12d**)

Yellow solid (*E*/*Z* isomer ratio: 88/12). Mp=154–156 °C; IR (KBr pellet) $\nu_{max}$=2953, 1772, 1720, 1629, 1591, 1493, 1437, 1346, 1328, 1302, 1234, 1161, 1126, 1046, 969, 941, 905, 845, 768, 690, 635, 595 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.67 (dd, 2H, $J$=8.0, 1.8 Hz, Ar–*H*), 7.56–7.31 (m, 8H, Ar–*H*), 7.23 (m, 2H, Ar–*H*), 7.12 (d, 2H, $J$=8.0 Hz, Ar–*H*), 4.96 (s, 2H, OC*H*$_2$Ph), 3.37 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=167.5, 166.6, 161.6, 141.2, 135.3, 133.9, 131.4, 131.0, 129.5, 129.2, 129.1, 128.82, 128.77, 128.70, 128.67, 127.1, 117.1, 107.4, 76.7, 52.4; HRMS (ESI-TOF) ($m/z$): calcd for $C_{26}H_{19}ClNaO_5$ $[M+Na]^+$ 469.0819, found: 469.0816.

#### 4.8.5. Methyl (3-benzyloxy-5-oxo-4-phenyl-5H-furan-2-ylidene)(4-benzyloxyphenyl)acetate (**12e**)

Orange solid (*E*/*Z* isomer ratio: 89/11). Mp=149–151 °C; IR (NaCl, film) $\nu_{max}$=2924, 2859, 2355, 2337, 1769, 1732, 1627, 1598, 1510, 1453, 1349, 1305, 1281, 1252, 1228, 1187, 1159, 1131, 1046, 936, 912, 841 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.65 (d, $J$=9.2 Hz, 2H, Ar–*H*), 7.53 (m, 2H, Ar–*H*), 7.48–7.32 (m, 11H, Ar–*H*), 7.23 (m, 2H, Ar–*H*), 7.01 (d, $J$=8.8 Hz, 2H, Ar–*H*), 5.11 (s, 2H, OC*H*$_2$Ph), 4.95 (s, 2H, OC*H*$_2$Ph), 3.37 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.0, 167.0, 161.5, 159.6, 140.1, 136.4, 134.2, 130.8, 130.2, 129.0, 128.94, 128.85, 128.8, 128.63, 128.58, 128.5, 128.1, 127.4, 123.8, 116.5, 115.2, 107.8, 75.4, 70.0, 52.3; MS (ESI-TOF) $m/z$ 519 (100, $[M+H]^+$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{33}H_{26}NaO_6$ $[M+Na]^+$ 541.1627, found: 541.1631.

#### 4.8.6. Methyl [3-benzyloxy-4-(4-methoxyphenyl)-5-oxo-5H-furan-2-ylidene](4-benzyloxy-phenyl)acetate (**12f**)

Solid (*E*/*Z* isomer ratio: 95/5). Mp=155–156 °C; IR (NaCl, film) $\nu_{max}$=3033, 2947, 2846, 1770, 1727, 1624, 1600, 1511, 1452, 1382, 1345, 1285, 1252, 1183, 1160, 1050, 1024, 961, 942, 918, 834, 777, 753, 698, 834, 777, 753, 698, 662, 613, 550 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.64 (d, $J$=9.0 Hz, 2H, Ar–*H*), 7.50 (d, $J$=8.9 Hz, 2H, Ar–*H*), 7.45–7.32 (m, 10H, Ar–*H*), 7.01 (d, $J$=9.1 Hz, 2H, Ar–*H*), 6.98 (d, $J$=9.0 Hz, 2H, Ar–*H*), 5.11 (s, 2H, OC*H*$_2$Ph), 4.96 (s, 2H, OC*H*$_2$Ph), 3.86 (s, 3H, ArOC*H*$_3$), 3.38 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.2, 167.1, 160.9, 160.1, 159.5, 140.3, 136.4, 134.4, 131.3, 130.8, 129.0, 128.7, 128.62, 128.57, 128.56, 128.1, 127.4, 123.8, 120.8, 116.1, 115.1, 114.0, 108.1, 75.0, 70.0, 55.3, 52.4; MS (ESI-TOF) $m/z$ 549 (100, $[M+H]^+$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{34}H_{28}NaO_7$ $[M+Na]^+$ 571.1733, found: 571.1736.

#### 4.8.7. Methyl [3-benzyloxy-4-(4-chlorophenyl)-5-oxo-5H-furan-2-ylidene](4-benzyloxyphenyl)acetate (**12g**)

Yellow solid (*E*/*Z* isomer ratio: 90/10). IR (NaCl, film) $\nu_{max}$=3033, 2920, 1754, 1729, 1589, 1511, 1491, 1454, 1433, 1384, 1343, 1304, 1280, 1254, 1228, 1189, 1156, 1093, 1046, 1014, 999, 982, 942, 904, 865, 833, 776, 755, 735, 697, 613, 574, 547, 514 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.63 (d, $J$=9.0 Hz, 2H, Ar–*H*), 7.48 (d, $J$=8.5 Hz, 2H, Ar–*H*), 7.45–7.33 (m, 10H, Ar–*H*), 7.24 (m, 2H, Ar–*H*), 7.01 (d, $J$=9.0 Hz, 2H, Ar–*H*), 5.11 (s, 2H, OC*H*$_2$Ph), 4.95 (s, 2H, OC*H*$_2$Ph), 3.38 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=167.7, 166.9, 161.8, 159.7, 139.8, 136.4, 135.1, 134.0, 131.3, 130.9, 129.2, 128.8, 128.7, 128.6, 128.1, 127.5, 127.3, 123.6, 117.0, 115.2, 106.9, 75.6, 70.0, 52.4; HRMS (ESI-TOF) ($m/z$): calcd for $C_{33}H_{25}ClNaO_6$ $[M+Na]^+$ 575.1237, found: 575.1233.

#### 4.8.8. Benzyl (3-benzyloxy-5-oxo-4-phenyl-5H-furan-2-ylidene)(4-benzyloxyphenyl)acetate (**12h**)

Yellow solid (*E*/*Z* isomer ratio: 95/5). Mp=129 °C; IR (NaCl, film) $\nu_{max}$=3033, 2918, 2860, 1768, 1726, 1632, 1598, 1468, 1510, 1494, 1455, 1422, 1408, 1382, 1347, 1307, 1283, 1249, 1219, 1184, 1158, 1074, 1038, 939, 920, 785, 771, 752, 723, 696, 678, 612, 594, 546, 518 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.61 (d, $J$=8.8 Hz, 2H, Ar–*H*), 7.52–7.28 (m, 16H, Ar–*H*), 7.23–7.14 (m, 4H, Ar–*H*), 6.97 (d, $J$=9.2 Hz, 2H, Ar–*H*), 5.10 (s, 2H, OC*H*$_2$Ph), 4.91 (s, 2H, OC*H*$_2$Ph), 4.78 (s, 2H, OC*H*$_2$Ph); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.0, 166.3, 161.5, 159.5, 140.1, 136.4, 134.9, 134.3, 130.8, 130.2, 129.0, 128.92, 128.85, 128.61, 128.57, 128.41, 128.35, 128.1, 127.5, 123.8, 116.4, 115.1, 107.8, 75.1, 70.0, 67.4; MS (ESI-TOF) $m/z$ 595 (100, $[M+H]^+$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{39}H_{30}NaO_6$ $[M+Na]^+$ 617.1940, found: 619.1967.

#### 4.8.9. Benzyl [3-benzyloxy-4-(4-methoxyphenyl)-5-oxo-5H-furan-2-ylidene](4-benzyloxy-phenyl)acetate (**12i**)

Yellow solid (*E*/*Z* isomer ratio: 95/5). Mp=131–132 °C; IR (NaCl, film) $\nu_{max}$=3064, 3033, 2935, 2838, 1767, 1728, 1627, 1601, 1510, 1455, 1424, 1379, 1347, 1282, 1252, 1219, 1183, 1158, 1104, 1081, 1038, 963, 938, 833, 771, 734, 696, 643, 612, 518 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.60 (d, $J$=9.0 Hz, 2H, Ar–*H*), 7.49–7.28 (m, 13H, Ar–*H*), 7.24 (m, 2H, Ar–*H*), 7.17 (m, 2H, Ar–*H*), 6.98 (d, $J$=8.6 Hz, 2H, Ar–*H*), 6.96 (d, $J$=8.9 Hz, 2H, Ar–*H*), 5.10 (s, 2H, OC*H*$_2$Ph), 4.92 (s, 2H, OC*H*$_2$Ph), 4.79 (s, 2H, OC*H*$_2$Ph), 3.86 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.2, 166.4, 160.9, 160.0, 159.4, 140.3, 136.4, 134.9, 134.5, 131.3, 130.8, 128.9, 128.6, 128.5, 128.40, 128.38, 128.3, 128.1, 127.4, 123.9, 120.8, 116.0, 115.1, 114.0, 108.1, 74.7, 70.0, 67.4, 55.3; MS (ESI-TOF) $m/z$ 647 (100, $[M+H]^+$); HRMS (ESI-TOF) ($m/z$): calcd for $C_{40}H_{32}NaO_7$ $[M+Na]^+$ 647.2046, found: 647.2038.

#### 4.8.10. Benzyl [3-benzyloxy-4-(3,4-bis-benzyloxyphenyl)-5-oxo-5H-furan-2-ylidene](4-benzyloxyphenyl)acetate (**12j**)

Yellow solid (*E*/*Z* isomer ratio: 93/7). IR (NaCl, film) $\nu_{max}$=3057, 3026, 2934, 2872, 1767, 1728, 1629, 1599, 1510, 1455, 1381, 1347, 1323, 1308, 1274, 1255, 1216, 1185, 1135, 1078, 1040, 1026, 971, 907, 879, 855, 838, 809, 735, 696 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.61 (d, $J$=8.8 Hz, 2H, Ar–*H*), 7.49–7.28 (m, 21H, Ar–*H*), 7.20 (m, 2H, Ar–*H*), 7.15 (m, 2H, Ar–*H*), 7.07 (m, 2H, Ar–*H*), 6.98 (m, 3H,

Ar–*H*), 5.23 (s, 2H, OC$H_2$Ph), 5.12 (s, 2H, OC$H_2$Ph), 10 (s, 2H, OC$H_2$Ph), 4.85 (s, 2H, OC$H_2$Ph), 4.83 (s, 2H, OC$H_2$Ph); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.1, 166.4, 160.9, 159.5, 149.5, 148.5, 140.2, 136.9, 136.4, 134.9, 134.5, 130.8, 128.1, 128.6, 128.51, 128.49, 128.43, 128.41, 128.36, 128.3, 128.1, 127.9, 127.4, 127.3, 127.2, 123.8, 123.6, 121.6, 116.4, 116.1, 115.1, 114.4, 107.9, 74.5, 71.07, 71.04, 69.99, 67.5; HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{53}H_{42}NaO_8$ $[M+Na]^+$ 829.2777, found: 829.2757.

### 4.9. Typical procedure for the hydrogenolysis

To a suspension of 10% Pd/C (26 mg) and compound **12b** (23 mg, 0.052 mmol) in DMF (2 mL) was added two drops of concentrated HCl. The reaction mixture was placed under a hydrogen atmosphere at 1 atm, under vigorous stirring, for 2.5 h. Hydrogen was replaced by argon, then the suspension was filtered over a short pad of Celite, which was washed with THF. After concentration, ether (20 mL) was added and the organic phase was washed several times with water, dried ($Na_2SO_4$), filtered, and concentrated under vacuum. Silica gel chromatography (9:1 to 1:3 pentane/AcOEt) afforded pinastric acid **13b** as a yellow solid (13 mg, 71%).

#### *4.9.1. Methyl [3-benzyloxy-4-(4-methoxyphenyl)-5-oxo-5H-furan-2-ylidene](4-benzyloxy-phenyl)acetate; vulpinic acid (**13a**)*

Yellow solid. Mp=151 °C (lit.[10b] 146–147 °C, lit.[13e] 146–148 °C, lit.[10c] 150–151 °C); TLC: $R_f$=0.15 (8:2 pentane/AcOEt); IR (KBr pellet) $\nu_{max}$=2962, 2513, 1768, 1679, 1609, 1436, 1302, 1070, 952, 689 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=13.79 (br s, 1H, OH), 8.14 (m, 2H, Ar–*H*), 7.50–7.30 (m, 6H, Ar–*H*), 7.27 (m, 2H, Ar–*H*), 3.88 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.2, 166.4, 160.9, 160.0, 159.4, 140.3, 136.4, 134.9, 134.5, 131.3, 130.8, 128.9, 128.6, 128.5, 128.40, 128.38, 128.3, 128.1, 127.4, 123.9, 120.8, 116.0, 115.1, 114.0, 108.1, 74.7, 70.0, 67.4, 55.3; MS (ESI-TOF) *m*/*z* 647 (100, $[M+H]^+$).

#### *4.9.2. Methyl [3-hydroxy-4-(4-methoxyphenyl)-5-oxo-5H-furan-2-ylidene]phenylacetate; pinastric acid (**13b**)*

Mp=203–205 °C (lit.[10c] 207–209 °C); IR (KBr pellet) $\nu_{max}$=3745, 3018, 2959, 2841, 2535, 1772, 1674, 1600, 1514, 1493, 1441, 1370, 1308, 1278, 1254, 1189, 1063, 1024, 959, 905, 844, 700 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=8.14 (d, *J*=8.9 Hz, 2H, Ar–*H*), 7.45–7.40 (m, 3H, Ar–*H*), 7.30–7.25 (m, 2H, Ar–*H*), 6.98 (d, *J*=8.9 Hz, 2H, Ar–*H*), 3.89 (s, 3H, $CH_3$), 3.86 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=171.7, 166.1, 159.6, 158.6, 155.0, 132.1, 130.0, 129.4, 128.5, 128.1, 121.6, 115.2, 113.9, 105.3, 55.3, 54.3.

#### *4.9.3. Methyl [3-hydroxy-4-(3-hydroxyphenyl)-5-oxo-5H-furan-2-ylidene]phenylacetate (**13c**)*

Yellow solid. Mp=192–194 °C; IR (KBr pellet) $\nu_{max}$=3368, 3056, 2925, 2472, 2361, 1745, 1715, 1674, 1608, 1493, 1437, 1381, 1323, 1305, 1287, 1230, 1157, 1078, 1063, 998, 966, 853, 793, 733, 695, 642, 600 cm$^{-1}$; $^1$H NMR (400 MHz, acetone-$d_6$): $\delta$=8.28 (s, 1H, OH), 7.71 (m, 1H, Ar–*H*), 7.67 (d, *J*=8.0 Hz, 1H, Ar–*H*), 7.50–7.35 (m, 5H, Ar–*H*), 7.23 (t, *J*=8.0 Hz, 2H, Ar–*H*), 7.77 (dd, *J*=8.4, 2.0 Hz, 1H, Ar–*H*), 3.90 (s, 3H, $CO_2CH_3$); HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{19}H_{14}NaO_6$ $[M+Na]^+$ 361.0688, found: 361.0694.

#### *4.9.4. Methyl [3-hydroxy-4-(4-methoxyphenyl)-5-oxo-5H-furan-2-ylidene](4-hydroxyphenyl)acetate (**13i**)*

Orange solid. Mp=210–212 °C; IR (KBr pellet) $\nu_{max}$=3412, 3243, 3007, 2921, 2841, 2549, 1732, 1678, 1596, 1514, 1439, 1413, 1371, 1314, 1278, 1248, 1187, 1177, 1158, 1107, 1064, 1028, 973, 912, 885, 841, 784, 769, 752, 711, 682, 648, 583, 535, 522 cm$^{-1}$; $^1$H NMR (400 MHz, acetone-$d_6$): $\delta$=8.80 (dd, *J*=7.2, 2.0 Hz, 2H, Ar–*H*), 7.25 (dd, *J*=6.8, 2.0 Hz, 2H, Ar–*H*), 7.02 (d, *J*=8.8 Hz, 2H, Ar–*H*), 6.89 (dd, *J*=6.8, 2.0 Hz, 2H, Ar–*H*), 3.91 (s, 3H, $CH_3$), 3.85 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, acetone-$d_6$): $\delta$=173.1, 166.8, 160.5, 160.0, 158.5, 154.6, 132.6, 129.9, 124.5, 122.8, 116.7, 115.6, 114.7, 104.9, 55.6, 54.8; MS (ESI-TOF) *m*/*z* 369 (100, $[M+H]^+$); HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{20}H_{16}NaO_7$ $[M+Na]^+$ 391.0794, found: 391.0803.

#### *4.9.5. [4-(3,4-Dihydroxyphenyl)-3-hydroxy-5-oxo-5H-furan-2-ylidene](4-hydroxy-phenyl)acetic acid; xerocomic acid (**13j**)*

Red solid. Mp=292–293 °C (lit.[13e] 295–297 °C); IR (KBr pellet) $\nu_{max}$=3493, 3185, 2926, 24.78, 1736, 1679, 1593, 1513, 1480, 1434, 1368, 1306, 1256, 1210, 1191, 1149, 1133, 1095, 1057, 980, 956, 894, 873, 831, 814, 796, 744, 701, 663, 582, 561, 531 cm$^{-1}$; $^1$H NMR (400 MHz, acetone-$d_6$): $\delta$=7.73 (d, *J*=2.0 Hz, 1H, Ar–*H*), 7.58 (dd, *J*=8.4, 2.0 Hz, 1H, Ar–*H*), 7.28 (d, *J*=8.6 Hz, 2H, Ar–*H*), 6.89 (m, 3H, Ar–*H*); $^{13}$C NMR (100 MHz, acetone-$d_6$): $\delta$=174.1, 166.9, 159.6, 158.3, 155.2, 146.3, 145.5, 132.5, 125.2, 122.3, 121.1, 116.7, 116.0, 115.5, 115.4, 104.9; HRMS (ESI-TOF negatif) (*m*/*z*): calcd for $C_{18}H_{11}O_8$ $[M-H]^+$ 355.0454, found: 355.0459.

### Acknowledgements

A financial support by the CNRS to C.W. is gratefully acknowledged.

### References and notes

1. For reviews, see: (a) Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157–3188; (b) Gill, M.; Steglich, W. *Prog. Chem. Org. Nat. Prod.* **1987**, *51*, 1–317; (c) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625–694.
2. Benedict, R. G.; Brady, L. R. *J. Pharm. Sci.* **1972**, 1820–1822.
3. Foden, F.; McCormick, J.; O'Mant, D. *J. Med. Chem.* **1975**, *18*, 199–203.
4. Söderberg, U. *Acta Physiol. Scand.* **1952**, *27*, 97–98.
5. Dias, D.; White, J. M.; Urban, S. *Nat. Prod. Res.* **2007**, *21*, 366–376.
6. 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.
7. Meunier, S.; Hanédanian, M.; Desage-El Murr, M.; Nowaczyk, S.; Le Gall, T.; Pin, S.; Renault, J.-P.; Boquet, D.; Créminon, C.; Mioskowski, C.; Taran, F. *Chem. Bio. Chem.* **2005**, *6*, 1234–1241.
8. For a report of the antioxidant properties of a pulvinic acid, variegatic acid, see: Kasuga, A.; Aoagi, Y.; Sugahara, T. *J. Food Sci.* **1995**, *60*, 1113–1115.
9. Volhard, J. *Liebigs Ann. Chem.* **1894**, *282*, 1–21.
10. (a) Frank, R. L.; Clark, G. R.; Coker, J. N. *J. Am. Chem. Soc.* **1950**, *72*, 1824–1826; (b) Wikholm, R. J.; Moore, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 6152–6158; (c) Pattenden, G.; Pegg, N.; Kenyon, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2363–2371.
11. Heurtaux, B.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2005**, *70*, 1474–1477.
12. (a) Åkermark, B. *Acta Chem. Scand.* **1961**, *15*, 1695–1700; (b) Beaumont, P. C.; Edwards, R. L.; Elsworthy, G. *J. Chem. Soc. C* **1968**, 2968–2974; (c) Edwards, R. L.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1529–1537.
13. (a) Weinstock, J.; Blank, J. E.; Oh, H. J.; Sutton, B. M. *J. Org. Chem.* **1979**, *44*, 673–675; (b) Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 84–88; (c) Pattenden, G.; Pegg, N.; Smith, A. G. *Tetrahedron Lett.* **1986**, *27*, 403–406; (d) Gedge, D. R.; Pattenden, G.; Smith, A. G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2127–2131; (e) Ramage, R.; Griffiths, G. J.; Sweeney, J. N. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1547–1553; (f) Pattenden, G.; Turvill, M. W.; Chorlton, A. P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2357–2361.
14. (a) Desage-El Murr, M.; Nowaczyk, S.; Le Gall, T.; Mioskowski, C.; Amekraz, B.; Moulin, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1289–1293; (b) Desage-El Murr, M.; Nowaczyk, S.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **2006**, 1489–1498.
15. (a) Ahmed, Z.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3753–3757; (b) Ahmed, Z.; Langer, P. *Tetrahedron* **2005**, *61*, 2055–2063.
16. Bourdreux, Y.; Nowaczyk, S.; Billaud, C.; Mallinger, A.; Willis, C.; Desage-El Murr, M.; Toupet, L.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2008**, *73*, 22–26.
17. (a) Langer, P.; Schneider, T.; Stoll, M. *Chem.—Eur. J.* **2000**, *6*, 3204–3214; (b) Langer, P.; Eckardt, T.; Schneider, T.; Göbel, C.; Herbst-Irmer, R. *J. Org. Chem.* **2001**, *66*, 2222–2226; (c) Langer, P. *Synlett* **2006**, 3369–3381.
18. (a) For reviews on the Suzuki–Miyaura reaction, see: Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*,. 9633–9695; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
19. For examples of syntheses of butenolides that make use of both an alkylidenation and a Suzuki cross-coupling, see: (a) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett.* **1998**, *39*, 7665–7668; (b) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023–2027; (c) Boukouvalas, J.; Pouliot, M. *Synlett* **2005**, 343–345; (d) Antane, S.; Caufield, C. E.; Hu, W.; Keeney, D.; Labthavikul, P.; Morris, K.; Naughton, S. M.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y. *Bioorg. Med. Chem. Lett.* **2006**, 176–180.

20. Willis, C.; Bodio, E.; Bourdreux, Y.; Billaud, C.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 6421–6424.
21. Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1990**, *31*, 6973–6976.
22. (a) Cossy, J.; Bellosta, V.; Ranaivosata, J. L.; Gille, B. *Tetrahedron* **2001**, *57*, 5173–5182; (b) Narasaka, K. *Org. Synth.* **1987**, *65*, 12–14.
23. Zhang, F. J.; Li, Y. L. *Synthesis* **1993**, 565–567 and references therein.
24. Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459–2465.
25. Paintner, F. F.; Allmendinger, L.; Bauschke, G. *Synlett* **2003**, 83–86.
26. Pollet, P.; Gelin, S. *Tetrahedron* **1978**, *34*, 1453–1455.
27. Gordon, E. M.; Pluščec, J. *J. Org. Chem.* **1979**, *44*, 1218–1221.
28. Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557–1564.