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Tetrahedron
Tetrahedron 62 (2006) 2545–2554

A facile access to spiro furanone skeleton based on Pd(II)-mediated cyclization–carbonylation of propargylic esters

Keisuke Kato,[a,*] Hideaki Nouchi,[a] Keisuke Ishikura,[a] Satoshi Takaishi,[a] Satoshi Motodate,[a] Hikaru Tanaka,[a] Kazuho Okudaira,[a] Tomoyuki Mochida,[b] Ryuichiro Nishigaki,[a] Koki Shigenobu[a] and Hiroyuki Akita[a,*]

[a]*Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*
[b]*Department of Chemistry, Faculty of Science, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*

Received 2 December 2005; revised 15 December 2005; accepted 16 December 2005

Available online 18 January 2006

Abstract—The oxidative cyclization–carbonylation of propargylic esters mediated by Pd(II) afforded cyclic orthoesters, which were hydrolyzed into γ-acetoxy-β-ketoesters. Based on the NMR experiments, it was presumed that the cyclization reaction was initiated by a nucleophilic attack of carbonyl oxygen to the alkyne carbon coordinated to palladium(II). When the γ-acetoxy-β-ketoesters were treated with a basic condition, Knoevenagel–Claisen type condensation took place, and spiro furanone derivatives were obtained in good yields. We applied these reactions to steroid derivatives, and steroid derivatives having a spiro furanone fragment were synthesized. Among them, the spiro furanone **4j** had vasorelaxant and bradycardiac activities. Compounds **2i**–**4k** had inhibitory effect on CYP3A.

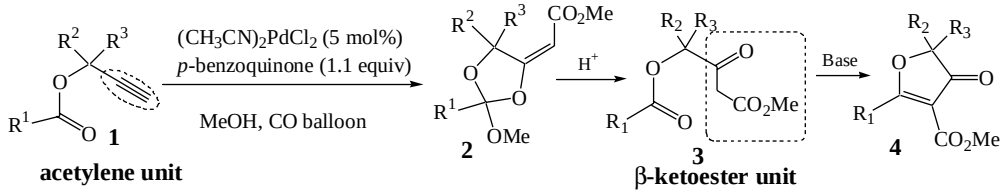
1. Introduction

Palladium(II)-catalyzed reactions are fundamentally important in organic transformations.[1] Propargylic esters undergo a number of palladium catalyzed transformations,[2] such as nucleophilic substitution,[3] oxidative rearrangement[4] and carbonylation reactions.[5] Recently, we have reported cyclization–carbonylation of 4-yne-1-ols,[6] 4-yne-1-ones[7] and propargylic esters.[8] These reactions are considered to be a useful method for the conversion of the acetylene unit to a β-ketoester unit.[9] We would like to report here mechanistic insight into the Pd(II)-mediated cyclization–carbonylation of propargylic esters and an application to the construction of a spiro furanone skeleton by using Knoevenagel–Claisen type condensation of γ-acetoxy-β-ketoesters (Scheme 1).

2. Results and discussion

2.1. Cyclization–carbonylation of propargylic esters

The cyclization–carbonylation of propargylic acetate **1a**–**d** in the presence of $(CH_3CN)_2PdCl_2$/*p*-benzoquinone in methanol at 0 °C–rt under carbon monoxide atmosphere (balloon) afforded methoxycarbonylated orthoesters **2a**–**d** in 61–71% yields (Scheme 2, Table 1, entries 1–4). In the case



Scheme 1.

Keywords: Palladium; Orthoester; Cyclization–carbonylation; Propargylic ester; β-Ketoesters; Spiro furanone; 3(2*H*)-Furanone; Ethisterone; Mestranol; Ethynylestradiol.
* Corresponding authors. Tel./fax: +81 474 72 1825; e-mail: kkk@phar.toho-u.ac.jp

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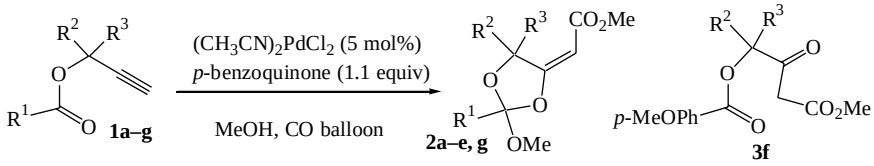
doi:10.1016/j.tet.2005.12.033



Scheme 2.

Table 1. The cyclization–alkoxycarbonylation of propargylic esters

Entry	1	Condition	R^1	R^2	R^3	Product	Yield (%)
1	**1a**	0 °C, 7 h	Me		$-(CH_2)_6-$	**2a**	65
2	**1b**	0 °C, 3 h	Me		$-(CH_2)_5-$	**2b**	65
3	**1c**	0 °C, 5 h	Me		$-(CH_2)_2NBoc(CH_2)_2-$	**2c**	71
4	**1d**	rt, 0.5 h	Me	Me	CH_2CH_2Ph	**2d**[a]	61
5	**1e**	0 °C, 4.5 h	Ph		$-(CH_2)_5-$	**2e**	80
6	**1f**	rt, 1 h	*p*-MeOPh		$-(CH_2)_5-$	**3f**	83
7	**1g**	rt, 1 h	*p*-NO_2Ph		$-(CH_2)_5-$	**2g**	21

[a] The product **2d** was obtained as a 2:1 diastereomeric mixture.

of benzoates **1e–g**, electronic effect of the *p*-substituents on the phenyl group was observed. When benzoate **1e** and *p*-methoxy derivative **1f** bearing an electron-donating group were subjected to similar reaction conditions, the yields of the products **2e** and **3f** were improved in comparison with acetate **1a** (entries 5 and 6). However, the reaction of *p*-nitrobenzoate **1g** having an electron-withdrawing group scarcely proceeded and **2g** was obtained in 21% yield together with recovery of the substrate (65%) (entry 7). In addition, in the case of a phenylacetylene derivative of **1b** and a TBDMS ether derivative of **1d**, the reactions did not proceed under similar reaction conditions. These results suggested that the presence of neighboring group participation and nucleophilicity of the carbonyl oxygen play an important role for initiating the reaction. The substrate **1h** bearing two phenyl groups in propargylic position afforded different products **5**[10] (36%) and **6** (23%) from those of Table 1 (Fig. 1). These products **5** and **6** should be produced by S_N1-type substitution of the acetoxy group with MeOH and by oxidative rearrangement of propargylic acetate,[4] respectively.

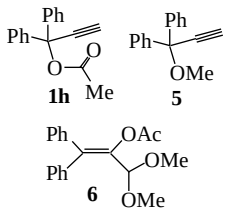


Figure 1.

Selected data of the NMR spectra measured in CD_3-$COCD_3$ of **2b** are shown in Figure 2. The quaternary carbon of orthoester appeared in 124 ppm and its HMBC correlations with proton of the methyl group (1.6 ppm) and with proton of the methoxy group (3.24 ppm) were clearly observed. These results indicated the presence of an orthoester structure. In addition, the structure of **2c** was unequivocally determined by X-ray crystallographic analysis.

Two kinds of mechanistic pathways have been proposed for the intramolecular cyclization of alkynes with a C=O group. Yamamoto et al. reported the cyclization of alkynyl aldehydes takes place via a hemiacetal intermediate based on NMR experiment,[11] and then we have also reported the asymmetric cyclization–carbonylation of 2-alkynyl-1,3-diketone proceeded through a similar pathway.[12] On the other hand, in the case of alkynyl ketones and propargylic esters, we have proposed an alternative pathway.[7,8] The reaction could be initiated by a nucleophlic attack of the C=O group to the triple bond coordinated to palladium(II) followed by orthoester formation. Recently, Bacchi et al. have reported oxidative cyclization–alkoxycarbonylation of prop-2-ynyl α-ketoesters afforded the products, resulting from MeOH attack on the ester carbonyl group followed by cyclization and carbonylation.[5a] Thus, to clarify the mechanism of the Pd(II)-mediated cyclization of propargylic esters, NMR studies of a 1:1 mixture of **1b** and $(CH_3CN)_2PdCl_2$ in CD_2Cl_2 at rt were carried out according to the precedent.[11] The ^1H and ^{13}C NMR spectra clearly showed the disappearance of acetylenic proton (δ 2.61) and carbons (δ 84.2, 74.3), newly generated proton (δ 5.46) and carbons appeared. The three secondary carbon signals (δ 37.3, 25.5, 22.8) split into five secondary carbon resonances (δ 34.9, 31.8, 30.0, 27.3, 26.5), which suggest that the symmetry of the cyclohexane moiety was lost. To our regret, the mixtures became black after 30 min. We tentatively proposed the above mixtures to be vinyl palladium complex **A** such as shown in Figure 3.[13,14] Although the structure of the above mixtures could not be clarified,[15] it is possible that the reaction is initiated by a nucleophilic attack of the carbonyl oxygen to the triple bond coordinated with palladium(II).

A plausible mechanism of the present reactions would be proposed as shown in Scheme 3. Propargylic acetate **1** reacts with Pd(II) to generate vinyl palladium intermediate **B**, which was subjected to the nucleophilic attack of MeOH on the carbon atom of the carbonyl group followed by CO insertion to provide the orthoester products **2**. In the case of benzoate **1e** and *p*-methoxybenzoate **1f**, the cationic intermediate **B** (R_3=Ph and *p*-MeO–Ph) should be stabilized by an electron-donating group, and

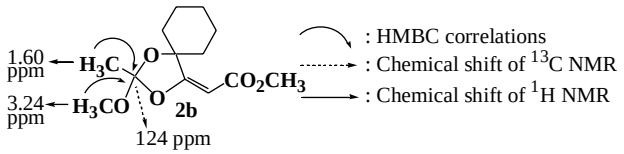


Figure 2. Selected data of ^{1}H, ^{13}C NMR and HMBC spectra of **2b**.

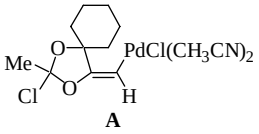
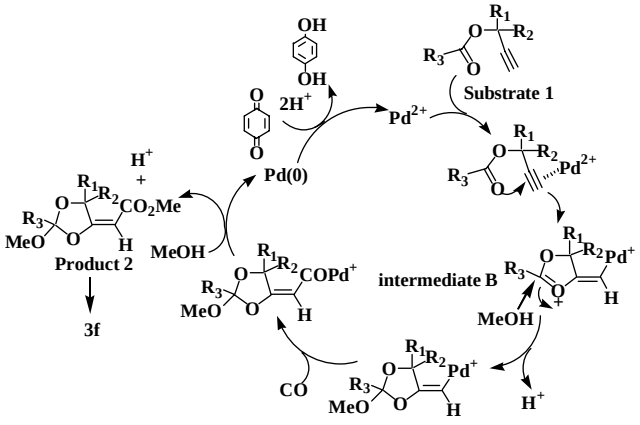


Figure 3. Proposed vinyl palladium complexes **A**.



Scheme 3.

nucleophilicity of the carbonyl oxygen should be increased. Therefore, the yield of the products could be improved. While the electron-withdrawing effect of the nitro group caused decreased nucleophilicity of the carbonyl oxygen in **1g**, the reaction scarcely proceeded. In the case of *p*-methoxybenzoate **1f**, the orthoester bond of **2f** (R_3 = *p*-MeO–Ph) should be easily cleaved, to afford β-ketoester **3f** directly.

2.2. Synthesis of spiro furanones

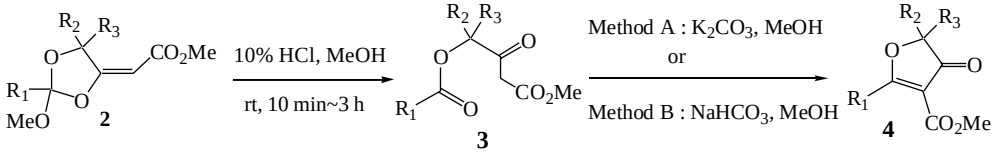
3(2*H*)-Furanones are of pharmacological significance and represent important building blocks for natural product synthesis.[16] A number of syntheses[17] and biological activities, such as selective inhibitory activity on COX-2 (cyclooxygenase-2),[18] inhibitory activity on MAO (monoamine oxidase),[19] anti-cataract effect on spontaneous cataract rats,[20] cytotoxic activity against human tumor cell[21] and antiallergic activity[22] have been reported. As an application of the above cyclization–carbonylation reaction, the facile synthesis of 3(2*H*)-furanones have been achieved (Scheme 4, Table 2). The cyclic orthoesters **2** were converted to the corresponding γ-acetoxy-β-ketoesters **3** by acid treatment in good yields. When γ-acetoxy-β-ketoesters **3** were treated with a base, Knoevenagel–Claisen type condensation took place, furanones **4** were obtained in good yields. In some cases (**3c** and **3d**), though the use of K_2CO_3 leads to decrease in yield, it has been improved by using $NaHCO_3$.

2.3. Synthesis of steroid derivatives containing spiro furanone fragment

Next, we applied these reaction sequences to steroid derivatives, acetates of ethisterone, mestranol and ethynylestradiol. The cyclization–carbonylation of propargylic acetate **1i** and **1j** in the presence of $(CH_3CN)_2PdCl_2$/*p*-benzoquinone in methanol at 0 °C under carbon monoxide atmosphere (balloon) afforded the corresponding orthoesters **2i** and **2j** in 100 and 86% yields, respectively (Scheme 5, Table 3). In the case of diacetate **1k**, partial deacetylation was observed, **2k** was obtained in 30% yield together with acetate **2l** (43% yield). Treatment of **2i–2k** with 10% HCl in MeOH gave the corresponding β-ketoesters **3i–3k** in 88–98% yields. The spiro furanones **4i–4k** were obtained by treatment of **3i–3k** under basic conditions in 92–99% yields.

2.4. Biological activity

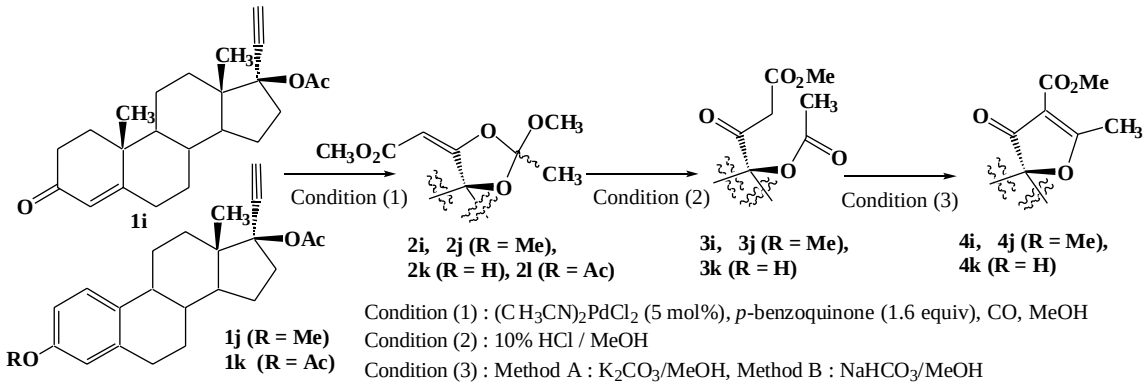
Steroid compounds in general are known for their effects on various receptors, ion channels and enzymes. In the present



Scheme 4.

Table 2. The conversion of orthoesters **2** into furanones **4**

Entry	**2**	R^1	R^2	R^3	Product **3** (yield %)	Condition (method A or B)	Product **4** (yield %)
1	**2a**	Me		$-(CH_2)_6-$	**3a** (98)	rt 3 h (A)	**4a** (quant.)
2	**2b**	Me		$-(CH_2)_5-$	**3b** (96)	rt 3 h (A)	**4b** (96)
3	**2c**	Me		$-(CH_2)_2NBoc(CH_2)_2-$	**3c** (quant.)	rt 1.5 h (A) rt 24 h (B)	**4c** (57) **4c** (96)
4	**2d**	Me	Me	$PhCH_2CH_2$	**3d** (83)	rt 3 h (A) rt 24 h (B)	**4d** (28) **4d** (89)
5	**2e**	Ph		$-(CH_2)_5-$	**3e** (91)	rt 48 h (B)	**4e** (84)



Scheme 5.

Table 3. The reaction of 17-alkynylsteroid derivatives **1i–1k**

Entry	**1**	Condition (1)	Product **2** (yield %)	Condition (2)	Product **3** (yield %)	Condition (3)	Product **4** (yield %)
1	**1i**	0 °C, 15 h	**2i** (quant.)	rt, 0.5 h	**3i** (88)	Method A, rt, 1 h	**4i** (92)
2	**1j**	0 °C, 72 h	**2j** (86)	rt, 3 h	**3j** (98)	Method B, rt, 24 h	**4j** (99)
3	**1k**	0 °C, 24 h	**2k** (30) (R=H) and **2l** (43) (R=Ac)	rt, 1 h	**3k** (95 from **2k**)	Method B, rt, 24 h	**4k** (94 from **3k**)

study, we examined the effects of synthesized compounds **2i–4k** on isolated cardiovascular preparations and on CYP3A activity.

(1) Cardiovascular effect: in aortic rings precontracted with 10^{-5} M norepinephrine, test compounds (10^{-5} M), showed endothelium-independent relaxant effects. The relaxation was expressed as a percentage of the maximum relaxation by 10^{-4} M papaverine and summarized (Table 4). The spontaneous beating rate of isolated right atria was 193–200 beats per minute. The test compounds (10^{-5} M) slightly affected the beating rate. The change in beating rate was expressed as a percentage of the basal beating rate and summarized (Table 4). Among them, the spiro furanone **4j** had vasorelaxant and bradycardiac activities.

Table 4. Cardiovascular effects of test compounds

Compound no.	Relaxation (%)	Changes in heart rate (%)
2i	9.0±1.4	1.2±1.1
3i	5.4±2.6	1.0±3.0
4i	4.2±2.3	−1.3±1.1
2j	10.0±3.7	2.9±2.6
3j	9.5±1.6	−1.7±7.2
4j	18.7±3.4	−11.4±1.8
4k	7.9±2.2	−2.7±3.9
2l	1.3±1.0	3.9±1.9
2k	13.0±1.9	0.4±3.2
2a	3.1±0.5	5.7±5.1
Estradiol	29.2±5.8	−0.03±5.3

Values are the mean±standard error of the mean from 3 to 5 preparations.

Table 5. Effect of test compounds **2i–4k** on midazolam hydroxylation

Compound no.	Activity
2i	63.8±2.5
3i	69.8±13.9
4i	92.2±2.8
2j	45.2±10.4
3j	47.3±3.2
4j	57.1±3.5
4k	61.5±5.6
2l	60.8±6.5
2k	44.9±5.4

Values are the mean±standard deviation of three experiments.

(2) Inhibitory effect on CYP 3A activity: test compounds **2i–4k** have inhibitory effect on CYP3A activity assessed by midazolam 1′-hydroxylation. Preincubated with 3×10^{-5} M of the test compounds, the activity of rat hepatic microsomes was decreased to 40–90% of control values (Table 5). Some steroid compounds such as 17α-ethynylestradiol and danazol containing a terminal acetylene moiety on the C17 position have been known to decrease CYP3A activity and cause drug–drug interactions in the clinical situation. Though compounds **2i–4k** do not contain the terminal acetylene moiety, they also have inhibitory effect on CYP3A. These results might be a clue to clarifying the mechanism of the inhibition.

3. Conclusion

We have reported Pd(II)-mediated cyclization–carbonylation of propargylic esters. This reaction is considered to be a useful method for the conversion of the acetylene unit to a γ-acetoxy-β-ketoester unit. Based on the NMR experiments, it was presumed that the cyclization reaction was initiated by a nucleophilic attack of carbonyl oxygen to the alkyne carbon coordinated to palladium(II). As an application of this reaction, we have developed a new method for the construction of a spiro furanone skeleton, and steroid derivatives having a spiro furanone fragment were synthesized. Among them, the spiro furanone **4j** had vasorelaxant and bradycardiac activities. Compounds **2i–4k** had inhibitory effect on CYP3A.

4. Experimental

4.1. General experimental methods

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H, ^{13}C NMR and HMBC spectra were recorded on JEOL AL 400 and JEOL Lambda 500 spectrometer in $CDCl_3$ with Me_4Si as an internal reference. In the case of acetone-d_6, solvent peak were used as a reference (2.04 ppm for ^{1}H and 29.8 ppm for ^{13}C). High-resolution mass spectra (HR-MS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL GC mate II and a JEOL JMS 600 H spectrometer, respectively. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica-gel (Kieselgel 60) was employed.

4.2. Preparation of substrates

The substrates **1** were prepared by acetylation (Ac_2O/pyridine) of the corresponding alcohols. The acetates **1** except **1f** were known compounds.[23]

4.2.1. 1-Ethynyl-1-cyclohexyl 4-methoxybenzoate 1f. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.37–1.57 (2H, m), 1.63–1.75 (4H, m), 2.05–2.24 (4H, m), 2.64 (1H, s), 3.84 (3H, s), 6.90 (2H, d, J=6.8 Hz), 7.99 (2H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.4 (2C), 25.2, 37.1 (2C), 55.4, 74.2, 75.1, 84.0, 113.5 (2C), 123.4, 131.6 (2C), 163.3, 164.4; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{18}O_3$ 258.1256; found 258.1246; IR (KBr) 2937, 1719, 1606, 1253 cm^{-1}. Anal. Found: C, 73.95; H, 7.02 Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02%.

4.3. General procedure for the cyclization–carbonylation of propargylic esters 1a–1h

A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $(CH_3CN)_2PdCl_2$ (0.05 mmol), *p*-benzoquinone (1.1 mmol) and MeOH (6 mL) was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping–filling via the three-way stopcock. A solution of the substrate **1** (1 mmol) in MeOH (3 mL) was added dropwise to the stirred mixture via a syringe at 0 °C. After being stirred for the appropriate period of time, the mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% NaOH aq (40 mL), and dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (100/1–30/1) afforded **2** or **3f**.

4.3.1. Methyl (2*E*)-(2-methoxy-2-methyl-1,3-dioxaspiro[4.6]undec-4-ylidene)acetate 2a. Hexane/ethyl acetate=50:1. Colorless needles. Mp 42 °C (MeOH); ^{1}H NMR (CD_3COCD_3) δ 1.58–1.82 (9H, m), 1.60 (3H, s), 1.90–1.97 (1H, m), 2.53–2.60 (1H, m), 2.67–2.76 (1H, m), 3.24 (3H, s, orthoester), 3.61 (3H, s, ester), 5.21 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 3.2, 23.2, 25.4, 27.9, 27.9, 36.4, 37.6, 49.6 (O*Me* of orthoester), 51.1 (O*Me* of ester), 88.1 (quaternary, O–*C*), 90.2 (OC=*C*H), 124.3 (quaternary, orthoester), 167.1 (*C*O of ester), 176.7 (O*C*=CH); EI-MS *m/z*: 270 (M^+); IR (KBr) 2932, 1714, 1642, 1141, 1044 cm^{-1}. Anal. Found: C, 61.88; H, 8.29 Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.

4.3.2. Methyl (2*E*)-(2-methoxy-2-methyl-1,3-dioxaspiro[4.5]dec-4-ylidene)acetate 2b. Hexane/ethyl acetate=50:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.33–1.41 (1H, m), 1.60 (3H, s), 1.56–1.70 (6H, m), 1.75–1.81 (1H, m), 2.48–2.57 (1H, m), 2.61–2.69 (1H, m), 3.24 (3H, s, O*Me* of orthoester), 3.61 (3H, s, O*Me*), 5.27 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 22.5, 22.7, 25.2, 25.2, 32.1, 33.2, 49.7 (O*Me* of orthoester), 51.1 (O*Me* of ester), 87.4 (quaternary, O–*C*), 89.2 (OC=*C*H), 124.1 (quaternary, orthoester), 167.0 (*C*O of ester), 171.6 (O*C*=CH); EI-MS *m/z*: 256 (M^+); IR (KBr) 2862, 1716, 1649, 1075, 1052, 977 cm^{-1}. Anal. Found: C, 61.22; H, 8.12 Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.

4.3.3. *tert*-Butyl (4*E*)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-methyl-1,3-dioxa-8-azaspiro[4.5]-decane-8-carboxylate 2c. Hexane/ethyl acetate=30:1. Colorless needles. Mp 78 °C (hexane); ^{1}H NMR (CD_3COCD_3) δ 1.46 (9H, s), 1.58–1.64 (1H, m), 1.65 (3H, s), 1.73–1.79 (1H, m), 2.67–2.85 (2H, m), 2.94–3.10 (2H, m), 3.27 (3H, s), 3.61 (3H, s), 4.01–4.12 (2H, m), 5.34 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 24.8, 28.6, 31.9, 32.9, 40.5 (br), 41.2 (br), 49.9, 51.2, 79.4, 85.4, 89.9, 124.1, 154.8, 166.6, 172.5; FAB-MS *m/z*: 380 (M^++Na); IR (KBr) 1690, 1652, 1135, 1077, 1045 cm^{-1}. Anal. Found: C, 57.27; H, 7.47 Calcd for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61%.

4.3.3.1. X-ray crystallographic analysis. X-ray diffraction data for **2c** were collected on a Bruker SMART APEX CCD diffractometer equipped with a graphite crystal and

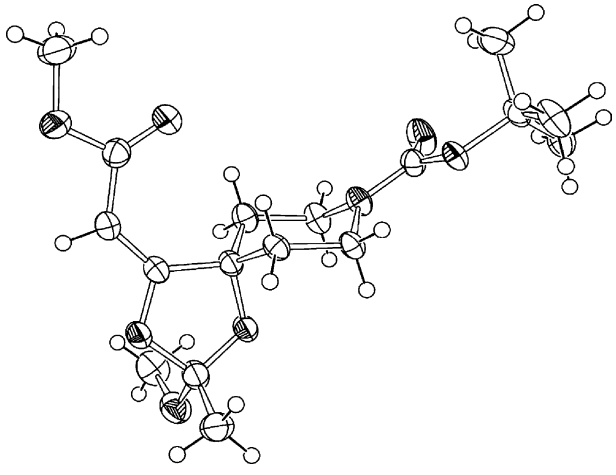


Figure 4.

incident beam monochromator using Mo Kα radiation (λ=0.71073 Å). The structures were solved by the direct method (SHELXS 97[24]) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The crystal contains two crystallographically independent molecules, one of which exhibits disorder with respect to

the methyl and methoxy substituents attached to the five-membered ring. An ORTEP[25] diagram of the disorder-free molecule is shown in Figure 4. Crystallographic parameters: $C_{17}H_{27}NO_7$, $M_W=357.40$, triclinic, space group $P\bar{1}$, with unit cell $a=10.4863(7)$ Å, $b=12.5804(8)$ Å, $c=15.345(1)$ Å, $\alpha=74.778(1)°$, $\beta=74.247(1)°$, $\gamma=79.900(1)°$, and $V=1868.2(2)$ Å^3. $Z=4$, $D_{calcd}=1.271$ g cm^{-3}, $T=173$ K, λ(Mo Kα)$=0.71073$ Å. $R1(I>2\sigma(I))=0.0574$, $wR2=0.1602$, $R1$(all data)$=0.0730$, $wR2=0.1732$, 9154 independent reflections (R(int)$=0.0154$), 488 parameters refined on F^2. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.

4.3.4. Methy (2*E*)-[2-methoxy-2,5-dimethyl-5-(phenylethyl)-1,3-dioxolan-4-ylidene]acetate 2d. Hexane/ethyl acetate=50:1. Colorless oil. Mixture of two diastereomers (ratio=2:1). ^{1}H NMR (CD_3COCD_3) (major diastereomer) δ 1.69 (3H, s), 1.77 (3H, s), 2.25–2.51 (2H, m), 2.55–2.77 (2H, m), 3.31 (3H, s), 3.62 (3H, s), 5.37 (1H, s), 7.13–7.28 (5H, m); (minor diastereomer) δ 1.65 (3H, s), 1.73 (3H, s), 3.35 (3H, s), 3.61 (3H, s), 5.32 (1H, s); ^{13}C NMR (CD_3COCD_3) (major diastereomer) δ 22.9, 23.7, 30.9, 40.0, 50.5, 51.2, 88.1, 89.9, 124.0, 126.6, 129.2, 129.2, 142.7, 167.1, 174.1; EI-MS *m*/*z*: 275 (M^+-OMe); IR (KBr) 2946, 1715, 1652, 1142, 1104, 1055 cm^{-1}. Anal. Found: C, 66.52; H, 7.32 Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24%.

4.3.5. Methyl (2*E*)-(2-methoxy-2-phenyl-1,3-dioxaspiro[4.5]dec-4-ylidene)acetate 2e. Hexane/ethyl acetate=100:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.40–1.50 (2H, m), 1.63–1.75 (5H, m), 1.91–1.94 (1H, m), 2.44 (1H, dt, $J=5.2$, 13.2 Hz), 2.66–2.71 (1H, m), 3.32 (3H, s), 3.64 (3H, s), 5.43 (1H, s), 7.36–7.37 (3H, m), 7.55–7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.1, 24.4, 31.7, 31.7, 50.5, 51.0, 87.6, 89.6, 122.1, 125.8, 128.3, 129.5, 137.6, 166.7, 173.5; FAB-MS *m*/*z*: 319 (M^++H); IR (KBr) 2934, 1715, 1652, 1135, 1043 cm^{-1}. Anal. Found: C, 68.19; H, 6.82 Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97%.

In the case of *p*-methoxybenzoate **1f**, γ-acetoxy-β-ketoester **3f** was obtained directly.

4.3.6. 1-(3-Methoxy-1,3-dioxopropyl)cyclohexyl 4-methoxy-benzoate 3f. Hexane/ethyl acetate=30:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.29–1.38 (1H, m), 1.58–1.81 (7H, m), 2.20–2.23 (2H, m), 3.59 (2H, s), 3.62 (3H, s), 3.90 (3H, s), 7.06 (2H, d, $J=8.8$ Hz), 8.05 (2H, d, $J=8.8$ Hz); ^{13}C NMR (CD_3COCD_3) δ 22.1 (2C), 25.6, 31.4 (2C), 43.5, 52.2, 56.0, 85.8, 114.9 (2C), 122.7, 132.7 (2C), 165.0, 165.9, 168.2, 202.1; HRMS-FAB *m*/*z*: [M^++H] calcd for $C_{13}H_{23}O_6$ 335.1495; found 335.1495; IR (KBr) 2939, 1752, 1707, 1605, 1255 cm^{-1}. Anal. Found: C, 63.41; H, 6.52 Calcd for $C_{18}H_{22}O_6 1/2H_2O$: C, 62.96; H, 6.75%.

4.3.7. Methyl (2*E*)-[2-methoxy-2-(4-nitrophenyl)-1,3-dioxaspiro[4.5]dec-4-ylidene]acetate 2g. Hexane/ethyl acetate=70:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.39–1.42 (2H, m), 1.61–1.76 (5H, m), 1.93–1.97 (1H, m), 2.47 (1H, dt, $J=5.2$, 13.2 Hz), 2.67–2.76 (1H, m), 3.39 (3H, s), 3.64 (3H, s), 5.48 (1H, s), 7.85 (2H, d, $J=8.8$ Hz), 8.31 (2H, d, $J=8.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 22.5, 22.7, 25.1, 32.3, 32.4, 50.7, 51.4, 88.6, 90.8, 121.9, 124.4, 128.0, 145.5, 149.6, 166.8, 173.4; HRMS-FAB *m*/*z*: [M^++H] calcd for $C_{18}H_{22}NO_7$ 364.1396; found 364.1385; IR (KBr) 2934, 1716, 1655, 1528, 1354, 1134 cm^{-1}. Anal. Found: C, 57.65; H, 5.82; N, 3.41 Calcd for $C_{18}H_{21}NO_7 1/2H_2O$: C, 58.06; H, 5.96%; N, 3.76.

4.3.8. 1,1′-(1-Methoxy-2-propynylidene)bisbenzene 5. Hexane/ethyl acetate=50:1. Colorless oil. Spectral data was identical with that of literature's.[10]

4.3.9. 3,3-Dimethoxy-1,1-diphenyl-1-propen-2-ol acetate 6. Hexane/ethyl acetate=50:1. Colorless needles. Mp 74 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.97 (3H, s), 3.36 (6H, s), 4.77 (1H, s), 7.20–7.40 (10H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 54.9, 101.1, 127.6, 127.9, 128.1, 128.3, 129.8, 135.7, 138.1, 138.3, 140.7, 168.4; FAB-MS *m*/*z*: 281 (M^+-MeO); IR (KBr) 1764, 1193, 1074, 1228 cm^{-1}. Anal. Found: C, 72.80; H, 6.44 Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45.

4.4. Preparation of γ-hydroxy-β-ketoesters 3

A solution of the orthoester **2** (1 mmol) in MeOH (10 mL), H_2O (2 mL) and 10% HCl aq (1 mL) was stirred for the appropriate period of time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (10/1–4/1) afforded **3**.

4.4.1. Methyl 3-(1-acetoxycycloheptyl)-3-oxopropanoate 3a. Hexane/ethyl acetate=10:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.59 (9H, br s), 1.94–2.10 (3H, m), 2.11 (3H, s), 3.48 (2H, s), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$) δ 21.1, 22.7, 29.4, 34.2, 42.7, 52.4, 89.2, 167.7, 170.5, 201.0; FAB-MS *m*/*z*: 257 (M^++H); IR (KBr) 2931, 1737, 1247 cm^{-1}. Anal. Found: C, 60.62; H, 7.82 Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.

4.4.2. Methyl 3-(1-acetoxycyclohexyl)-3-oxopropanoate 3b. Hexane/ethyl acetate=10:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22–1.32 (1H, m), 1.47–1.61 (2H, m), 1.66–1.73 (5H, m), 2.02–2.06 (2H, m), 2.13 (3H, s), 3.50 (2H, s), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.2, 24.9, 30.7, 42.8, 52.4, 85.2, 167.6, 170.4, 201.2; EI-MS *m*/*z*: 242 (M^+); IR (KBr) 2942, 1739, 1234 cm^{-1}. Anal. Found: C, 59.28; H, 7.48 Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%.

4.4.3. Methyl 3-(4-acetoxy-1-*tert*-butoxycarbonylpiperidin-4-yl)-3-oxopropanoate 3c. Hexane/ethyl acetate=4:1. Colorless needles. Mp 99 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.89–2.04 (4H, m), 2.15 (3H, s), 3.03–3.10 (2H, m), 3.51 (2H, s), 3.73 (3H, s), 3.89–4.02 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 28.4, 30.4, 38.8 (br), 42.8, 52.5, 80.0, 83.0, 154.6, 167.3, 170.3, 199.9; FAB-MS *m*/*z*: 344 (M^++H); IR (KBr) 1754, 1682, 1273, 1228 cm^{-1}. Anal. Found: C, 55.91; H, 7.27; N, 3.83 Calcd for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34; N, 4.08%.

4.4.4. Methyl 4-acetyloxy-4-methyl-3-oxo-6-phenylhexanoate 3d. Hexane/ethyl acetate=10:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.60 (3H, s), 2.04–2.28 (2H, m), 2.06

(3H, s), 2.56–2.67 (2H, m), 3.50 (1H, d, $J=15.6$ Hz), 3.58 (1H, d, $J=15.6$ Hz), 3.72 (3H, s), 7.14–7.21 (3H, m), 7.26–7.30 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.4, 21.0, 29.5, 37.7, 43.4, 52.4, 86.1, 126.2, 128.3, 128.5, 140.8, 167.4, 170.3, 201.0; FAB-MS *m/z*: 293 ($M^+ + H$); IR (KBr) 2951, 1741, 1249 cm^{-1}. Anal. Found: C, 65.44; H, 6.88 Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90%.

4.4.5. 1-(3-Methoxy-1,3-dioxopropyl)cyclohexyl benzoate 3e. Hexane/ethyl acetate=50:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.30–1.37 (1H, m), 1.58–1.85 (7H, m), 2.23–2.26 (2H, m), 3.57 (2H, s), 3.71 (3H, s), 7.47–7.51 (2H, m), 7.58–7.64 (1H, m), 8.07–8.10 (2H, m); ^{13}C NMR (CD_3COCD_3) δ 21.4 (2C), 25.0, 31.8 (2C), 42.8, 52.4, 85.7, 128.6, 129.4, 129.9, 133.7, 165.6, 167.7, 201.3; EI-MS *m/z*: 304 (M^+); IR (KBr) 2940, 1752, 1717, 1292 cm^{-1}. Anal. Found: C, 67.12; H, 6.80 Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62%.

4.5. Preparation of furanones 4a–4e

(*Method A*). A solution of the γ-hydroxy-β-ketoester **3** (1 mmol) in MeOH (8 mL) and K_2CO_3 (138 mg, 1 mmol) was stirred for the period of time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (20/1–3/1) afforded **4**.

(*Method B*). $NaHCO_3$ (2 equiv) was used instead of K_2CO_3 (1 equiv).

4.5.1. Methyl 2-methyl-4-oxo-1-oxaspiro[4.6]undec-2-en-3-carboxylate 4a. Hexane/ethyl acetate=5:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.61–1.76 (10H, m), 1.87–1.95 (2H, m), 2.60 (3H, s), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$) δ 18.0, 22.3, 29.2, 35.2, 51.5, 95.0, 106.4, 163.7, 195.3, 201.2; HRMS-EI *m/z*: [M^+] calcd for $C_{13}H_{18}O_4$ 238.1205; found 238.1210; IR (KBr) 2929, 1710, 1594, 1441, 1205, 1146 cm^{-1}.

4.5.2. Methyl 2-methyl-4-oxo-1-oxaspiro[4.5]dec-2-en-3-carboxylate 4b. Hexane/ethyl acetate=2:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.33–1.42 (1H, m), 1.57–1.81 (9H, m), 2.63 (3H, s), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$) δ 18.0, 21.4, 24.3, 31.6, 51.5, 92.2, 107.1, 163.7, 195.3, 201.2; HRMS-EI *m/z*: [M^+] calcd for $C_{12}H_{16}O_4$ 224.1049; found 224.1048; IR (KBr) 2939, 1709, 1593, 1442, 1199 cm^{-1}.

4.5.3. Methyl 8-*tert*-butoxycarbonyl-2-methyl-4-oxo-1-oxa-8-azaspiro[4.5]dec-2-en-3-carboxylate 4c. Hexane/ethyl acetate=2:1. Colorless needles. Mp 110 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.50–1.63 (2H, d-like, br), 1.89–1.97 (2H, m), 2.66 (3H, s), 3.15 (2H, br), 3.84 (3H, s), 4.11 (2H, br); ^{13}C NMR ($CDCl_3$) δ 18.0, 28.4, 31.3, 39.3 (br), 51.7, 80.1, 89.4, 107.5, 154.5, 163.2, 195.5, 198.7; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{23}NO_6$ 325.1525; found 325.1536; IR (KBr) 2871, 1705, 1604, 1426, 1167 cm^{-1}.

4.5.4. Methyl 2,5-dimethyl-4-oxo-5-(1-phenylethyl)-4,5-dihydrofuran-3-carboxylate 4d. Hexane/ethyl acetate=5:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, s), 2.04–2.17 (2H, m), 2.53 (2H, t, $J=8.0$ Hz), 2.60 (3H, s), 3.85 (3H, s), 7.12–7.28 (5H, m); ^{13}C NMR ($CDCl_3$) δ 17.8, 22.1, 29.3, 38.1, 51.6, 92.4, 107.9, 126.2, 128.3, 128.5, 140.5, 163.3, 196.0, 199.8; HRMS-FAB *m/z*: [$M^+ + H$] calcd for $C_{16}H_{19}O_4$ 275.1283; found 275.1285; IR (KBr) 2950, 1709, 1592, 1443, 1199 cm^{-1}. Anal. Found: C, 69.6; H, 6.70 Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61%.

4.5.5. Methyl 4-oxo-2-phenyl-1-oxaspiro[4.5]dec-2-en-3-carboxylate 4e. Hexane/ethyl acetate=20:1. Colorless needles. Mp 63 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.38–1.47 (1H, m), 1.65–1.87 (9H, m), 3.83 (3H, s), 7.46–7.63 (3H, m), 7.91–7.94 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.6 (2C), 24.4, 31.9 (2C), 51.9, 91.3, 106.8, 128.3, 129.3, 129.4, 133.1, 163.6, 187.3, 201.2; FAB-MS *m/z*: 287 ($M^+ + H$); IR (KBr) 2947, 1702, 1604, 1567, 1387, 1089 cm^{-1}. Anal. Found: C, 71.28; H, 6.39 Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%.

4.6. Reaction of steroids

The cyclization–carbonylation of propargylic esters **1i–1k**

A 100 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $(CH_3CN)_2PdCl_2$ (0.025 mmol), *p*-benzoquinone (0.8 mmol) and MeOH (7 mL) was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping–filling via the three-way stopcock. A solution of the substrate **1** (0.5 mmol) in MeOH (35 mL) was added dropwise to the stirred mixture via a syringe at 0 °C. After being stirred for the appropriate period of time at 0 °C, the mixture was diluted with CH_2Cl_2 (70 mL), washed with 5% NaOH aq (50 mL), and dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (30/1–10/1) afforded **2**.

4.6.1. Steroidal spiro orthoester 2i. Hexane/ethyl acetate=10:1. Colorless needles. Mp 70 °C (MeOH); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.84–1.05 (2H, m), 0.98 (3H, s), 1.19 (3H, s), 1.35–1.50 (3H, m), 1.59–1.74 (4H, m), 1.66 (3H, s), 1.91–2.03 (4H, m), 2.14–2.47 (5H, m), 2.85–2.93 (1H, m), 3.19 (3H, s), 3.65 (3H, s), 5.62 (1H, s), 5.73 (1H, s); (minor diastereomer) δ 0.96, 1.19, 1.59, 3.38, 3.64 (s each, Me), 5.52, 5.73 (s each, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.8, 17.3, 20.8, 24.5, 24.5, 31.8, 32.1, 32.8, 33.4, 33.9, 35.6, 36.6, 38.5, 48.8, 49.7, 50.5, 51.3, 53.2, 93.5, 98.1, 120.8, 123.9, 166.5, 169.9, 171.0, 199.4; HRMS-EI *m/z*: [M^+] calcd for $C_{26}H_{36}O_6$ 444.2512; found 444.2512; IR (KBr) 2946, 1721, 1675, 1437, 1196 cm^{-1}.

4.6.2. Steroidal spiro orthoester 2j. Hexane/ethyl acetate=30:1. Colorless needles. Mp 129 °C (MeOH); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.98 (3H, s), 1.32–1.60 (5H, m), 1.67 (3H, s), 1.71–2.32 (7H, m), 2.84–3.00 (3H, m), 3.21 (3H, s), 3.64 (3H, s), 3.77 (3H, s), 5.65 (1H, s), 6.63 (1H, br s), 6.69 (1H, dd, $J=8.8$, 1.6 Hz), 7.15 (1H, d, $J=8.8$ Hz); (minor diastereomer) δ 0.95, 1.61, 3.40, 3.63, 3.77 (s each, Me), 5.54

(s, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.8, 24.1, 24.6, 26.4, 27.6, 29.8, 32.3, 33.8, 39.2, 43.4, 48.8, 50.3 (2C), 51.2, 55.2, 93.4, 98.3, 111.5, 113.8, 120.9, 126.2, 132.3, 138.0, 157.5, 166.7, 169.9; EI-MS *m/z*: 442 (M^+); IR (KBr) 2937, 1722, 1650, 1252, 1082, 1049 cm^{-1}. Anal. Found: C, 70.37; H, 7.83 Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74%.

4.6.3. Steroidal spiro orthoester 2k. Hexane/ethyl acetate=20:1. Colorless needles. Mp 172 °C (hexane/$CHCl_3$); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.96 (3H, s), 1.24–1.74 (7H, m), 1.67 (3H, s), 1.91–2.28 (5H, m), 2.73–2.98 (3H, m), 3.20 (3H, s), 3.63 (3H, s), 4.80 (1H, br), 5.63 (1H, s), 6.53 (1H, d, J=2.4 Hz), 6.59 (1H, dd, J=8.4, 2.4 Hz), 7.07 (1H, d, J=8.4 Hz); (minor diastereomer) δ 0.93, 1.59, 3.38, 3.62 (s each, Me), 5.54 (s, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.8, 24.1, 24.6, 26.4, 27.5, 29.6, 32.3, 33.8, 39.1, 43.3, 48.8, 50.2 (2C), 51.3, 93.4, 98.3, 112.6, 115.2, 120.9, 126.4, 132.3, 138.2, 153.4, 166.8, 169.9; EI-MS *m/z*: 428 (M^+); IR (KBr) 3444, 2932, 1723, 1689, 1644, 1199, 1126 cm^{-1}. Anal. Found: C, 68.31; H, 7.61 Calcd for $C_{25}H_{32}O_6 1/2H_2O$: C, 68.68; H, 7.60%.

4.6.4. Steroidal spiro orthoester 2l. Hexane/ethyl acetate=20:1. Colorless needles. Mp 129 °C (MeOH); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.95 (3H, s), 1.30–1.55 (6H, m), 1.67 (3H, s), 1.70–1.81 (1H, m), 1.93–2.23 (5H, m), 2.25 (3H, s), 2.82–2.98 (3H, m), 3.19 (3H, s), 3.62 (3H, s), 5.63 (1H, s), 6.77 (1H, d, J=2.4 Hz), 6.82 (1H, dd, J=8.4, 2.4 Hz), 7.21 (1H, d, J=8.4 Hz); (minor diastereomer) δ 0.93, 1.59, 2.02, 3.38 (s each, Me), 5.54 (s, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.7, 21.1, 24.1, 24.6, 26.2, 27.3, 29.5, 32.3, 33.7, 38.8, 43.5, 48.8, 50.2, 50.2, 51.2, 93.4, 98.2, 118.5, 120.9, 121.5, 126.2, 137.7, 138.2, 148.4, 166.7, 169.8 (2C); EI-MS *m/z*: 470 (M^+); IR (KBr) 2931, 1767, 1721, 1651, 1206, 1082, 1047 cm^{-1}. Anal. Found: C, 68.86; H, 7.33 Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28%.

4.7. Preparation of γ-hydroxy-β-ketoesters 3i–3k

A solution of the orthoester **2** (0.27 mmol) in MeOH (10 mL), H_2O (0.5 mL) and 10% HCl aq (0.5 mL) was stirred for the appropriate period of time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (10/1–2/1) afforded **3i–3k**.

4.7.1. Methyl 17-acetoxy-3,20-dioxo-pregna-4-en-21-carboxylate 3i. Hexane/ethyl acetate=2:1. Colorless needles. Mp 61 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 0.85–1.47 (6H, m), 1.02 (3H, s), 1.15 (3H, s), 1.55–1.98 (8H, m), 2.10 (3H, s), 2.22–2.42 (4H, m), 2.72–2.80 (1H, m), 3.34 (1H, d, J=15.6 Hz), 3.52 (1H, d, J=15.6 Hz), 3.70 (3H, s), 5.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.0, 17.3, 20.6, 21.0, 24.5, 31.4, 32.6, 33.2, 33.3, 33.9, 35.6, 35.7, 38.4, 45.9, 46.9, 47.8, 52.3, 52.7, 95.9, 124.0, 167.3, 170.4, 171.3, 199.2, 202.5; HRMS-EI *m/z*: [M^+] calcd for $C_{25}H_{34}O_6$ 430.2355; found 430.2371; IR (KBr) 2948, 1741, 1671, 1253, 1029 cm^{-1}.

4.7.2. Methyl 17-acetoxy-3-methoxy-20-oxo-19-nor-pregna-1,3,5(10)-trien-21-carboxylate 3j. Hexane/ethyl acetate=10:1. Colorless needles. Mp 168 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s), 1.35–1.69 (7H, m), 1.88–1.91 (3H, m), 2.10–2.17 (1H, m), 2.13 (3H, s), 2.31–2.46 (1H, m), 2.79–2.87 (3H, m), 3.41 (1H, d, J=15.6 Hz), 3.61 (1H, d, J=15.6 Hz), 3.74 (3H, s), 3.76 (3H, s), 6.62 (1H, d, J=2.4 Hz), 6.69 (1H, dd, J=8.4, 2.4 Hz), 7.14 (1H, d, J=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.0, 21.1, 24.3, 26.2, 27.3, 29.7, 33.4, 33.6, 38.9, 43.0, 46.0, 46.5, 48.4, 52.3, 55.2, 96.2, 111.5, 113.8, 126.2, 132.1, 137.9, 157.5, 167.4, 171.4, 202.7; EI-MS *m/z*: 428 [M^+]; IR (KBr) 2946, 1754, 1610, 1501, 1251, 1033 cm^{-1}. Anal. Found: C, 69.97; H, 7.57 Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53%.

4.7.3. Methyl 17-acetoxy-3-hydroxy-20-oxo-19-nor-pregna-1,3,5(10)-trien-21-carboxylate 3k. Hexane/ethyl acetate=3:1. Colorless needles. Mp 189 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, s), 1.29–1.69 (7H, m), 1.82–2.03 (4H, m), 2.14 (3H, s), 2.21–2.26 (1H, m), 2.77–2.86 (3H, m), 3.43 (1H, d, J=15.6 Hz), 3.62 (1H, d, J=15.6 Hz), 3.75 (3H, s), 5.18 (1H, br), 6.55 (1H, d, J=2.4 Hz), 6.61 (1H, dd, J=8.4, 2.4 Hz), 7.04 (1H, d, J=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.0, 21.1, 24.3, 26.1, 27.2, 29.5, 33.4, 33.6, 38.8, 42.8, 46.1, 46.5, 48.4, 52.4, 96.2, 112.7, 115.3, 126.4, 132.0, 138.1, 153.6, 167.8, 171.5, 202.8; HRMS-EI *m/z*: [M^+] calcd for $C_{24}H_{30}O_6$ 414.2042; found 414.2034; IR (KBr) 3467, 2947, 1739, 1252, 1024 cm^{-1}. Anal. Found: C, 69.08; H, 7.26 Calcd for $C_{24}H_{30}O_6 1/4H_2O$: C, 68.80; H, 7.34%.

4.8. Preparation of spiro furanones 4i–4k

4.8.1. 4′-Methoxycarbonyl-5′-methyl-(17*S*)-spiro[androst-4-ene-17,2′-(3′*H*)-furan]-3,3′-dione 4i. Hexane/ethyl acetate=2:1. Colorless needles. Mp 194 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.92–1.17 (2H, m), 1.00 (3H, s), 1.13 (3H, s), 1.29–1.63 (6H, m), 1.78–1.96 (3H, m), 2.00–2.40 (8H, m), 2.57 (3H, s), 3.77 (3H, s), 5.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.1, 17.4, 17.6, 20.3, 23.9, 31.2, 31.2, 31.4, 32.6, 33.8, 35.4, 35.6, 38.4, 47.5, 48.6, 51.4, 52.7, 100.5, 107.7, 124.0, 163.3, 170.5, 196.2, 199.2, 200.5; EI-MS *m/z*: (M^+); 412; IR (KBr) 2941, 1704, 1584, 1438, 1402 cm^{-1}. Anal. Found: C, 72.86; H, 7.74 Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82%.

4.8.2. 4′-Methoxycarbonyl-5′-methyl-(17*S*)-spiro[3-methoxyestra-1,3,5-(10)-triene-17,2′(3′*H*)-furan]-3′-one 4j. Hexane/ethyl acetate=5:1. Colorless needles. Mp 144 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, s), 1.40–1.64 (6H, m), 1.88–2.22 (4H, m), 2.23–2.39 (3H, m), 2.62 (3H, s), 2.84–2.87 (2H, m), 3.77 (3H, s), 3.82 (3H, s), 6.62 (1H, d, J=1.6 Hz), 6.69 (1H, dd, J=8.8, 1.6 Hz), 7.14 (1H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 15.2, 17.7, 23.8, 26.0, 27.4, 29.8, 31.4, 31.6, 38.7, 42.9, 47.2, 49.3, 51.5, 55.2, 101.0, 107.7, 111.5, 113.8, 126.3, 132.3, 137.9, 157.5, 163.5, 196.2, 200.8; EI-MS *m/z*: 410 (M^+); IR (KBr) 2939, 1741, 1706, 1601, 1402, 1146 cm^{-1}. Anal. Found: C, 73.09; H, 7.41 Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37%.

4.8.3. 4′-Methoxycarbonyl-5′-methyl-(17*S*)-spiro[3-hydroxyestra-1,3,5-(10)-triene-17,2′(3′*H*)-furan]-3′-one 4k. Hexane/ethyl acetate=2:1. Colorless needles. Mp 272 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, s),

1.34–1.66 (6H, m), 1.85–1.95 (3H, m), 2.05–2.30 (4H, m), 2.62 (3H, s), 2.79–2.81 (2H, m), 3.84 (3H, s), 5.47 (1H, br), 6.59–6.62 (2H, m), 7.00 (1H, d, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 15.3, 17.8, 23.8, 25.8, 27.3, 29.6, 31.3, 31.5, 38.4, 42.6, 47.2, 49.4, 51.5, 101.2, 107.7, 113.0, 115.7, 126.4, 132.0, 137.8, 153.6, 163.4, 196.4, 201.3; HRMS-EI *m/z*: [M^+] calcd for $C_{24}H_{28}O_5$ 396.1937; found 396.1934; IR (KBr) 3349, 2918, 1707, 1684, 1584, 1443, 1160 cm^{-1}. Anal. Found: C, 72.3; H, 7.12 Calcd for $C_{24}H_{28}O_5$: C, 72.7; H, 7.12%.

4.9. NMR experiments

To a stirred solution of **1b** (10 mg, 0.06 mmol) in CD_2Cl_2 (0.5 mL) was added $(CH_3CN)_2PdCl_2$ (16 mg, 0.06 mmol). After the $(CH_3CN)_2PdCl_2$ dissolved completely (ca. 5 min), the spectra was measured immediately.

^{1}H NMR (CD_2Cl_2) δ 1.41–1.64 (5H, m), 1.77–1.94 (4H, m), 1.97 (6H, s, C*H*$_3$CN), 1.99–2.07 (1H, m), 2.29 (3H, s), 5.47 (1H, s); ^{13}C NMR (CD_2Cl_2) δ 2.0, 20.5, 26.5, 27.3, 30.0, 31.8, 34.9, 72.4, 94.1, 116.9, 128.0, 168.5.

4.10. Method for the biological activity test (1)

All experiments comply with the Guiding Principles for the Care and Use of Laboratory Animals Approved by the Japanese Pharmacological Society. The right atria was rapidly isolated from 1 to 3 day old chicks and beating rate measurements were performed as described previously.[26] The aorta was rapidly isolated from male rats (350–450 g) and contractile force measurements with endothelium-denuded aortic rings were performed as described previously.[26] The test compounds were dissolved in DMSO and small alliquots were applied to the organ bath to yield a final concentration of 10^{-5} M.

4.11. Method for the biological activity test (2)

Assay for CYP3A activity (midazolam 1′-hydroxylation) was assessed according to a previously published procedure.[27] Hepatic microsomes isolated from male Splague–Dawley rats (250 g) was preincubated with 3×10^{-5} M of the test compounds and 1 mM NADPH at 37 °C for 20 min, before assaying for CYP3A activity.

Acknowledgements

We are grateful for the financial support of the Eisai Award in Synthetic Organic Chemistry Japan (2002), Takeda Science Foundation (2003) and The Research Foundation for Pharmaceutical Sciences (2002).

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