Extension of the Library of Biologically Active γ-Alkylidene Butenolides

Petr Novák,[a] Milan Pour,[b] Marcel Špulák,[b] Ivan Votruba,[c] Martin Kotora*[a,c]

[a] Department of Organic and Nuclear Chemistry and Centre for New Antivirals and Antineoplastics, Faculty of Science, Charles University, Hlavova 8, 128 43 Praha 2, Czech Republic
Fax +420(2)21951326; E-mail: kotora@natur.cuni.cz

[b] Centre for New Antivirals and Antineoplastics, Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, 500 05 Hradec Králové, Czech Republic

[c] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Praha 6, Czech Republic

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Abstract: γ-Alkylidene butenolides bearing a deoxyriboside, a steroid, and a metallocene moiety were synthesized by stereoselective sequential cross-coupling lactonization procedure from the corresponding functionalized terminal alkynes with 3-iodopropenoic acids. The high selectivity of the butenolide ring formation was secured by the Pd/Cu salt ratio. The resulting compounds were tested for antifungal and cytostatic properties. Most notably, γ-alkylidene butenolides bearing deoxyriboside moiety showed promising cytostatic activity in the micromolar range.

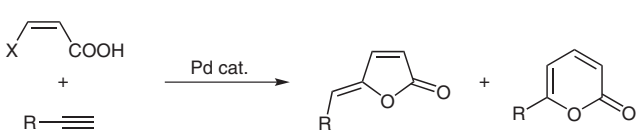
Key words: cross-coupling, lactones, catalysis, antitumor agents, palladium

γ-Alkylidene butenolide moiety is a structural feature of many compounds produced by nature or synthesized in the laboratory. A number of them are of pharmacological interest as they have a broad array of potentially useful medicinal and biological properties such as antibacterial, cytotoxic, antitumor, and enzyme inhibitory activity. The most simple compound in this series is protoanemonin (*Anemone pulsatilla*),[1] which is well known for its strong antibacterial and antifungal properties. All other γ-alkylidene butenolides can be considered as its substituted congeners. Examples of these substances are melodorinol[2a] and its oxidized derivatives (*Melodorum fruticosum*),[2b] rubrolides (colonial tunicate *Ritterella rubra*),[3] dihydroxerulin, xeruline and xerulinic acid (*Xerula melanotricha*),[4] goniobutenolide A (*Goniothalamus giganteus*),[5] freelingyne (*Eremophila freelingii*),[6] maculalactones (*Kyrtuthrix maculans*),[7] cochinolide (*Homalium cochinchinensis*),[8] lissoclinolide (*Amphidinium carterae*),[9] peridinin (*Amphidinium carterae*),[10] didehydrostemofoline (*Stemona collinsae*),[11] nostoclide I (*Peltigera canina*),[12] neopatulin (*Aspergillus clavatus*),[13] ellipsoidone A and B (*Hemsleya ellipsoidea*),[14] aporpinone A (*Aporpium caryae*),[15] acetoxyfimbrolide B (*Delicea fimbrilata*),[16] uncinine (*Artabotrys uncinatus*),[17] pyrrhoxanthine (*Gyrodinium resplendens*),[10c,18] ligustilide and related compounds (genera within the family Apiaceae),[19] eremolactone (*Eremophila freelingii*),[20] tetrenoline (*Micropolyspora venezuelensis*),[21] thiophenebutenolide (*Chamaemelum nobile*),[22] and bovolide (isolated from butter).[23] Among the synthesized γ-alkylidene butenolides, cardenolide[24] and digoxin[25] derivatives are worth mentioning.

Although the mechanism of the biological effect of these agents is still unclear, we can speculate that their activity could be attributed to an interaction with the cystein residues of functional proteins resulting in covalent bond formation via a Michael type addition.[26] Indeed, thiols such as *N*-acetylcysteamine were shown to add smoothly across the exo-methylene moiety of tetrodecamycine furnishing the corresponding S-alkylation products.[27] However, these derivatives continued to possess a marked antibacterial activity in vitro. This may be due to a retro-Michael reaction regenerating tetrodecamycin as the biologically active component.

The synthesis of the γ-alkylidene butenolide framework can be accomplished by various methodologies. Generally, existing methods can be divided into two categories: i) transition metal catalyzed procedures and ii) condensation reactions.[28] The aforementioned transition metal based procedures are based on three strategies: i) reaction of terminal alkynes with halopropenoic acids,[29] ii) cyclization of enynoic acids,[30] and iii) cyclocarbonylation of halovinyl ketones.[31] Among these methods, the former is of special interest, because it uses easily accessible reactants (terminal alkynes and halopropenoic acids) and is usually carried out under mild reaction conditions with a high degree of selectivity with respect to the stereochemistry on the γ-alkylidene moiety. However, it should be noted that the formation of α-pyrones as side products can be observed (Scheme 1). Herein we would like to report the synthesis of new γ-alkylidene butenolides and their antifungal and cytostatic activity.

The choice of moieties in new γ-alkylidene butenolide was based on the following presumptions. The deoxyribo-



Scheme 1

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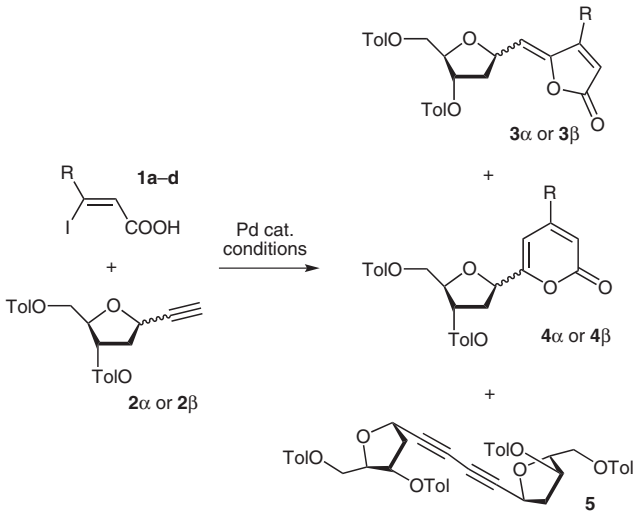
side moiety was chosen because of its structural resemblance to ester groups in melodorinol.[2] The estrone moiety was chosen because isoprenoids (cardenolides, etc.) with similar structure were prepared and new type of γ-alkylidene butenolide would represent its positional isomer.[24,25] Finally, the ferrocene moiety was selected because of its beneficial influence on many biological properties.[32]

As a standard method for the construction of the γ-alkylidene butenolide moiety, we decided to use a simple, yet stereoselective sequential cross-coupling lactonization procedure based on the Sonogashira reaction of terminal alkynes with (*Z*)-3-halopropenoic acids followed by Pd-catalyzed addition of the carboxylic moiety onto the triple bond.[29,33] Considering the attached functional groups, our effort was aimed at varying the substitution at both γ-alkylidene and position 4 of the butenolide moiety. At the outset, we decided to study the preparation of γ-alkylidene butenolides prepared from the reaction of α- and β-anomers of 1-ethynyl-1,2-dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranose (**2**α and **2**β) and representatives of propenoic acids such as (*Z*)-3-iodopropenoic acid (**1a**), (*Z*)-3-iodo-3-methylpropenoic acid (**1b**), (*Z*)-3-iodo-3-phenylpropenoic acid (**1c**), and (*Z*)-3-iodo-3-(biphenyl-1-yl)propenoic acid (**1d**) (Scheme 2). As expected, initial experiments of the reaction of **2** with **1a** indicated that it would be necessary to tune the reaction conditions to achieve high selectivity of γ-alkylidene butenolide formation while minimizing the amount of α-pyranones (Table 1). When the reaction of **2**α with **1a** was catalyzed by $Pd(PPh_3)_4$ or $Pd(PhCN)_2Cl_2$ (5 mol%) in combination with CuI (5 mol%), mixtures of butenolide **3a**α and pyrone **4a**α were obtained in 2:1 and 3:2 ratios, respectively (entries 1 and 2). In addition, considerable amounts (22 and 20%) of 1,3-diyne **5**, the product of the starting alkyne **2**α dimerization, were isolated. The substitution of CuI by silver salts, AgCl (entries 3 and 4) or Ag_2CO_3 (entry 5) which are known to promote the formation of the butenolide moiety[34] as well as the coupling reaction,[35] did not have the expected effect: in all cases only mixtures of **3a**α and **4a**α were obtained. Moreover, the presence of AgCl also had a detrimental effect on the overall yields of the desired products (10 and 12%). The use of $Pd(PPh_3)_4$ catalyzed only the oxidative dimerization of the starting alkyne to form dimer **5**α (entry 6). Gratifyingly, using a combination of 10 mol% of $Pd(PPh_3)_4$ and 20 mol% of CuI led selectively to γ-alkylidene butenolide **3a**α (entry 7). A similar phenomenon was also observed in the reaction of **2**β with **1a**. Catalysis of the reaction by $Pd(PPh_3)_4$ or $Pd(PhCN)_2Cl_2$ (5 mol%) in combination with CuI (5 mol%) yielded mixtures of butenolide **3a**β and pyranone **4a**β in 4:1 and 3:1 ratios, respectively (entries 8 and 9). However, in these cases the formation of the dimer **5**β was not observed. This result is in accordance with previous observations pertaining to the different behavior of both anomeric alkynes.[36] On the other hand, the combination of 10 mol% of $Pd(PPh_3)_4$ and 20 mol% of CuI led again selectively to γ-alkylidene butenolide **3a**β (entry 10).



Scheme 2 Formation of γ-alkylidene butenolides **3** and pyranones **4**

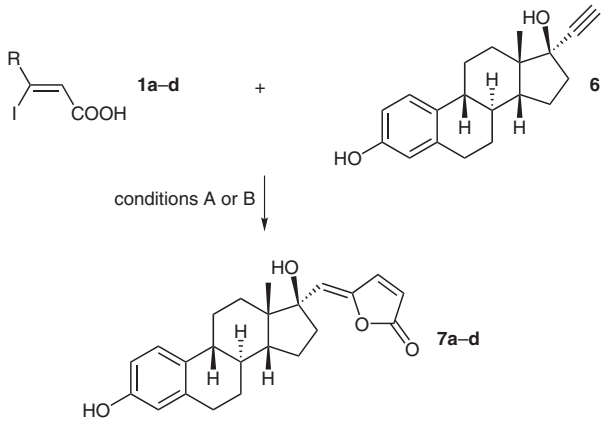
Table 1 Reaction Conditions for the Coupling of **1a** with **2**α and **2**β

Entry	**2**	Pd cat.[a]	Additive[a]	**3** + **4** (%)[b]	**3**/**4**	**5** (%)[b]
1	**2**α	$Pd(PPh_3)_4$	CuI	41	2:1	22
2	**2**α	$Pd(PhCN)_2Cl_2$	CuI	28	3.2	20
3	**2**α	$Pd(PPh_3)_4$	AgCl	12	1:1	–
4	**2**α	$Pd(PhCN)_2Cl_2$	AgCl	10	1:1	–
5	**2**α	$Pd(PPh_3)_4$	Ag_2CO_3	44	1:1	–
6	**2**α	$Pd(PPh_3)_4$	–	–	–	60
7	**2**α	$Pd(PPh_3)_4$[c]	CuI[d]	47[e]	–	–
8	**2**β	$Pd(PPh_3)_4$	CuI	37	4:1	–
9	**2**β	$Pd(PhCN)_2Cl_2$	CuI	67	3:1	–
10	**2**β	$Pd(PPh_3)_4$[c]	CuI[d]	63[f]	–	–

[a] Amount used: 5 mol%, unless otherwise noted.
[b] Isolated yields.
[c] Amount used: 10 mol%.
[d] Amount used: 20 mol%.
[e] γ-Alkylidene butenolide **3a**α was formed selectively.
[f] γ-Alkylidene butenolide **3a**β was formed selectively.

With optimized reaction conditions in hand, we decided to extend the reaction of **2**α and **2**β to other 3-iodopropenoic acid derivatives **1b–d** as well (Table 2). The reaction of **2**α with **1b–d** afforded selectively the corresponding products **3b**α–**3d**α in 87, 90, and 48% isolated yields (entries 1–3). Similar results were also obtained for the reactions of **2**β giving rise to **3b**β, **3c**β, and **3d**β in 85, 88 and 50% isolated yields, respectively (entries 4–6).

Next we turned our attention to the synthesis of γ-alkylidene butenolides bearing a steroid moiety. As a starting compound, we decided to use the commercially available



Scheme 3 Formation of γ-alkylidene butenolides **7**

Table 2 Butenolides **3** Prepared from **1** and **2**

Entry	1	2	Product 3	Yield (%)[a]
1	**1b**, R = Me	**2α**	**3bα**	87
2	**1c**, R = Ph	**2α**	**3cα**	90
3	**1d**, R = C_6H_4Ph	**2α**	**3dα**	48
4	**1b**, R = Me	**2β**	**3bβ**	85
5	**1c**, R = Ph	**2β**	**3cβ**	88
6	**1d**, R = C_6H_4Ph	**2β**	**3dβ**	50

[a] Isolated yields.

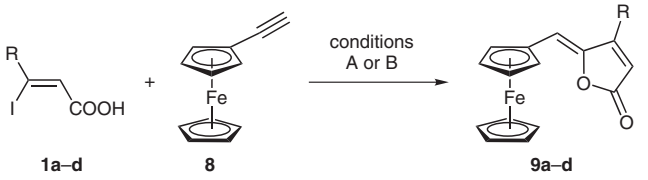
Table 3 Butenolides **7** Prepared from **1** and **6**

Entry	1	7	A, Yield (%)[a]	B, Yield (%)[a]
1	**1a**, R = H	**7a**	26	69
2	**1b**, R = Me	**7b**	78	74
3	**1c**, R = Ph	**7c**	12	60
4	**1d**, R = C_6H_4Ph	**7d**	47	

[a] Isolated yields.

17α-ethynylestradiol (**6**). The reactions of **6** with various 3-iodopropenoic acids **1a–d** were carried out under two different catalytic conditions A [10 mol% $Pd(PPh_3)_4$, 10 mol% CuI] and B [10 mol% $Pd(PPh_3)_4$, 20 mol% CuI] (Scheme 3). These two catalytic systems were used to evaluate the effect of CuI amount on the course of the reaction. Surprisingly, both systems resulted in the selective formation of γ-alkylidene butenolides **7a–d**, unlike the reactions with **2**. On the other hand, the yields of the products were generally higher under conditions B (Table 3). Most markedly it was shown in the reactions with **1a** (A, 12%; B, 69%, entry 1) and **1c** (A, 10%; B, 60%, entry 3).

Finally, we studied the formation of γ-alkylidene butenolides bearing the ferrocenyl moiety by the reaction of ethynylferrocene (**8**) with 3-iodopropenoic acids **1a–d**



Scheme 4 Formation of γ-alkylidene butenolides **9**

Table 4 Butenolides **9** Prepared from **1** and **8**

Entry	1	9	A, Yield (%)[a]	B, Yield (%)[a]
1	**1a**, R = H	**9a**	62	56
2	**1b**, R = Me	**9b**	79	85
3	**1c**, R = Ph	**9c**	76	99
4	**1d**, R = C_6H_4Ph	**9d**	–	99

[a] Isolated yields.

(Scheme 4). In this instance, the above mentioned catalytic systems A and B were also used. Under both reaction conditions (A and B) only the formation of the corresponding γ-alkylidene butenolides **9a–d** was observed again in good yields (Table 4). As in the case of compounds **7**, the yields of **9** were generally higher or even quantitative when conditions B were employed (entries 2–4).

Given the numerous biological activities of the γ-alkylidene butenolides and the antifungal activity of the parent protoanemonin,[37] we decided to investigate the activity of the prepared compounds against potentially pathogenic yeasts and molds by using the microdilution broth method. The strains included *Candida albicans*, *Candida tropicallis*, *Candida krusei*, *Candida glabrata*, *Trichosporon beigelii*, *Trichosporon mentagrophytes*, *Aspergillus fumigatus*, and *Absidia corymbifera.* Disappointingly, none of the tested compounds exhibited potentially useful levels of inhibition (IC_{80} >125 μmol/L). The only exception was the ferrocene-containing γ-alkylidene butenolide **9a**, the IC_{80} of which was 31.25 μmol/L against *Candida albicans*.

Preliminary in vitro cytostatic activity tests of the representatives of the prepared γ-alkylidene butenolides were performed using the following cell cultures: mouse leukemia L1210 cells; human promyelocytic leukemia HL60 cells; human cervix carcinoma HeLa S3 cells; and human T lymphoblastoid CCRF-CEM cell line. Out of the set of compounds, only those bearing the deoxyriboside moiety **3cα**, **3dα**, **3cβ**, and **3dβ**, showed promising activity (Table 5). Interestingly, while the phenyl derivatives **3c**α and **3c**β showed activity against HeLa S3 and CCRF-CEM cell lines, the biphenyl **3dα** and **3dβ** derivatives were active against L1210 and leukemia HL60 cells. With the activities being in lower level of the micromolar range, this novel type of compounds represents a new potential structural lead in the search for antiproliferative drugs. In this regard it is worth of mentioning that butenolide **3dβ**

Table 5 Cytostatic Activity Test of γ-Alkylidene Butenolides **3**

Butenolide	IC_{50}, μmol/L[a]			
	L1210	HL60	HeLa S3	CCRF-CEM
3aα	NA	NA	24.64 ± 0.22	NA
3dα	NA	34.32 ± 0.58	NA	NA
3cα	NA	NA	23.86 ± 0.34	12.99 ± 0.14
3dβ	22.50 ± 1.02	8.68 ± 1.18	NA	NA

[a] NA: not available.

had cytostatic activity in the similar range as natural melodorinol.[2]

In conclusion, we have shown that stereoselective sequential cross coupling-lactonization of 3-halopropenoic acid with terminal alkynes bearing deoxyriboside, steroid and metallocene moiety is a synthetically useful and efficient method that allows the preparation of variously substituted γ-alkylidene butenolides. Moreover, the screening of different reaction conditions revealed that the competition between the formation of γ-alkylidene butenolide and pyranone rings can be easily controlled by using excess CuI, the use of which is more economical than that of Ag salts. In addition, biological evaluation of the prepared compounds revealed that the deoxyribose functionalized γ-alkylidene butenolides could be promising leads in the research of new potential antineoplastic agents.

Starting 3-iodopropenoic acids **1** were prepared by standard procedures by the reaction of corresponding propynoic acids with NaI under acidic conditions.[1] $Pd(PPh_3)_4$[2] and ethynylferrocene (**8**)[3] were prepared according to the previously reported procedures. 17α-Ethynylestradiol (**6**) and MeCN were purchased from Sigma-Aldrich. NMR spectra were recorded on a Varian Unity 400 INOVA instrument at 400 MHz (^{1}H) and 100.6 MHz (^{13}C) or Varian 300 MHz (^{1}H) and 75.5 MHz (^{13}C) as solutions in C_6D_6, CD_3OD, or $CDCl_3$, and are referenced to the residual solvent signal. IR spectra were recorded on a Bruker IFS 88 instrument. Mass spectra were recorded on a Finnigan MAT Incos 50 spectrometer. HR mass spectra were recorded on a ZAB-SEQ VG Analytical spectrometer. Optical rotations were measured using an Autopoll III polarimeter (Rudolph Research) at 20 °C.

Reaction of Ethynyldeoxyribosides 2 with 3-Iodopropenoic Acids 1; General Procedure

Into degassed MeCN (4 mL) were added 1α- or 1β-ethynyl-1,2-dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranose (**2**α or **2**β; 0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and the appropriate 3-iodopropenoic acid **1** (79 mg, 0.4 mmol). Et_3N (0.8 mmol, 110 μL) was then added and the mixture was stirred at 50 °C for 48 h. The volatiles were evaporated under reduced pressure and the residue was subjected to column chromatography.

(5*Z*)-5-{[1α-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}furan-2(5*H*)-one (3aα)

From **1a** (0.4 mmol, 79 mg), **2**α (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 42 mg (47%) of the title compound as a colorless oil; R_f = 0.23 (2:1 hexane–EtOAc); $[\alpha]_D$ 0 (*c* 0.00145 g/mL, $CHCl_3$).

IR (ATR Ge): 1780, 1717, 1613, 1274, 1179, 1106, 758 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ =1.81–1.87 (m, 1 H), 1.96 (s, 3 H), 1.99 (s, 3 H), 2.33–2.40 (m, 1 H), 4.33 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.43 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.47 (td, *J* = 4.8, 2.4 Hz, 1 H), 5.01 (d, *J* = 8 Hz, 1 H), 5.15–5.20 (m, 1 H), 5.32–5.35 (m, 1 H), 5.41 (d, *J* = 4.8 Hz, 1 H), 6.14 (d, *J* = 4.8 Hz, 1 H), 6.89–6.93 (m, 4 H), 8.01–8.05 (m, 2 H), 8.14–8.18 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.03, 22.06, 39.40, 65.27, 74.47, 77.66, 83.00, 116.17, 120.90, 128.24, 128.58, 130.10 (4 ×), 130.70 (2 ×), 130.82 (2 ×), 143.47, 144.36, 144.64, 149.72, 166.49, 166.84, 169.08.

HRMS (FAB+): *m*/*z* calcd for $C_{26}H_{24}O_7$ + Na^+: 471.141973; found: 471.143262.

(5*Z*)-5-{[1α-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}-4-methylfuran-2(5*H*)-one (3bα)

From **1b** (0.4 mmol, 85 mg), **2**α (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 80 mg (87%) of the title compound as a colorless oil; R_f = 0.29 (2:1 hexane–EtOAc); $[\alpha]_D$ –13.3 (*c* 0.003 g/mL, $CHCl_3$).

IR (ATR Ge): 1780, 1717, 1610, 1271, 1176, 1103, 751 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.23 (s, 3 H), 1.84–1.90 (m, 1 H), 1.96 (s, 3 H), 1.99 (s, 3 H), 2.36–2.42 (m, 1 H), 4.33 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.45 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.50 (td, *J* = 5.2, 2.8 Hz, 1 H), 5.20 (d, *J* = 7.6 Hz, 1 H), 5.23–5.28 (m, 1 H), 5.27 (s, 1 H), 5.36–5.39 (m, 1 H), 6.89–6.92 (m, 4 H), 8.01–8.05 (m, 2 H), 8.15–8.19 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 11.52, 22.12, 22.14, 39.51, 65.39, 74.81, 77.80, 83.15, 112.32, 118.17, 128.33, 128.64, 130.15 (2 ×), 130.21 (2 ×), 130.76 (2 ×), 130.92 (2 ×), 144.44, 144.71, 150.97, 154.65, 166.47, 166.94, 168.54.

HRMS (FAB+): *m*/*z* calcd for $C_{27}H_{26}O_7$ + Na^+: 485.157623; found: 485.157022.

(5*Z*)-5-{[1α-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}-4-phenylfuran-2(5*H*)-one (3cα)

From **1c** (0.4 mmol, 110 mg), **2**α (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 94 mg (90%) of the title compound as a colorless oil; R_f = 0.26 (2:1 hexane–EtOAc); $[\alpha]_D$ –37.7 (*c* 0.0061 g/mL, $CHCl_3$).

IR (ATR Ge): 1766, 1715, 1610, 1270, 1177, 1102, 752 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.79–1.85 (m, 1 H), 1.96 (s, 3 H), 2.00 (3 H), 2.32–2.39 (m, 1 H), 4.30–4.42 (m, 3 H), 5.33–5.38 (m, 2 H), 5.62 (d, *J* = 8 Hz, 1 H), 5.64 (s, 1 H), 6.84 (d, *J* = 7.6 Hz, 2 H), 6.90–6.95 (m, 5 H), 7.00–7.05 (m, 2 H), 7.90–7.95 (m, 2 H), 8.16–8.20 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.03, 22.08, 39.34, 65.29, 75.00, 77.65, 83.19, 116.42, 117.40, 128.21, 128.94, 129.19 (2 ×), 129.59 (2 ×), 130.04 (2 ×), 130.12 (2 ×), 130.64 (2 ×), 130.77, 130.84 (2 ×), 131.11, 144.34, 144.39, 149.19, 156.94, 166.34, 166.83, 167.80.

HRMS (FAB+): *m*/*z* calcd for $C_{32}H_{28}O_7$ + Na^+: 547.173273; found: 547.173843.

(5*Z*)-5-{[1α-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}-4-(1″,1‴-biphenyl-4″-yl)furan-2(5*H*)-one (3dα)

From **1d** (0.4 mmol, 140 mg), **2**α (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 57 mg (48%) of the title compound as a colorless oil; $[\alpha]_D$ 0 (*c* 0.00755 g/mL, $CHCl_3$); R_f = 0.30 (2:1 hexane–EtOAc) .

IR (ATR Ge): 1765, 1714, 1610, 1268, 1179, 1103, 751 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.86–2.08 (m, 1 H), 1.87 (s, 3 H), 1.96 (s, 3 H), 2.30–2.36 (m, 1 H), 4.30 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.40 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.45 (td, *J* = 5.2, 1.6 Hz, 1 H), 5.37–5.40 (m, 1 H), 5.41–5.47 (m, 1 H), 5.74–5.76 (m, 2 H), 6.76–6.78 (m, 2 H), 6.90–6.92 (m, 2 H), 7.01–7.03 (m, 2 H), 7.16–7.22 (m, 2 H), 7.24–7.27 (m, 3 H), 7.40–7.42 (m, 2 H), 7.87–7.89 (m, 2 H), 8.17–8.19 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 21.93, 22.04, 39.08, 65.30, 75.03, 77.84, 83.50, 116.50, 117.21, 127.95, 128.30, 128.82 (2 ×), 1 signal was overlapped by C_6D_6 signals, 129.23, 129.77 (2 ×), 129.94 (2 ×), 130.07 (2 ×), 130.13 (2 ×), 130.62 (2 ×), 130.85 (2 ×), 140.95, 143.82, 144.35, 144.46, 149.15, 156.69, 166.29, 166.83, 167.90.

HRMS (FAB+): *m*/*z* calcd for $C_{38}H_{32}O_7 + Na^+$: 623.204573; found: 623.203877.

(5*Z*)-5-{[1β-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}furan-2(5*H*)-one (3aβ)

From **1a** (0.4 mmol, 79 mg), **2**β (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 56 mg (63%) of the title compound as a colorless oil; R_f = 0.23 (2:1 hexane–EtOAc); $[\alpha]_D$ –16.8 (*c* 0.0199 g/mL, $CHCl_3$).

IR (ATR Ge): 1781, 1718, 1610, 1273, 1180, 1108, 755 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.72–4.80 (m, 1 H), 1.966 (s, 3 H), 1.998 (s, 3 H), 2.14–2.19 (m, 1 H), 4.24 (td, *J* = 4.4, 2 Hz, 1 H), 4.38 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.54 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.78 (d, *J* = 7.6 Hz, 1 H), 5.24–5.29 (m, 1 H), 5.38 (d, *J* = 5.6 Hz, 1 H), 5.43–5.45 (m, 1 H), 6.09 (d, *J* = 5.6 Hz, 1 H), 6.89–6.93 (m, 4 H), 8.03–8.07 (m, 2 H), 8.14–8.18 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.03, 22.09, 39.86, 65.48, 74.70, 77.74, 83.92, 114.80, 120.97, 128.26, 128.58, 130.11 (2 ×), 130.14 (2 ×), 130.83 (4 ×), 143.49, 144.35, 144.67, 150.57, 166.65, 166.77, 169.05.

HRMS (FAB+): *m*/*z* calcd for $C_{26}H_{24}O_7 + Na^+$: 471.141973; found: 471.142390.

(5*Z*)-5-{[1β-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}-4-methylfuran-2(5*H*)-one (3bβ)

From **1b** (0.4 mmol, 85 mg), **2**β (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 78.5 mg (85%) of the title compound as a colorless oil; R_f = 0.29 (2:1 hexane–EtOAc); $[\alpha]_D$ 0 (*c* 0.001 g/mL, $CHCl_3$).

IR (ATR Ge): 1780, 1708, 1613, 1271, 1179, 1103, 755 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.24 (s, 3 H), 1.79–1.87 (m, 1 H), 1.96 (s, 3 H), 2.00 (s, 3 H), 2.22–2.27 (m, 1 H), 4.27 (td, *J* = 4.8, 2.4 Hz, 1 H), 4.40 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.59 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.98 (d, *J* = 8 Hz, 1 H), 5.22 (s, 1 H), 5.32–5.38 (m, 1 H), 5.45–5.47 (m, 1 H), 6.87–6.93 (m, 4 H), 8.05–8.09 (m, 2 H), 8.13–8.17 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 11.39, 22.02, 22.10, 39.95, 65.56, 74.98, 77.81, 83.94, 110.78, 118.14, 128.26, 128.58, 130.08 (2 ×), 130.15 (2 ×), 130.80 (2 ×), 130.84 (2 ×), 144.31, 144.67, 151.88, 154.70, 166.69, 166.76, 168.42.

HRMS (FAB+): *m*/*z* calcd for $C_{27}H_{26}O_7 + Na^+$: 485.157623; found: 485.155809.

(5*Z*)-5-{[1β-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}-4-phenylfuran-2(5*H*)-one (3cβ)

From **1c** (0.4 mmol, 110 mg), **2**β (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 92 mg (88%) of the title compound as a colorless oil; R_f = 0.26 (2:1 hexane–EtOAc); $[\alpha]_D$ –65.5 (*c* 0.00275 g/mL, $CHCl_3$).

IR (ATR Ge): 1730, 1704, 1610, 1283, 1264, 1182, 1100, 1065, 751 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.72–1.80 (m, 1 H), 1.95 (s, 3 H), 2.01 (s, 3 H), 2.22–2.27 (m, 1 H), 4.28 (td, *J* = 4.8, 2.4 Hz, 1 H), 4.37 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.48 (dd, *J* = 11.6, 5.2 Hz, 1 H), 5.37–5.43 (m, 1 H), 5.44–5.48 (m, 2 H), 5.63 (s, 3 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.90–6.96 (m, 5 H), 6.99–7.01 (m, 2 H), 8.07–8.10 (m, 4 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.02, 22.10, 39.84, 65.60, 75.26, 77.86, 84.00, 114.91, 117.49, 128.20, 129.18 (2 ×), 129.60 (2 ×), 2 signals were overlapped by C_6D_6 signals, 130.02 (2 ×), 130.14, 130.74 (2 ×), 130.85 (2 ×), 130.92, 144.17, 144.64, 150.26, 157.01, 166.64, 166.73, 167.77.

MS (FAB+): *m*/*z* (%) = no molecular peak, 279 (9), 149 (8), 119 (100).

(5*Z*)-5-{[1β-1,2-Dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranosyl]-1′-methylene}-4-(1″,1‴-biphenyl-4″-yl)furan-2(5*H*)-one (3dβ)

From **1d** (0.4 mmol, 140 mg), **2**β (0.2 mmol, 75.6 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), CuI (0.04 mmol, 7.6 mg), and Et_3N (0.8 mmol, 110 μL). Column chromatography on silica gel (2:1 hexane–EtOAc) afforded 60 mg (50%) of the title compound as a colorless oil; R_f = 0.30 (2:1 hexane–EtOAc); $[\alpha]_D$ –39.5 (*c* 0.01075 g/mL, $CHCl_3$).

IR (CCl_4): 1777, 1725, 1611, 1266, 1178, 1102, 1021, 962, 839 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.80–1.85 (m, 1 H), 1.87 (s, 3 H), 2.01 (s, 3 H), 2.28–2.32 (m, 1 H), 4.27–4.31 (m, 1 H), 4.39 (dd, *J* = 12, 4 Hz, 1 H), 4.53 (dd, *J* = 12, 4 Hz, 1 H), 5.43 (m, 1 H), 5.47–5.55 (m, 1 H), 5.53 (s, 1 H), 5.72 (s, 1 H), 6.81 (d, *J* = 8 Hz, 2 H), 6.94 (d, *J* = 8 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 7.16–7.20 (m, 3 H), 7.22–7.29 (m, 4 H), 7.39–7.43 (m, 2 H), 8.08–8.11 (m, 4 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 21.99, 22.13, 39.92, 65.61, 75.30, 77.97, 84.05, 115.04, 117.21, 128.01 (2 ×), 128.32 (2 ×), 128.37, 128.59, 129.24, 129.62, 129.76 (2 ×), 129.91 (2 ×), 130.03 (2 ×), 130.17 (2 ×), 130.71 (2 ×), 130.86 (2 ×), 140.87, 144.05, 144.24, 144.69, 150.25, 156.67, 166.67, 166.74, 167.94.

MS (EI): *m*/*z* (%) = no molecular peak, 509 (0.3), 368 (2), 310 (4), 256 (5), 136 (10), 119 (22).

Reaction of 17α-Ethynylestradiol (6) with 3-Iodopropenoic Acids 1; General Procedures

Method A: Into degassed MeCN (7 mL) were added 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and the appropriate 3-iodopropenoic acid **1** (1 mmol). Et_3N (2 mmol, 278 μL) was then added and the mixture was stirred at 50 °C for 20 h. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel.

Method B: As above, but with 0.1 mmol of CuI (19 mg).

(5*Z*)-5-[(Estradiol-17′α-yl)methylene]furan-2(5*H*)-one (7a)

Method A: **1a** (1 mmol, 198 mg), 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 47 mg (26%) of the title compound as a white solid.

Method B: **1a** (1 mmol, 198 mg), 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.1 mmol, 19 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 126 mg (69%) of the title compound as a white solid. mp 269 °C; R_f = 0.17 (2:1 hexane–EtOAc); $[\alpha]_D$ +142.3 (*c* 0.0123 g/mL, $CHCl_3$).

IR (ATR Ge): 3402, 2981, 2927, 2863, 1779, 1753, 1498, 1243, 1114, 935 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.96 (s, 3 H), 1.22–1.32 (m, 1 H), 1.36–1.49 (m, 5 H), 1.72–1.78 (m, 1 H), 1.86–2.02 (m, 4 H), 2.26–2.27 (m, 1 H), 2.38–2.44 (m, 1 H), 2.71–2.78 (m, 2 H), 5.59 (s, 1 H), 6.21 (d, *J* = 5.6 Hz, 1 H), 6.46 (d, *J* = 2.8 Hz, 1 H), 6.52 (dd, *J* = 8.4, 2.8 Hz, 2 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 5.6 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 14.47, 24.43, 27.75, 28.85, 30.83, 33.88, 37.56, 41.34, 45.14, 50.25, 50.88, 84.92, 113.86, 116.20, 119.12, 123.62, 127.32, 132.57, 138.94, 147.74, 149.85, 156.07, 172.31.

MS (EI): *m*/*z* (%) = 366 (12), 256 (7), 226 (8), 213 (20), 185 (6), 159 (13), 41 (100).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{26}O_4$: 366.183110; found: 366.183936.

(5*Z*)-5-[(Estradiol-17′α-yl)methylene]-4-methylfuran-2(5*H*)-one (7b)

Method A: **1b** (1 mmol, 212 mg), 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 149 mg (78%) of the title compound as a white solid.

Method B: **1b** (1 mmol, 212 mg), 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.1 mmol, 19 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 140 mg (74%) of the title compound as a white solid; mp 264 °C; R_f = 0.20 (2:1 hexane–EtOAc); $[\alpha]_D$ +137.7 (*c* 0.0069 g/mL, $CHCl_3$).

IR (ATR Ge): 3387, 2924, 1741, 1228, 954 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.96 (s, 3 H), 1.23–1.32 (m, 1 H), 1.36–1.49 (m, 5 H), 1.76 (m, 1 H), 1.86–2.02 (m, 4 H), 2.21 (s, 3 H), 2.24 (m, 1 H), 2.41 (m, 1 H), 2.73 (m, 2 H), 5.56 (s, 1 H), 6.08 (s, 1 H), 6.45 (d, *J* = 2.8 Hz, 1 H), 6.51 (dd, *J* = 8.4, 2.8 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.15, 14.50, 24.48, 27.75, 28.83, 30.84, 33.96, 37.16, 41.34, 45.10, 50.35, 50.80, 84.88, 113.84, 116.19, 116.44, 119.16, 127.31, 132.59, 138.95, 150.58, 156.06, 158.62, 171.45.

MS (EI): *m*/*z* (%) = 380 (54), 362 (8), 239 (22), 226 (37), 213 (76), 159 (68), 41 (100).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{28}O_4$: 380.198760; found: 380.199325.

(5*Z*)-5-[(Estradiol-17′α-yl)methylene]-4-phenylfuran-2(5*H*)-one (7c)

Method A: **1c** (1 mmol, 274 mg), 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 26 mg (12%) of the title compound as a white solid.

Method B: **1c** (1 mmol, 274 mg), 17α-ethynylestradiol (**6**; 0.5 mmol, 148 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.1 mmol, 19 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 132 mg (60%) of the title compound as a white solid; mp 244 °C; R_f = 0.20 (2:1 hexane–EtOAc); $[\alpha]_D$ –11.1 (*c* 0.0009 g/mL, DMSO).

IR (ATR Ge): 3319, 2924, 1699, 1247, 768 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.86 (m, 1 H), 0.94 (s, 3 H), 1.23–1.52 (m, 4 H), 1.65–1.73 (m, 2 H), 1.83–1.97 (m, 4 H), 2.15–2.21 (m, 1 H), 2.31–2.34 (m, 1 H), 2.66–2.78 (m, 2 H), 5.62 (s, 1 H), 6.42 (d, *J* = 2.4 Hz, 1 H), 6.47 (dd, *J* = 8.6, 2.8 Hz, 1 H), 6.53 (d, *J* = 1.2 Hz, 1 H), 6.83 (d, *J* = 1.2 Hz, 1 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 7.53–7.56 (m, 3 H), 7.79–7.82 (m, 2 H), 8.96 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.59, 23.75, 26.08, 27.31, 29.15, 33.28, 35.68, 1 signal was overlapped by DMSO-d_6 signals, 43.18, 48.48, 48.87, 84.00, 102.02, 106.92, 112.66, 114.86, 125.95, 126.95 (2 ×), 129.20 (2 ×), 130.13, 130.78, 135.24, 137.05, 154.12, 154.89, 161.87, 170.19.

MS (EI): *m*/*z* (%) = 442 (1), 404 (1), 213 (10), 149 (14), 41 (100).

HRMS (EI): *m*/*z* calcd for $C_{29}H_{30}O_4$: 442.214410; found: 442.213063.

(5*Z*)-5-[(Estradiol-17′α-yl)methylene]-4-(1″,1‴-biphenyl-4″-yl)furan-2(5*H*)-one (7d)

Method A: **1d** (0.78 mmol, 270 mg), 17α-ethynylestradiol (**6**; 0.39 mmol, 115 mg), $Pd(PPh_3)_4$ (0.039 mmol, 45 mg), CuI (0.078 mmol, 7.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (1:1 hexane–EtOAc) afforded 95 mg (47%) of the title compound as a white solid; mp 253 °C; R_f = 0.11 (2:1 hexane–EtOAc); $[\alpha]_D$ +46.3 (*c* 0.00475, DMSO).

IR (ATR Ge): 3360, 2929, 1694, 1622, 1027, 1006, 767 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.75–0.87 (m,1 H), 0.95 (s, 1 H), 1.23–1.53 (m, 4 H), 1.66–1.95 (m, 6 H), 2.18–2.21 (m, 1 H), 2.32–2.36 (m, 1 H), 2.66–2.75 (m, 2 H), 5.66 (s, 1 H), 6.42 (s, 1 H), 6.47 (d, *J* = 8.8 Hz, 1 H), 6.59 (s, 1 H), 6.89 (s, 1 H), 6.97 (d, *J* = 8.8 Hz, 1 H), 7.41–7.53 (m, 4 H), 7.75–7.93 (m, 5 H), 8.98 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.61, 23.78, 26.10, 27.32, 29.16, 33.31, 35.69, 39.97, 1 signal was overlapped by DMSO-d_6 signals, 43.19, 48.50, 48.89, 84.04, 101.84, 106.66, 112.67, 114.87, 125.97, 126.78 (2 ×), 127.36 (2 ×), 127.63 (2 ×), 128.13, 129.07 (2 ×), 130.15, 134.06, 137.08, 138.94, 142.37, 153.50, 154.90, 161.91, 170.20.

HRMS (FAB+): *m*/*z* calcd for $C_{35}H_{34}O_4 + H^+$: 519.253535; found: 519.255786.

Reaction of Ethynylferrocene (8) with 3-Iodopropenoic Acids 1; General Procedure

Conditions A: Into degassed MeCN (4 mL) were added ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and the appropriate 3-iodopropenoic acid **1** (0.75 mmol). Et_3N (2 mmol, 278 μL) was then and the mixture was stirred at 50 °C for 20 h. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography.

Conditions B: As above, but with 0.1 mmol of CuI (19 mg).

(5*Z*)-5-(Ferrocenyl-1′-methylene)furan-2(5*H*)-one (9a)

Conditions A: **1a** (0.75 mmol, 149 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (2:1 $CHCl_3$–hexane) afforded 87 mg (62%) of the title compound as a dark red solid.

Conditions B: **1a** (1 mmol, 198 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.1 mmol, 19 mg),

and Et_3N (2.9 mmol, 400 μL). Column chromatography on silica gel (2:1 $CHCl_3$–hexane) afforded 78 mg (56%) of the title compound as a dark red solid; mp 112 °C; R_f = 0.14 (1:2 hexane–$CHCl_3$).

IR ($CHCl_3$): 2968, 2914, 2866, 1774, 1748, 1649, 1105, 818 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 5 H), 4.44–4.48 (m, 2 H), 4.76–4.80 (m, 2 H), 5.95 (s, 1 H), 6.13 (d, *J* = 4.8 Hz, 1 H), 7.35 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.74 (5 ×), 70.76 (2 ×), 71.18 (2 ×), 76.00, 115.94 (2 ×), 143.44, 146.73, 170.68.

MS (EI): *m*/*z* (%) = 280 (100), (4), 224 (12), 158 (8).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}FeO_2$: 280.018669; found: 280.019412.

(5*Z*)-5-(Ferrocenyl-1′-methylene)-4-methylfuran-2(5*H*)-one (9b)

Conditions A: **1b** (0.75 mmol, 159 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (2:1 $CHCl_3$–hexane) afforded 117 mg (79%) of the title compound as a dark red solid.

Conditions B: **1b** (1 mmol, 212 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.1 mmol, 19 mg), and Et_3N (2.9 mmol, 400 μL). Column chromatography on silica gel (2:1 $CHCl_3$–hexane) afforded 126 mg (85%) of the title compound as a dark red solid; mp 83 °C; R_f = 0.21 (1:2 hexane–$CHCl_3$).

IR ($CHCl_3$): 3099, 2924, 2198, 1770, 1739, 1649, 1595, 1345, 923, 842, 814 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 4.15 (s, 5 H), 4.41–4.45 (m, 2 H), 4.75–4.79 (m, 2 H), 5.90 (s, 1 H), 5.95 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.76, 69.58 (5 ×), 70.55 (2 ×), 70.81 (2 ×), 76.14, 111.28, 113.81, 147.71, 154.31, 169.89.

MS (EI): *m*/*z* (%) = 294 (100), 279 (1), 229 (4), 149 (8).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}FeO_2$: 294.034319; found: 294.033806.

(5*Z*)-5-(Ferrocenyl-1′-methylene)-4-phenylfuran-2(5*H*)-one (9c)

Conditions A: **1c** (0.75 mmol, 205 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (2:1 $CHCl_3$–hexane) afforded 136 mg (76%) of the title compound as a dark red solid.

Conditions B: **1c** (1 mmol, 274 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.1 mmol, 19 mg) and Et_3N (2.9 mmol, 400 μL). Column chromatography on silica gel (2/1 $CHCl_3$/hexane) afforded 176 mg (99%) of the title compound as a dark red solid; mp 205–210 °C; R_f = 0.29 (1:2 hexane–$CHCl_3$).

IR ($CHCl_3$): 2962, 2920, 2866, 1760, 1754, 1745, 1739, 1643, 1353, 1090, 929, 818, 773, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.17 (s, 5 H), 4.46–4.50 (m, 2 H), 4.79–4.83 (m, 2 H), 6.10 (s, 1 H), 6.15 (s, 1 H), 7.46–7.54 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.72 (5 ×), 70.88 (2 ×), 71.22 (2 ×), 76.32, 112.56, 115.73, 128.42 (2 ×), 129.00 (2 ×), 130.18, 130.77, 145.97, 156.92, 169.26.

MS (EI): *m*/*z* (%) = 356 (100), 291 (4), 262 (16), 178 (10).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{16}FeO_2$: 356.049969; found: 356.049144.

(5*Z*)-5-(Ferrocenyl-1′-methylene)-4-(1″,1‴-biphenyl-4″-yl)furan-2(5*H*)-one (9d)

Conditions A: Prepared from **1d** (0.75 mmol, 263 mg), ethynylferrocene (**8**; 0.5 mmol, 105 mg), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), CuI (0.05 mmol, 9.5 mg), and Et_3N (2 mmol, 278 μL). Column chromatography on silica gel (2:1 $CHCl_3$–hexane) afforded 213 mg (99%) of the title compound as a dark red solid; mp 224 °C; R_f = 0.23 (1:2 hexane–$CHCl_3$).

IR ($CHCl_3$): 3098, 3079, 3025, 1753, 1747, 1643, 1579, 1483, 1345, 921, 830, 771 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.19 (s, 5 H), 4.48–4.52 (m, 2 H), 4.83–4.87 (m, 2 H), 6.16 (s, 1 H), 6.18 (s, 1 H), 7.39–7.43 (m, 1 H), 7.48–7.52 (m, 2 H), 7.54–7.58 (m, 2 H), 7.63–7.67 (m, 2 H), 7.73–7.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.91 (5 ×), 71.04 (2 ×), 71.39 (2 ×), 1 signal was overlapped by $CDCl_3$ signals, 112.40, 115.77, 127.10, 127.67, 128.03, 128.92, 128.99, 129.59, 139.87, 143.15, 146.00, 156.51, 169.25.

MS (EI): *m*/*z* (%) = 432 (100), 367 (4), 256 (7), 216 (7), 149 (22).

HRMS (EI): *m*/*z* calcd for $C_{27}H_{20}FeO_2$: 432.081269; found: 432.081759.

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References

(1) (a) Seegal, B. C.; Holden, M. *Science* **1945**, *101*, 413. (b) Baer, H.; Seegal, B. C.; Holden, M. *J. Biol. Chem.* **1946**, *162*, 65.
(2) (a) Jung, J. H.; Chang, C.-J.; Smith, D. L.; McLaughlin, J. L.; Pummangura, S.; Chaichantipyuth, C.; Patarapanich, C. *J. Nat. Prod.* **1991**, *54*, 500. (b) Chaichantipyuth, C.; Tiyaworanan, S.; Mekaroonreung, S.; Ngamrojnavanich, N.; Roengsumran, S.; Puthong, S.; Petsom, A.; Ishikawa, T. *Phytochemistry* **2001**, *58*, 1311.
(3) (a) Miao, S.; Andersen, R. J. *J. Org. Chem.* **1991**, *56*, 6275. (b) Ortega, M. J.; Zubía, E.; Ocaña, J. M.; Naranjo, S.; Salvá, J. *Tetrahedron* **2000**, *56*, 3963. (c) Pearce, A. N.; Chia, E. W.; Berridge, M. V.; Maas, E. W.; Page, M. J.; Webb, V. L.; Harper, J. L.; Copp, B. R. *J. Nat. Prod.* **2007**, *70*, 111.
(4) Kuhnt, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; Steffan, B.; Steglich, W. *J. Antibiot.* **1990**, *43*, 1413.
(5) Fang, X.; Anderson, J. E.; Chang, C.; McLaughlin, J. L. *Tetrahedron* **1991**, *47*, 9751.
(6) Massy-Westropp, R. A.; Reynolds, G. D.; Spotswood, T. M. *Tetrahedron Lett.* **1966**, 1939.
(7) Lee, S.-C.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 29.
(8) Ishikawa, T.; Nishigaya, K.; Uchikoshi, H.; Chen, I.-S. *J. Nat. Prod.* **1998**, *61*, 534.
(9) Davidson, B. S.; Ireland, C. M. *J. Nat. Prod.* **1990**, *53*, 1036.
(10) (a) Schutt, F. *Ber. Dtsch. Bot. Ges.* **1890**, *8*, 9. (b) Strain, H. H.; Svec, W. A.; Aitzetmuller, K.; Grandolfo, M. C.; Katz, J. J.; Kjosen, H.; Norgard, S.; Lieean-Jensen, S.; Haxo, F. T.; Wegfahrt, P.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 1823. (c) Johansen, J. E.; Borch, G.; Lieean-Jensen, S. *Phytochemistry* **1980**, *19*, 441.
(11) Jiwajinda, S.; Hirai, N.; Watanabe, K.; Santisopasri, V.; Chuengsamarnyart, N.; Koshimizu, K.; Ohigashi, H. *Phytochemistry* **2001**, *56*, 693.

(12) Yang, X.; Shimizu, Y.; Steiner, J. R.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 761.
(13) (a) Bergel, F.; Morrison, A. L.; Moss, A. R.; Rinderknecht, H. *J. Chem. Soc.* **1944**, 415. (b) Woodward, R. B.; Singh, G. *J. Am. Chem. Soc.* **1949**, *71*, 758.
(14) Hano, Y.; Shi, Y. Q.; Nomura, T.; Yang, P. Q.; Chang, W. J. *Phytochemistry* **1997**, *46*, 1447.
(15) Levy, L. M.; Cabrera, G. M.; Wright, J. E.; Seldes, A. M. *Phytochemistry* **2003**, *62*, 239.
(16) (a) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1977**, 37. (b) Pettus, J. A. Jr.; Wing, R. M.; Sims, J. J. *Tetrahedron Lett.* **1977**, 41.
(17) Hsieh, T.-J.; Chang, F.-R.; Chia, Y.-C.; Chen, C.-Y.; Lin, H.-C.; Chiu, H.-F.; Wu, Y.-C. *J. Nat. Prod.* **2001**, *64*, 1157.
(18) (a) Johansen, J. E.; Svec, W. A.; Liaaen-Jensen, S.; Haxo, F. T. *Phytochemistry* **1974**, *13*, 2261. (b) Aakermann, T.; Liaaen-Jensen, S. *Phytochemistry* **1992**, *31*, 1779.
(19) Beck, J. J.; Chou, S. C. *J. Nat. Prod.* **2007**, *70*, 891.
(20) Birch, A. J.; Grimshaw, J.; Turnbull, J. P. *J. Chem. Soc.* **1963**, 2412.
(21) Gallo, G. G.; Coronelli, C.; Vigevani, A.; Lancini, G. C. *Tetrahedron* **1969**, *25*, 5677.
(22) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1966**, *99*, 1226.
(23) Lardelli, G.; Dijkstra, G.; Harkes, P. D.; Boldingh, J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 43.
(24) Staroske, T.; Hennig, L.; Welzel, P.; Hofmann, H.-J.; Müller, D.; Häusler, T.; Sheldrick, W. S.; Zillikens, S.; G retzer, B.; Pusch, H.; Glitsch, H. G. *Tetrahedron* **1996**, *52*, 12723.
(25) Xu, H.-W.; Wang, J.-F.; Liu, G.-Z.; Hong, G.-F.; Liu, H.-M. *Org. Biomol. Chem.* **2007**, *5*, 1247.
(26) Paintner, F. F.; Allmendinger, L.; Bauschke, G.; Berns, C.; Heisig, P. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 2823.
(27) Tsuchida, T.; Iinuma, H.; Nakamura, K. T.; Nakamura, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1330.
(28) For reviews, see: (a) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, 53. 6707. (b) Brückner, R. *Chem. Commun.* **2001**, 141.
(29) (a) Kotora, M.; Negishi, E. *Tetrahedron Lett.* **1996**, *37*, 9041. (b) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121. (c) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591. (d) Lu, X.; Chen, G.; Xia, L.; Guo, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3067. (e) Negishi, E.; Xu, C.; Tan, Z.; Kotora, M. *Heterocycles* **1997**, *48*, 209. (f) Prim, D.; Fuss, A.; Kirsch, G.; Silva, A. M. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1175. (g) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65.
(30) Ag-catalyzed cyclization: (a) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431. (b) Pd-Cu catalyzed cyclization: Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903. (c) Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949.
(31) (a) Copéret, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422. (b) Fáková, H.; Pour, M.; Kuneš, J.; Šenel, P. *Tetrahedron Lett.* **2005**, *46*, 8137.
(32) (a) van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931. (b) Fouda, M. F. R.; Abd-Elzaher, M. M.; Abdelsamaia, R. A.; Labib, A. A. *Appl. Organomet. Chem.* **2007**, *21*, 613. (c) Nguyen, A.; Vessières, A.; Hillard, E. A.; Top, S.; Pigeon, P.; Jaouen, G. *Chimia* **2007**, *61*, 716.
(33) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1993**, *34*, 5963.
(34) (a) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, 41. 2587. (b) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871. (c) Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673.
(35) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.
(36) Novák, P.; Číhalová, S.; Otmar, M.; Hocek, M.; Kotora, M. *Tetrahedron* **2008**, *64*, 5200.
(37) (a) Martin, M. L.; Roman, L. S.; Dominguez, A. *Planta Med.* **1990**, *56*, 66. (b) Didry, N.; Dubreuil, L.; Pinkas, M. *Phytotherapy Res.* **1993**, *7*, 21.