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A Facile Synthesis of Spiroisoxazolines: Intramolecular Cyclization of 3-Aryl-2-nitroacrylates Promoted by Titanium Tetrachloride

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Abstract : Titanium tetrachloride-induced cyclization of 3-(*o*- or *m*-substituted *p*-methoxyphenyl)-2-nitro acrylates (**1**) provided stereoselectively (4α,5β)-1-oxa-2-azaspiro[4, 5]deca-2,6,9-trien-8-ones (**2**). *Ortho*-substituted *p*-methoxyphenyl nitroacrylates gave **2** in good yield. 3-(4'-methoxy-1'-naphthyl)-2-nitroacrylate also reacted with titanium tetrachloride to give quantitatively (4α,5β)-4'-oxospiro[isoxazole-(4*H*)5,1'(4'*H*)-naphthalene] . 3-(10'-methoxy-9'-anthryl)-2-nitroacrylate was converted to 10-oxospiro-[anthracene-(10*H*)9,5'(4'*H*)-isoxazole]. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: titanium tetrachloride; intramolecular cyclization; nitroacrylates; spiroisoxazolines

We have previously reported the reaction of 3-aryl-2-nitroacrylates **1** with titanium tetrachloride, where naphthyl or phenanthryl derivatives react with toluene in the presence of titanium tetrachloride to give tolylated spiroisoxazolines in a diastereoselective manner.[1] In an attempt of the application of this method to formation of a new type of spiroisoxazoline derivatives, we found that *p*-cyclohexadienone spiroisoxazolin **2a** was obtained from the reaction of 3-(*p*-methoxyphenyl)-2-nitroacrylate **1a** with titanium tetrachloride in dichloromethane. Under the similar reaction conditions, *o*-methoxyphenyl detivative gave 3-chloro-2-hydroxyimino propionate,[2] and *m*-methoxyphenyl derivative was converted into salicylaldehyde.[3] It is clear from the above examples that the position of methoxyl substituent on aryl ring governs the kind of the product. Cyclohexadienone spiroisoxazolines are important model compounds on syntheses of dibromotyrosine-derived marine metabolies,[4] which contain one or two spiroisoxazoline units. Additionally, it was reported that *p*-cyclohexadienone spiroisoxazolines were prepared as useful antitumor agents.[5] Several reports have been made on the synthetic approaches so far, which have been achieved through intramolecular oxidative cyclization of 1-hydroxyphenyl-2-propanone oximes,[6] or 1,3-dipolar cycloaddition of nitrile oxide to a quinone methide.[7] This paper describes a novel synthesis of spiroisoxazolines connecting arenone ring as well as it's scope and limitation.

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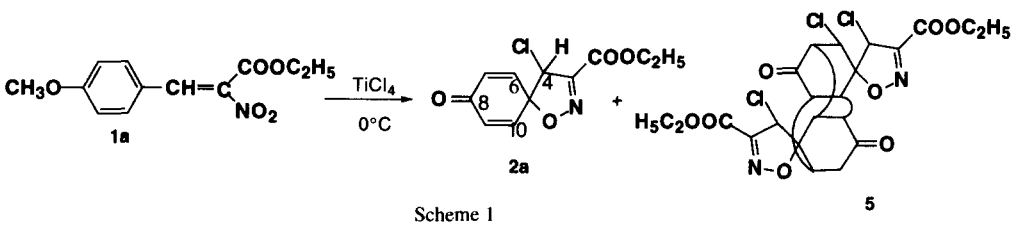
Result and Discussion

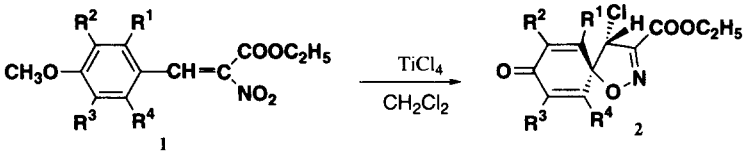
Ethyl 3-aryl-2-nitroacrylates **1** were prepared by the condensation of arylaldehydes and ethyl nitroacetate. A mixture of *E* and *Z* isomer of ethyl 3-(4'-methoxyphenyl)-2-nitroacrylate (**1a**) reacted at 0 ℃ with two equivalents of titanium tetrachloride to give spiroisoxazoline **2a** with a caged dimer **5**. The mass spectrum indicated the molecular formula for **5** with one more hydrogen and chlorine atom than 2 x **2a**. It was noted that the yield of **2a** was improved by suppression of formation of the dimer. The treatment of **1a** (1 mmol) with two equivalents titanium tetrachloride in 10 ml dichloromethane gave **2a** in 46% isolated yield along with **5** in 34% yield, while the reaction in 50 ml dichloromethane gave **2a** in 58% isolated yield with 4-methoxy-salicylaldehyde (**4a**) in 12% yield (Scheme 1 and Table 1). Spiroisoxazoline **2a** was unchanged upon treatment with titanium tetrachloride. Further changes in the reaction conditions failed to suppress these side-reactions. Perhaps the intermediate from **1a** might react with **2a** to yield **5**, or convert to **4a**.

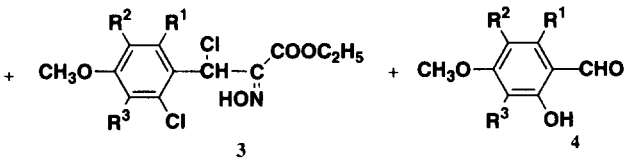


Scheme 1

The cyclization of several 3-(*o*-, or *m*-substituted *p*-methoxyphenyl)-2-nitroacrylates was attempted. The results are listed in Table 1. Nitroacrylates **1b** - **1g** and **1i** - **1l** showed high stereoselectivity, and afforded **2b** - **2d**, **2f**, **2g**, and **2i** - **2l** as a single diastereoisomer. Compounds **1b**, **1c** and **1d**, which have a substituent on *ortho* position of *p*-methoxy-phenyl group, cyclized to 4-chloro-6-substituted *p*-cyclohexadienone spiroisoxazolines **2b**, **2c** and **2d** in moderate to good yields. *o*-Methoxy derivative **1b** slowly reacted to give spiroisoxazolines, **2b** and **6b** in total 57% yield (a ratio 17:1), with **1b** in 11% recovery after 24 hours. **6b** was not *p*-cyclohexadienone but *o*-cyclohexadienone spiroisoxazoline (Scheme 3). In the case of *o*-bromo derivative **1e**, the expected **2e** was not detected but **2d** was formed via Br-Cl exchange reaction. Further the released bromide ion formed other spiroisoxazolines **2d'**, **2'd** and **2'd'** as shown in Table 1. The reaction of *meta* substituted *p*-methoxyphenyl nitroacrylates with titanium tetrachloride gave a drastic change in the product distribution resulting in the formation of 3-chloro-2-hydroxyimino propionates **3**. Oxime **3** was converted into corresponding salicylaldehyde **4** in ca. 40% yield under the work up conditions or column chromatography on silica gel . In the case of *m*-methyl derivative **1f**, **2f** and **3f** were obtained in a 9:8 ratio. *m*-Bromo derivative **1g** gave **3g** as a major product with **2g**. *m*-Methoxy derivative **1h** afforded only **3h** and **4h**, and spiroisoxazoline was not detected. Thus *o*-substituted *p*-methoxyphenyl group promoted the cyclization reaction effectively, while *m*-substituents decreased the rate of spiroisoxazolines. In case of *o*-, *m*- and *p*-trisubstituted nitroacrylate, 2,4,5-trimethoxy derivative **1k** gave **2k** in 57% yield. But, 2,3,4-trimethoxy derivative **1j** gave quantitatively **2j**. 2,3-Dimethyl-4-methoxy derivative **1i** also afforded **2i** quantitatively. 2,4,6-Trimethoxyphenyl nitroacrylate showed a low activity, and the starting material was recovered unchanged after 24 hours. In the case of 2,6-dichloro-4-methoxyphenyl derivative **1l**, this cyclization reaction proceeded slowly to give **2l** and **2l'** in total 48% yield with **1l** in 18% recovery .

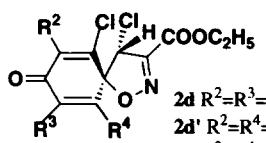
Table 1 The synthesis of spiroisoxazolines **2**



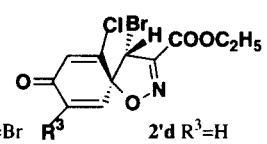


	R^1	R^2	R^3	R^4	Reaction time	**2**	Product (yield %)	**3**, **4** (yield %)			
1a	H	H	H	H	2h	**2a**	58	**4a**	12		
1b	CH_3O	H	H	H	2h 24h	**2b**	40 54				
1c	CH_3	H	H	H	2h	**2c**	93				
1d	Cl	H	H	H	2h	**2d**	78				
1e	Br	H	H	H	0.5h 2h	**2d**	60[1] 83[2]				
1f	H	CH_3	H	H	0.5h 2h	**2f**	42 42(52[3])	**3f**	24(48[3])		
1g	H	Br	H	H	2h	**2g**	11	**3g**	62	**4g**	17
1h	H	CH_3O	H	H	2h	**2h**	-	**3h**	47[3]	**4h**	33[3]
1i	CH_3	CH_3	H	H	2h	**2i**	92				
1j	CH_3O	CH_3O	H	H	24h	**2j**	90				
1k	CH_3O	H	CH_3O	H	24h	**2k**	57	**4h**	23		
1l	Cl	H	H	Cl	24h	**2l**	48[4]		17[5]		

1) **2d** (38%) + **2d'** (6%) + **2'd** (15%) + **2'd'**(1%)
2) **2d** (47%) + **2d'** (8%) + **2'd** (26%) + **2'd'**(2%)
3) Estimated by ^1H NMR of the crude product
4) **2l** (36%) + **2l'**(12%)

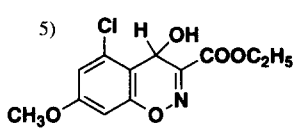


2d R^2=R^3=R^4=H
2d' R^2=R^4=H, R^3=Br
2l' R^2=R^4=Cl, R^3=H



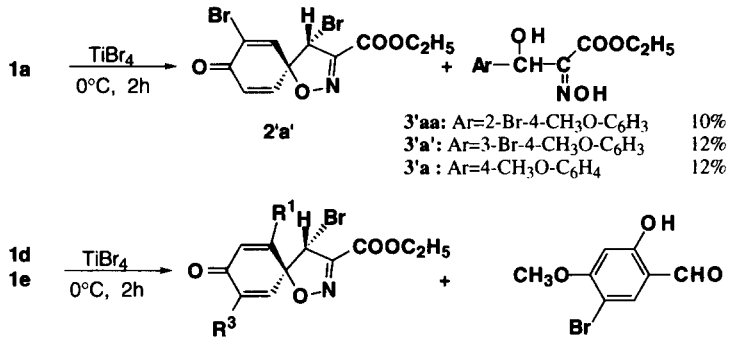
2'd R^3=H
2'd' R^3=Br

5)



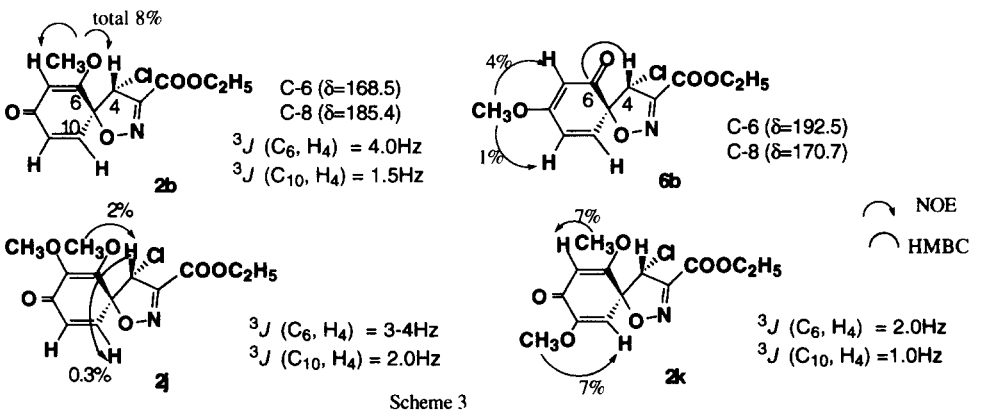
10l

To obtain more information with respect to the halogen exchange reaction, we carried out the reaction of titanium tetrabromide with **1a**, **1d** and **1e** (Scheme 2). Nitroacrylates **1a** and **1e** gave stereoselectively spiroisoxazoline **2'a'**, **2'e** and **2'e'** in low yield, 21% , 4% and 12%, respectively. Compound **1d** gave two corresponding **2'd** and **2'd'**, and two halogen-exchanged **2'e** and **2'e'** in total 17% yield. As main product, **1a** gave an inseparable mixture of three types of 3-aryl-3-hydroxy-2-hydroxyiminopropionates in ca. 30% yield. **1d** and **1e** gave 5-bromo-4-methoxysalicylaldehyde (**4g**) in 21-25% yield.



Scheme 2

The structures of **2** were established by IR, Mass, ^{1}H and ^{13}C NMR as shown in Table 2 and 3. The stereochemistry of 6-unsubstituted and 6-methylsubstituted spiroisoxazolines as (4α,5β)-isomer were clear from NOE experiments (**2c**, **2f**, **2g**, **2i** and **2'a'**) . 6-Methoxysubstituted spiroisoxazolines were confirmed by NOE experiment and long-rang heteronuclear coupling constants($J_{C,H}$).[8] For **2k**, NOE was not observed between H-4 and C_6-OCH_3, and also between H-4 and H-10. In **2b**, **2j** and **2k**, vicinal (^3J) C-H coupling constant was larger for C-6 than C-10. **2k** also has the same relative structure(4α,5β). Compound **6b** was determined by NOE experiments (CH_3O and H-7, CH_3O and H-9), and a HMBC cross peak ($^3J_{(CH)}$) which was seen between H-4 signal and CO carbon signal (δ=192.5).

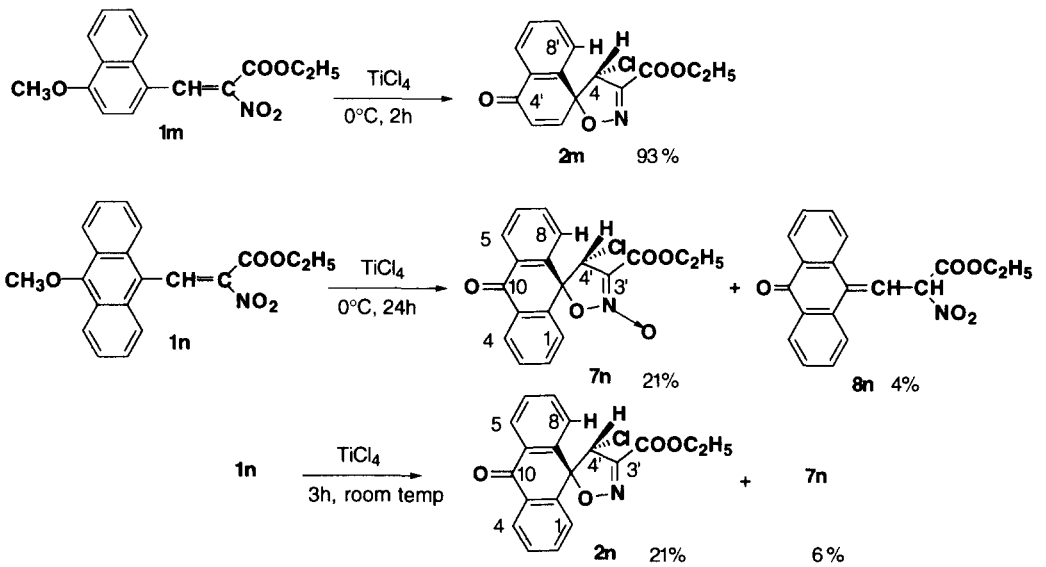


Scheme 3

On the basis of absence of NOE between H-4 and H-10, the stereochemistry of 6-halosubstituted spiroisoxazolines was deduced and they were confirmed by chemical shifts and/or $^3J_{C,H}$. Bromine atom

rather than chlorine atom affected downfield shift for H-10, and C-10 in *cis* relationship (example; **2d** (C_4-Cl): δ_H = 7.04, δ_C = 140.3, **2'd**(C_4-Br): δ_H = 7.07, δ_C = 142.8 ppm). In **21'**, **2'e** and **2'e'**, $^3J_{(C6.H4)}$ was larger than $^3J_{(C10.H4)}$.

The reaction could be extended to a range of aryl groups and the results are showed in scheme 4. Fortunately the reaction of 4-methoxy-1-naphthyl derivative **1m** gave near quantitative conversion to isolated spiroisoxazoline **2m** in 93% yield. H-4 of the isoxazoline ring and H-8' of the naphthalene ring were in a *cis*-orientation by NOE experiment. 10-Methoxy-9-anthryl derivative **1n** afforded spiroisoxazoline *N*-oxide **7n** as a major product and saturated nitro compound **8n**. The formation of **2n** from **1n** required a higher reaction temperature (room temp.) as compared with the reactions (0℃) of 4-methoxyphenyl derivatives **1b** - **1g** and **1i** - **1l** or 4-methoxy-1-naphthyl derivative **1m**. When the reaction was performed at room temperature, **2n** was formed in 21 % yield.



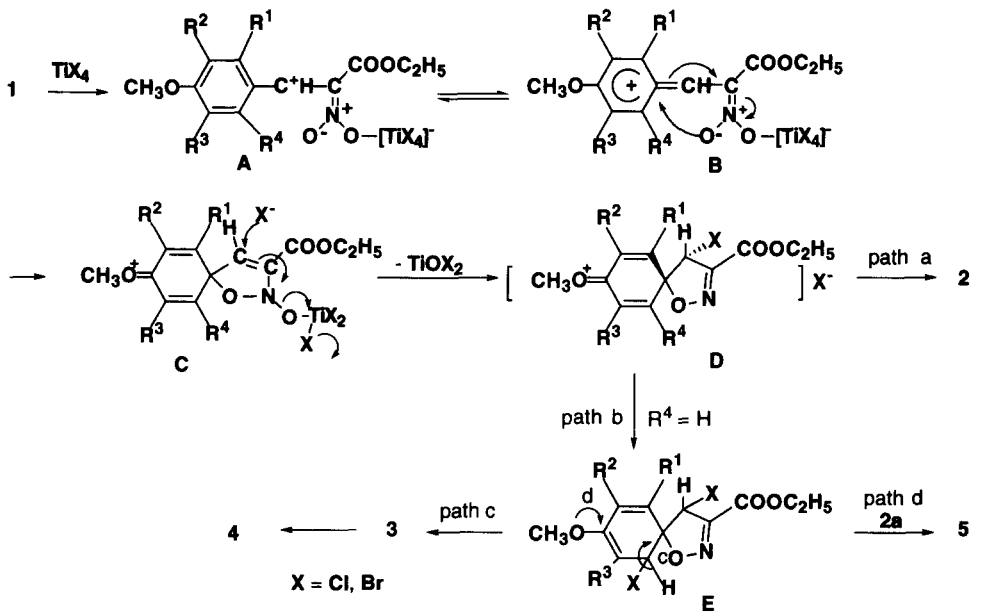
Scheme 4

A mechanism consistent with the results detailed above involves coordination of $TiCl_4$ to the oxygen of nitro group to give a complex that can be represented as intermediate **B** (scheme 5). An *ipso* attack by oxygen of nitro group yields spiro intermediate **C**, which undergoes an attack by chloride anion followed by loss of $TiOCl_2$[1,10] yielding **D**. Then, **D** converts to spiroisoxazoline **2** by demethylation (path a). The stereoselectivity of nucleophilic addition of X^- in **C** (R^4=H) is rationalized by steric hindrance. Intermediate **C** from **1n** leads to spiroisoxazoline N-oxide **7n** by no cleavages of N-O bond involving oxidation at a lower temperature. **D** undergoes an attack on *ortho* position by chloride anion yielding intermediate **E**[1] (path b). Demethylation of **E** is followed by addition of **2a** to a dimer **5**. Oxime **3** is formed *via* aromatization of **E** followed to give salicylaldehyde **4**.

In summary, a novel synthesis of spiroisoxazolines has been accomplished using 3-aryl-2-nitroacrylates through $TiCl_4$-inducced intramolecular *ipso* attack by oxygen of nitro group. The prepared (4α,5β)-4'-oxospiro-[isoxazole-(4*H*)5,1'(4'*H*)-naphthalene] (**2m**), 10-oxospiro[anthracene-(10*H*)9,5'(4'*H*)-isoxazole]

(**2n**) exhibited cytotoxicity against murine leukemia P388(IC_{50} Values : 0.12 and 42 μ g/ml, respectively) *in vitro*.

We express sincere thanks to Dr. Katsuharu Iinuma (Director, Pharmaceutical Technology Laboratories. Meiji Seika Kaisha Ltd., Kanagawa) for biological assay.



Scheme 5

Table 2 ^{13}C NMR data (δ, in $CDCl_3$) for **2**

	3	4	5	6	7	8	9	10	COO	OCH_2	CH_3	
2a	151.5	63.7	85.0	139.1	129.6	183.5	131.9	139.4	157.8	63.1	14.2	
2b	151.2	64.0	85.3	168.5	102.1	185.4	130.4	136.5	158.0	62.9	14.0	56.5(CH_3O)
2c	151.2	64.6	87.4	151.3	128.3	184.2	130.0	141.2	157.9	63.1	14.0	17.5 (CH_3)
2d	151.1	64.6	86.6	148.2	129.6	182.3	129.3	140.3	157.5	63.1	14.0	
2d'	151.2	64.3	88.2	148.3	128.2	175.3	126.0	140.2	157.3	63.3	14.0	
2f	151.7	63.7	85.8	134.5	137.2	184.5	132.0	139.3	158.1	63.0	14.0	15.5(CH_3)
2g	151.8	63.1	86.9	139.4	127.3	176.7	130.7	139.9	157.7	63.2	14.0	
2i	151.2	64.7	88.3	144.6	133.9	184.0	129.3	140.6	158.1	63.0	14.0	14.0(C_6-CH_3) 11.0(C_7-CH_3)
2j	151.3	63.7	88.2	155.1	136.5	186.7	129.6	136.3	158.0	62.8	14.0	61.6(C_6-OCH_3) 61.1(C_7-OCH_3)
2k	151.5	63.7	88.1	169.0	101.3	180.3	151.3	103.3	158.2	62.8	14.0	56.9(C_6-OCH_3) 55.7(C_9-OCH_3)
2l	150.2	64.3	89.6	148.7	129.5	180.3	129.9	148.7	157.4	63.4	14.0	
2l'	150.2	64.7	90.8	144.1	134.0	173.8	128.9	149.1	157.3	63.4	14.0	$^3J(C_6,H_4)$=6.5Hz,$^3J(C_{10},H_4)$=5.0Hz
2'a'	152.5	50.6	86.5	138.9	127.0	176.7	130.4	142.3	157.6	63.2	14.0	
2'd	151.7	51.9	86.1	147.9	129.4	182.4	128.7	142.8	157.6	63.1	14.0	
2'e	151.7	52.8	86.5	139.5	133.7	181.8	128.4	143.4	157.6	63.1	14.0	$^3J(C_6,H_4)$=5.5Hz,$^3J(C_{10},H_4)$=2.0Hz
2'd'	151.7	51.3	87.9	148.3	127.9	175.6	125.4	142.8	157.4	63.3	14.0	
2'e'	151.7	52.3	88.3	140.0	132.2	175.1	125.0	143.4	157.4	63.2	14.0	$^3J(C_6,H_4)$=5.5Hz,$^3J(C_{10},H_4)$=2.0Hz

Table3 ^{1}H NMR data (δ, in $CDCl_3$) for **2**

	H-4	H-6	H-7	H-9	H-10
2a	5.27	6.62(dd, 10.0,3.0)	6.32(dd, 10.0, 1.5)	6.48(dd, 10.0, 1.5)	7.10(dd, 10.0, 3.0)
2b	5.57	-	5.57(d, 1.5)	6.32(dd, 10.0, 1.5)	6.83(d, 10.0)
2c	5.38	-	6.11(dq, 1.9, 1.3)	6.37(dd, 10.0, 1.9)	7.01(d, 10.0)
2d	5.63	-	6.49(d, 1.9)	6.41(dd, 10.0, 1.9)	7.04(d, 10.0)
2d'	5.64	-	6.61	-	7.46
2f	5.26	6.39(dq, 3.0, 1.3)	-	6.46(d, 10.0)	7.07(dd, 10.0, 3.0)
2g	5.32	7.05(d, 3.0)	-	6.59(d, 10.0)	7.15(dd, 10.0, 3.0)
2i	5.38	-	-	6.36(d, 10.0)	6.93(d, 10.0)
2j	5.59	-	-	6.25(d, 10.0)	6.76(d, 10.0)
2k	5.50	-	5.54	-	5.66
2l	5.81	-	6.57	6.57	-
2l'	5.82	-	-	6.69	-
2'a'	5.36	7.08(d, 3.0)	-	6.55(d, 10.0)	7.17(dd, 10.0, 3.0)
2'd	5.63	-	6.46(d, 1.8)	6.36(dd, 10.0, 1.8)	7.07(d, 10.0)
2'e	5.60	-	6.72(d, 1.8)	6.38(dd, 10.0, 1.8)	7.13(d, 10.0)
2'd'	5.63	-	6.57	-	7.49
2'e'	5.60	-	6.82	-	7.55

	OCH_2	CH_3	others	NOE
2a	4.42(q, 7.1)	1.40(t, 7.1)	-	H-4 and H-6 (3%)
2b	4.42(q, 7.1)	1.40(t, 7.1)	3.75(CH_3O)	*
2c	4.43(q, 7.1)	1.40(t, 7.1)	1.88(d, 1.3, CH_3)	H-4 and CH_3 (2%)
2d	4.43(q, 7.1)	1.40(t, 7.1)	-	
2d'	4.44(q, 7.1)	1.41(t, 7.1)	-	
2f	4.43 and 4.44(dq, 10.5, 7.1)	1.41(t, 7.1)	1.93(d, 1.3, CH_3)	H-4 and H-6 (4%)
2g	4.42 and 4.43(dq, 10.5, 7.1)	1.43(t, 7.1)	-	H-4 and H-6 (5%)
2i	4.42(q, 7.1)	1.40(t, 7.1)	1.83(q, 1.0, C_6-CH_3), 1.91(q, 1.0, C_7-CH_3)	H-4 and C_6-CH_3 (4%)
2j	4.42(q, 7.1)	1.40(t, 7.1)	3.78(C_7-OCH_3), 4.05(C_6-OCH_3)	*
2k	4.42(q, 7.1)	1.40(t, 7.1)	3.74(C_6-OCH_3), 3.77(C_9-OCH_3)	*
2l	4.42 and 4.46(dq, 10.5, 7.1)	1.42(t, 7.1)		
2l'	4.42 and 4.46(dq, 10.5, 7.1)	1.42(t, 7.1)		
2'a'	4.42 and 4.45(dq, 10.5, 7.1)	1.40(t, 7.1)		H-4 and H-6 (6%)
2'd	4.44(q, 7.1)	1.41(t, 7.1)		
2'e	4.44(q, 7.1)	1.41(t, 7.1)		
2'd'	4.44(q, 7.1)	1.42(t, 7.1)		
2'e'	4.44(q, 7.1)	1.42(t, 7.1)		

Copling constants(Hz) in parenthesis

*) Scheme 3

Experimental

Melting points (uncorrected) were determined on a Yamatokagaku MP-1 apparatus. Mass spectra were obtained on JEOL JMS-AX505HA mass spectrometer. NMR spectra were recorded on Varian VXR-300 or XL-400 spectrometer. Infrared spectra were determined on a JASCO IR-810 spectrometer. Ethyl nitroacetate is commercially available (Fluka AG), but expensive. Therefore, it has been prepared.[11] 4-Methoxy-2-methylbenzaldehyde, 2-chloro-4-methoxybenzaldehyde, 2-bromo-4-methoxybenzaldehyde, 2,6-dichloro-4-methoxybenzaldehyde, 10-methyl-9-anthraldehyde were prepared by reaction of the corresponding arene with dichloromethyl methyl ether. Ethyl 3-(4'-methoxyphenyl)-2-nitroacrylate (**1a**),[12] ethyl 3-(3',4'-dimethoxy-phenyl)-2-nitroacrylate (**1h**),[13] ethyl 3-(2',4',6'-trimethoxyphenyl)-2-nitroacrylate[14]were reported.

General procedure for the synthesis of ethyl 3-aryl-2-nitroacrylates (1b-1g, 1i-1n)

Ethyl 3-aryl-2-nitroacrylates were prepared by the procedure of Dornow et al.[15] The reaction gave a mixture of *Z* and *E* isomers. The two isomers were separated by column chromatography followed by fractional recrystallization (**1d, 1e, 1l, 1m** and **1n**). Structural assignments were attempted on the basis of the work of

Watarai[16]or Babievskii.[17] The spectra data of **1b - 1g, 1i - 1n** are as follows.

Ethyl 3-(2',4'-dimethoxyphenyl)-2-nitroacrylate (1b) : Yield 64%. A 3:1 mixture of *Z* and *E* isomer: Mp 88.0 - 90.0℃(benzene-ligroin). IR(KBr, cm^{-1}): 1730(ester CO), 1540(NO_2), 1380 and 1330 (NO_2). ^1H NMR(300MHz, $CDCl_3$, δ): *Z* isomer; 1.35(3H, t, *J* =7.0Hz, CH_3), 3.84 and 3.85(3H, s, each CH_3O), 4.35(2H, q, *J* =7.1Hz, OCH_2), 6.43(1H, d, *J* =2.2Hz, H-3'), 6.47 (1H, dd, *J* = 8.5 and 2.2Hz, H-5'), 7.28(1H, d, *J* =8.5Hz, H-6'), 7.89 (1H, s, H-3); *E* isomer 1.35(3H, t, *J* =7.0Hz, CH_3), 3.86 and 3.87(3H, s, each CH_3O), 4.40(2H, q, *J* =7.1Hz, OCH_2), 6.44 (1H, d, *J* =2.2Hz, H-3'), 6.50(1H, dd, *J* = 8.5 and 2.2Hz, H-5'), 7.37(1H, d, *J* =8.5Hz, H-6'), 8.42 (1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ); *Z*-isomer 14.5(CH_3), 55.9(2 x CH_3O), 62.9(OCH_2), 98.7(C-3'), 106.4(C-5'), 111.5, 128.4(C-3), 130.9(C-6'), 138.6, 160.3, 160.7, 164.9; *E*-isomer; 13.8(CH_3), 55.6 and 55.7(CH_3O), 62.6(OCH_2), 98.3(C-3'), 106.2(C-5'), 111.1, 131.7(C-6'), 132.2(C-3), 139.8, 161.0, 162.1, 165.1. MS(*m/z*, rel.%): 281(M^+, 61), 162(100). Anal. Found: C 55.57, H 5.39, N 4.87. Calcd for $C_{13}H_{15}NO_6$: C 55.51, H 5.38, N 4.98.

Ethyl 3-(4'-methoxy-2'-methylphenyl)-2-nitroacrylate (1c) : Yield 28%. *Z* isomer : Mp 77-79℃ (dichloromethane-hexane). IR(KBr, cm^{-1}): 1700(ester CO), 1535 and 1375(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ): 1.35(3H, t, *J* =7.0Hz, CH_3), 2.41(3H, s, CH_3), 3.81(3H, s, CH_3O), 4.37(2H, q, *J* =7.1Hz, OCH_2), 6.72(1H, dd, *J* =9.0 and 2.5Hz, H-5'), 6.78(1H, d, *J* = 2.5Hz, H-3'), 7.29(1H, d, *J* =9.0 Hz, H-6'), 7.72(1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ):14.1(CH_3), 20.2(CH_3), 55.3(CH_3O), 62.8(OCH_2), 112.3(C-5'), 116.6(C-3'), 120.8, 129.4(C-6'), 130.9(C-3), 139.8, 141.2, 159.5, 162.2. HRMS: *m/z*, 265.0952, Calcd for $C_{13}H_{15}NO_5$: M, 265.0950.

Ethyl 3-(2'-chloro-4'-methoxyphenyl)-2-nitroacrylate (1d) : Yield 83%(*E*:*Z* = 1:1): MS(*m/z*, rel%): 287/285 (M^+, 18/52), 222(100). HRMS :*m/z*, 287.0377/285.0399, Calcd for $C_{12}H_{12}NO_5Cl$: M+2/M, 287.0375/285.0404. *Z* isomer : Mp 78-80 ℃(dichloromethane-hexane). IR(KBr, cm^{-1}) : 1720(ester CO), 1540 and 1370(NO_2). ^1H NMR(300 MHz, $CDCl_3$, δ): 1.36(3H, t, *J*=7.1Hz, CH_3), 3.83(3H, s, CH_3O), 4.38(2H, q, *J*=7.0Hz, OCH_2), 6.80 (1H, dd, *J*=9.0 and 2.5 Hz, H-5'), 7.00(1H, d, *J*=2.5 Hz, H-3'), 7.34(1H, d, *J*=9.0 Hz, H-6'), 7.89(1H, s, H-3). ^{13}C NMR(75MHz, $CDCl_3$, δ) : 14.0 (CH_3), 55.8(CH_3O), 63.0(OCH_2), 113.9(C-5'), 115.8(C-3'), 119.9, 128.9(C-3), 130.0(C-6'), 137.2, 140.4, 159.1, 162.7. *E* isomer : oil. IR(film, cm^{-1}); 1740(ester CO), 1540 and 1330(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.32(3H, t, *J*=7.0Hz, CH_3), 3.85(3H, s, CH_3O), 4.40(2H, q, J=7.0 Hz, OCH_2), 6.82(1H, dd, *J*=9.0 and 2.5 Hz, H-5'), 7.03(1H, d, *J*=2.5 Hz, H-3'), 7.45(1H, d, *J*=9.0 Hz, H-6'), 8.41(1H, s, C-3). ^{13}C NMR(75MHz, $CDCl_3$, δ):13.8(CH_3), 55.8(CH_3O), 63.0(OCH_2), 113.8(C-2'), 115.7 (C-3'), 119.9, 130.9(C-6'), 132.9(C-3), 138.2, 140.4, 161.1, 163.1.

Ethyl 3-(2'-bromo-4'-methoxyphenyl)-2-nitroacrylate (1e) : Yield 82% (*E* :*Z* =1:1). *Z* isomer : Mp 77.0-79.0 ℃(ethyl acetate-hexane). IR(KBr, cm^{-1}) : 1710(ester CO), 1535 and 1370(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.35(3H, t, *J* =7.1Hz, CH_3), 3.81(3H, s, CH_3O), 4.37(2H, q, *J* =7.1Hz, OCH_2), 6.82(1H, dd, *J* =9.0 and 3.0Hz, H-5'), 7.18(1H, d, *J* = 3.0Hz, H-3'), 7.30(1H, d, *J* =9.0Hz, H-6'), 7.83(1H, s, CH). ^{13}C NMR(100MHz, $CDCl_3$, δ) : 14.0(CH_3), 55.7(CH_3O), 63.0(OCH_2), 114.2(C-5'), 119.0(C-3'), 121.7(C-2'), 127.0(C-1'), 130.0(C-6'), 131.5(C-3), 140.6(C-2), 159.0(COO), 162.4(C-4'). MS(*m/z*, rel%): 331/329(M^+, 45/44), 222(100). Anal. Found : C 43.62, H 3.74, N 4.14, Br 24.20. Calcd for $C_{12}H_{12}BrNO_5$: C 43.66, H 3.66, N 4.24, Br 24.20. *E* isomer : oil. IR(film, cm^{-1}) : 1740 (ester CO), 1540 and 1330(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.30(3H, t, *J* =7.0Hz, CH_3), 3.84(3H, s, CH_3O), 4.38(2H, q, *J* =7.1Hz, OCH_2), 6.86(1H, dd, *J* =9.0 and 3.0Hz, H-5'), 7.21(1H, d, *J* = 3.0Hz, H-3'), 7.42(1H, d, *J* =9.0Hz, H-6'), 8.35(1H, s, CH). ^{13}C NMR(100MHz, $CDCl_3$, δ) : 13.7(CH_3), 55.8(CH_3O), 63.0 (OCH_2), 114.1(C-5'), 119.0 (C-3'), 121.5(C-2'), 128.0(C-1'), 130.9(C-6'), 135.3(C-3), 141.7(C-2), 160.9(COO),

162.8(C-4'). HRMS: *m/z*, 330.9921/328.9903. Calcd for $C_{12}H_{12}BrNO_5$: M+2/M, 330.9878/328.9899.

Ethyl 3-(4'-methoxy-3'-methylphenyl)-2-nitroacrylate (1f) : Yield 64%. *Z* isomer : Mp 114.0-115.5 ℃ (benzene-hexane). IR(KBr, cm^{-1}): 1720(ester CO), 1540 and 1385(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ): 1.35(3H, t, *J* =7.0Hz, CH_3), 2.19(3H, s, CH_3), 3.87(3H, s, CH_3O), 4.35(2H, q, *J* =7.1Hz, OCH_2), 6.83(1H, d, *J* =8.5Hz, H-5'), 7.20(1H, dd, *J* = 2.2 and 0.5Hz, H-2'), 7.29(1H, dd, *J* =8.5 and 2.2Hz, H-6'), 7.43(1H, s, H-3). ^{13}C NMR (100MHz, $CDCl_3$, δ):14.1(CH_3), 16.1(CH_3), 55.5(CH_3O), 62.7(OCH_2), 110.4(C-5'), 120.9, 128.0, 130.1(C-6'), 132.4(C-2'), 132.9(C-3), 137.9, 159.7(COO), 161.2(C-4'). Anal. Found: C 58.58, H 5.68, N 5.24. Calcd for $C_{13}H_{15}NO_5$: C 58.86, H 5.71, N 5.28.

Ethyl 3-(3'-bromo-4'-methoxyphenyl)-2-nitroacrylate (1g) : Yield 87%. *Z* isomer : Mp 142.6-144.3 ℃ (toluene-hexane). IR(KBr, cm^{-1}):1715(ester CO), 1530 and 1365(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ): 1.35(3H, t, *J* = 7.0Hz, CH_3), 3.94(3H, s, CH_3O), 4.37(2H, q, *J* =7.5 and 3.5Hz, CH_2), 6.91(1H, d, *J* =8.5Hz, H-5'), 7.37 (1H, dd, *J* = 8.5 and 2.5Hz, H-6'), 7.39(1H, s, CH), 7.62(1H, d, *J* =2.5Hz, H-2'). ^{13}C NMR(100MHz, $CDCl_3$, δ); 14.0(CH_3), 56.5(CH_3O), 63.0(OCH_2), 112.2(C-5'), 112.6(C-3'), 122.6(C-1'), 130.4(C-6'), 131.1(C-3), 135.3(C-2'), 139.2(C-2), 158.9(COO), 159.2(C-4'). MS(*m/z*, rel%) : 331/329(M^+, 90/89), 212(100). Anal. Found: C 43.49, H 3.59, N 4.25, Br 24.15. Calcd for $C_{12}H_{12}BrNO_5$: C 43.66, H 3.66, N 4.24, Br 24.20.

Ethyl 3-(4'-methoxy-2',3'-dimethylphenyl)-2-nitroacrylate (1i) : Yield 35%. A 4:9 mixture of *Z* and *E* isomer : Mp 75-76℃(dichloromethane-hexane). IR(KBr, cm^{-1}) : 1730 (ester CO), 1530, 1330 and 1305(NO_2). ^1H NMR (300MHz, $CDCl^3$, δ): *Z* isomer ; 1.36(3H, t, *J*=7.0Hz, CH_3), 2.16(3H, s, C_3-CH_3), 2.30(3H, C_2-CH_3), 3.82(3H, s, CH_3), 4.37(2H, q, *J*=7.0Hz, OCH_2), 6.69(1H, d, *J*=8.2Hz, H-5'), 7.18(1H, d, *J*=8.2Hz, H-6'), 7.82(1H, s, H-3); *E* isomer ; 1.30(3H, t, *J*=7.1Hz, CH_3), 2.18(3H, s, C_3-CH_3), 2.34(C_2-CH_3), 3.85(3H, s, CH_3), 4.36(2H, q, *J*=7.1Hz, CH_2), 6.72(1H, d, *J*=8.2Hz, H-5'), 7.28(1H, d, *J*=8.2Hz, H-6'), 8.38(1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ) : *Z* isomer ;11.8(C_3-CH_3), 14.0(ester CH_3), 16.4(C_2-CH_3), 55.5(CH_3O), 62.7(OCH_2), 108.2(C-5'), 121.1(C-1'), 126.1, 126.4(C-6'), 133.1(C-3), 138.2, 140.6(C-2), 160.0, 160.6; *E* isomer; 11.8(C_3-CH_3), 13.7(ester CH_3), 16.4(C_2-CH_3), 55.5(CH_3O), 62.7(OCH_2), 107.9(C-5'), 120.9(C-1'), 126.4, 127.6(C-6'), 136.4(C-3), 139.4, 141.1(C-2), 159.4, 161.5. MS(*m/z*, rel%) : 279(M^+, 100). HRMS : *m/z*, 279.1097 Calcd for $C_{14}H_{17}NO_5$: M, 279.1107.

Ethyl 3-(2',3',4'-trimethoxyphenyl)-2-nitroacrylate (1j) : Yield 78% (*E* :*Z* =1:1). *Z* isomer : Mp 69.5 ℃ (toluene-hexane). IR(KBr,cm^{-1}); 1720(ester CO), 1520 and 1380(NO_2) ^1H NMR(300MHz, $CDCl_3$, δ) : 1.35(3H, t, *J* =7.1Hz, CH_3), 3.85(3H, s, C_3-OCH_3), 3.89(3H, s, C_4-OCH_3), 3.95(3H, s, C_2-OCH_3), 4.36(2H, q, *J* =7.1Hz, CH_2), 6.65(1H, s, *J* =9.0Hz, H-5'), 7.09 (1H, s, *J* =9.0Hz, H-6'), 7.83(1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ) : 14.1(CH_3), 56.1(C_4-OCH_3), 60.9(C_3-OCH_3), 61.9(C_2-OCH_3), 62.7 (OCH_2), 107.8(C-5'), 116.0(C-1'), 124.0(C-6'), 127.8(C-3), 139.2(C-2), 142.0, 153.9, 157.3, 159.6 (COO). MS(m/z, rel%): 311(M^+, 100). HRMS:*m/z*, 311.1018, Calcd for $C_{14}H_{17}O_7N$: M, 311.1005. *E* isomer from the mixture of *E* and *Z* isomer : ^1H NMR (300MHz, $CDCl_3$, δ); 1.34(3H, t, *J* =7.0Hz, CH_3), 3.85(3H, s, C_3-CH_3O), 3.91(3H, s, C_2-CH_4O), 3.94(3H, s, C_2-OCH_3), 4.40(2H, q, *J* =7.0Hz, CH_2), 6.69(1H, s, *J* =8.0Hz, H-5'), 7.19 (1H, s, *J* =8.0Hz, H-6'), 8.30(1H, s, H-3) ^{13}C NMR(100MHz, $CDCl_3$, δ); 13.8(CH_3), 56.2(C_4-OCH_3), 60.9(C_3-OCH_3), 61.9(C_2-OCH_3), 62.7(OCH_2), 107.7(C-5'), 116.0(C-1'), 125.6(C-6'), 132.1(C-3), 140.9(C-2), 142.2, 154.3, 157.7, 161.7(COO).

Ethyl 3-(2',4',5'-trimethoxyphenyl)-2-nitroacrylate (1k) : Yield 46%(*E* :*Z* =1:7). *Z* isomer : Mp 93.4-94.8℃ (toluene-hexane). IR(KBr,cm^{-1}) : 1730(ester CO), 1520 and 1320(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ): 1.34(3H,

t, J =7.0Hz, CH_3), 3.77 (3H, s, C_5-CH_3O), 3.87 (3H, s, C_2-CH_3O), 3.93(3H, s, C_4-CH_3O), 4.35(2H, q, J =7.1Hz, CH_2), 6.47(1H, s, H-3'), 6.80 (1H, s, H-6'), 7.92(1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ): 14.1(CH_3), 56.1(C_4-CH_3O), 56.2(C_2-CH_3O),56.3(C_5-CH_3O), 62.5(OCH_2), 96.2(C-3'), 109.3 (C-1'), 110.6(C-6'), 127.3(C-3), 138.0(C-2), 143.4(C-5'), 154.1(C-4'), 155.1(C-2'), 160.0 (COO). MS(*m/z*, rel%) : 311(M^+, 100). Anal. Found : C 53.75, H 5.46, N 4.50. Calcd for $C_{14}H_{17}NO_7$: C 54.01, H 5.50, N 4.50. *E* isomer from the mixture of *E* and *Z* isomer : ^1H NMR (300MHz, $CDCl_3$, δ); 1.35(3H, t, J =7.0Hz, CH_3), 3.79(3H, s, C_5-CH_3O), 3.89(3H, s, C_2-CH_3O), 3.95(3H, s, C_4-CH_3O), 4.40(2H, q, J =7.1Hz, CH_2), 6.48(1H, s, H-3'), 6.96 (1H, s, H-6'), 8.47(1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ); 13.5(CH_3), 56.1(C_4-CH_3O), 56.3(C_2-CH_3O), 56.3(C_5-CH_3O), 62.7(OCH_2), 96.1(C-3'), 109.2(C-1'), 111.7(C-6'), 131.9(C-3), 139.4(C-2), 143.3(C-5'), 154.8(C-4'), 156.01(C-2'), 162.3(COO).

Ethyl 3-(2',6'-dichloro-4'-methoxyphenyl)-2-nitroacrylate (1l) : Yield 76%(*E* :*Z* =5:2). *Z* isomer : Mp 75.0℃ (toluene-hexane). IR(KBr, cm^{-1}) : 1730(ester CO), 1540 and 1370(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.39 (3H, t, J=7.0Hz, CH_3), 3.81(3H, s, CH_3O), 4.41(2H, q, J=7.0Hz, CH_2), 6.85(2H, s, H-3' and H-5'), 7.63(1H, s, H-3). ^{13}C NMR (100MHz, $CDCl_3$, δ); 14.0(CH_3), 55.9(CH_3O), 63.3(CH_2), 114.4(C-3' and C-5'), 120.5, 131.7(C-3), 134.7(C-2' and 6'), 145.1, 158.7, 161.0. HRMS : *m/z*, 320.9998/ 318.9995. Calcd for $C_{12}H_{11}NO_5Cl_2$: M+2/M, 320.9987/ 319.0014. *E* isomer : Mp 123-125 ℃(ethyl acetate -hexane). IR(KBr, cm^{-1}) : 1745(ester CO), 1540 and 1340(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ): 1.18(3H, t, J=7.0Hz, CH_3), 3.84(3H, s, CH_3O), 4.26(2H, q, J=7.0Hz, CH_2), 6.93(2H, s, H-3' and H-5'), 7.92(1H, s, H-3). ^{13}C NMR(100MHz, $CDCl_3$, δ) : 13.6(CH_3), 56.0(CH_3O), 62.8(CH_2), 114.4(C-3' and C-5'), 120.9, 134.0(C-3), 135.1(C-2' and 6'), 146.1, 159.1, 161.2. MS(*m/z*, rel%); 321/319(M^+, 6/9), 258/256(100/31). HRFABMS: *m/z*, 322.0047/ 320.0079 Calcd for $C_{12}H_{12}NO_5Cl_2$: MH^++2/MH^+, 322.0065/ 320.0093.

Ethyl 3-(4'-methoxy-1'-naphthyl)-2-nitroacrylate (1m) : Yield 66%(*E* :*Z* =1:7). *Z* isomer : Mp 92.5-93.0℃ (ethyl ether-petroleum ether). IR(KBr, cm^{-1}) : 1730(ester CO), 1540 and 1370(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.40(3H, t, J=7.1Hz, CH_3), 4.03(3H, s, CH_3O), 4.43(2H, q, J=7.1Hz, OCH_2), 6.80(1H, d, J=8.0Hz, H-3'), 7.56(1H, m, H-6'), 7.59(1H, dd, J=8.0 and 1.0Hz, H-2'), 7.64(1H, td, J=8.0 and 1.7Hz, H-7'), 7.95(1H, d, J=8.0Hz, H-8'), 8.27(1H, s, H-3), 8.33(1H, dd, J=8.0 and 1.5Hz, H-5'). ^{13}C NMR (100MHz, $CDCl_3$, δ) : 14.1(CH_3), 55.7(CH_3O), 62.9(OCH_2), 104.0(C-3'), 118.4(C-4a'), 122.8(C-8'), 122.9(C-5'), 125.5, 126.0(C-6'), 128.1(C-7'), 128.3(C-2'), 131.1(C-3), 132.5, 141.2(C-2), 158.6(COO), 159.4(C-4'). Anal. Found : C 63.56, H 4.97, N 4.58. Calcd for $C_{16}H_{15}NO_5$: C 63.78, H 5.02, N 4.65. *E* isomer : Mp 90.5-92.5℃(ethyl ether-petroleum ether). IR(KBr, cm^{-1}) : 1730(ester CO), 1520 and 1330(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.28(3H, t, J=7.1Hz, CH_3), 4.06(3H, s, CH_3O), 4.37(2H, q, J=7.1Hz, OCH_2), 6.83(1H, d, J=8.0Hz, H-3'), 7.57(1H, m, H-6'), 7.64(1H, m, H-7'), 7.69(1H, dd, J=8.0 and 1.0Hz, H-2'), 8.00(1H, d, J=8.0Hz, H-8'), 8.35(1H, dd, J=8.0 and 1.5Hz, H-5'), 8.72(1H, s, H-3). ^{13}C NMR (100 MHz, $CDCl_3$, δ) : 13.7(CH_3), 55.8(CH_3O), 62.8(OCH_2), 103.6(C-3'), 118.4(C-4a'), 123.0(C-8'), 123.0(C-5'), 125.6, 126.2(C-6'), 128.3(C-7'), 129.5(C-2'), 132.9, 134.6(C-3), 141.2(C-2), 159.3(COO), 161.5(C-4'). Anal. Found: C 64.05, H 5.07, N 4.79.

Ethyl 3-(10'-methoxy-9'-anthryl)-2-nitroacrylate (1n) : Yield 21%(*E* :*Z* =7:6). *Z* isomer : Mp 127.0-128.0 ℃(ethyl ether). IR(KBr, cm^{-1}) : 1720(ester CO), 1540 and 1370(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) : 1.35(3H, t, J=7.0Hz, CH_3), 4.16(3H, s, CH_3O), 4.51(2H, q, J=7.0Hz, OCH_2), 7.52(2H, dd, J=8.5 and 6.5Hz, H-3' and H-6'), 7.56(2H, m, H-2' and H-7'), 7.92-7.97(2H, m, H-1' and H-8'), 8.32-8.36(2H, m, H-4' and H-5'), 8.50(1H, s, H-3). ^{13}C NMR (100MHz, $CDCl_3$, δ) : 14.1(CH_3), 63.4(OCH_2), 63.6(CH_3O), 118.7(C-4a' and C-10a'), 123.0(C-4' and C-5'), 124.1(2C), 125.0(C-1' and C-8'), 125.5(C-3' and C-6'), 127.1(C-2' and C-7'), 129.7(C-9'), 134.6(C-3),

146.3(C-2), 154.7(C-10'), 158.6(COO). Anal. Found : C 68.37, H 4.88, N 3.99. Calcd for $C_{20}H_{17}NO_5$: C 68.30, H 4.85, N 3.86. *E* isomer : oil. IR(film, cm^{-1}) : 1740(ester CO), 1540 and 1335(NO_2). ^1H NMR(300MHz, $CDCl_3$, δ) :0.56(3H, t, *J*=7.1Hz, CH_3), 3.83(2H, q, *J*=7.0Hz, OCH_2), 4.18(3H, s, CH_3O), 7.54(2H, td, *J*=6.5 and 2.0Hz, H-3' and H-6'), 7.58(2H, td, *J*=6.5 and 2.0Hz, H-2' and H-7'), 7.95-8.01(2H, m, H-1' and H-8'), 8.35-8.39(2H, m, H-4' and H-5'), 8.91(1H, s, H-3). ^{13}C NMR (100MHz, $CDCl_3$, δ) : 12.9(CH_3), 62.3(OCH_2), 63.7(CH_3O), 119.1(C-4a' and C-10a'), 123.0(C-4' and C-5'), 124.1(2C), 124.9(C-1' and C-8'), 125.5(C-3' and C-6'), 127.3(C-2' and C-7'), 130.2(C-9'), 136.8(C-3), 146.5(C-2), 155.1(C-10'), 159.5(COO). Anal. Found : C 68.53, H 4.96, N 3.70.

General procedure for the synthesis of spiroisoxazolines (2)

Titanium tetrachloride(0.22 ml, 2 mmol) was added to a solution of **1a** - **1g**, **1j** - **1n** (1 mmol) in dichloromethane (20 ml) at 0 ℃. The reaction mixture was stirred during two hours. Water (20 ml) was added and resulting solution was exracted with dichloromethane (3 x 40 ml), washed with water (3 x 60 ml), dried oved Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (toluene→toluene: ethyl acetate 10:1 gradient) to give **2a** - **2g**, **2i** - **2n**. ^1H and ^{13}C NMR data for **2a** - **2g**, **2i** - **2l** is listed in Table 2 and 3.

Ethyl 4-chloro-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2a), and **Ethyl 4,2',4"'-trichloro-4',4"-dioxodispiro[isoxazole-5(4*H*),1'-3',2":5',6":6',3"-bicyclohexane-1",5"'(4"'*H*)-isoxazole]-3,3"'-dicarboxylate (5)**. (1)Reaction in 20 ml of dichloromethane : A solution of hexane and ethyl acetate (8:1) was added to the crude product obtained from **1a**. The precipitates were filtered to give **5** (76 mg, 28%). Evaporation of the filtrate gave a residue, which was chromatographed on silica gel(toluene: ethyl acetate 10:1) to give **1a** (10 mg, 4%) and **2a** (120 mg, 47%). (2)Reaction in 50 ml of dichloromethane: The crude product was chromatographed on silica gel(toluene: ethyl acetate 10:1) to give 2-hydroxy-4-methoxybenzaldehyde (**4a**) (18 mg, 12%), **1a** (31 mg, 12%) and **2a** (147 mg, 58%). **2a** : Mp 62.0-64.0℃. IR(KBr, cm^{-1}) : 1730 (ester CO), 1675(CO). MS(*m/z*, rel%) : 257/255(M^+, 0.8/2.1), 142/140(M^+-115, 34/100). Anal. Found : C 51.86, H 4.00, N 5.45, Cl 14.07, Calcd for $C_{11}H_{10}NO_4Cl$: C 51.68, H 3.64, N 5.48, Cl 13.87. **5** : Mp 206-210℃ (dichloromethane-methanol). ^1H NMR(400MHz, $CDCl_3$, δ) : 1.37 and 1.38(each 3H, t, *J*=7.0Hz, CH_3), 2.76(1H, dd, *J*=5.5 and 1.8Hz, H-3'), 2.77(1H, dd, *J*=18.8 and 1.8Hz, H-5"), 3.03(1H, ddd, *J*=6.5, 5.5 and 1.8Hz, H-2"), 3.15(1H, ddd, *J*=6.5, 4.0 and 1.8Hz, H-6"), 3.17(1H, d, *J*=6.5Hz, H-6'), 3.19(1H, d, *J*=6.5Hz, H-3"), 3.28(1H, dd, *J*=18.8 and 4.0Hz, H-5"), 3.38(1H, t, *J*=6.5Hz, H-5'), 4.39(2H, q, *J*=7.1Hz, OCH_2), 4.38 and 4.40(each 1H, dq, *J*=10.5 and 7.1Hz, OCH), 4.51(1H, d, *J*=1.8Hz, H-2'), 4.85(1H, s, H-4'"), 5.60(1H, s, H-4). ^{13}C NMR (100MHz , $CDCl_3$, δ) : 14.0(2 x CH_3), 37.0(C-6"), 38.2(C-5"), 40.9(C-3"), 41.4(C-6'), 41.6(C-2"), 45.1(C-5'), 50.8(C-3'), 59.8(C-4'"), 60.9(C-4), 62.0(C-2'), 63.0 and 63.3(OCH_2), 91.0(C-5), 91.7(C-5'"), 152.8(C-3), 154.4(C-3'"), 157.3 and 157.8(COO), 205.6(C-4'), 206.8(C-4"). FABMS : *m/z*, 573.0256/571.0207/569.0305 Calcd for $C_{22}H_{21}N_2O_8Cl_3Na$: MNa^++4/MNa^++2/MNa^+ 573.0214/ 571.0236/ 569.0261.

(4α,5β)-Ethyl 4-chloro-6-methoxy-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2b), and **4-chloro-8-methoxy-6-oxo-1-oxa-2-azaspiro[4,5]deca-2,7,9-triene-3-carboxylate (6b)**. The crude product was chromatographed on silica gel (toluene: ethyl acetate 10:1) to give **1b** (30 mg, 11%), **6b** (9 mg, 3%) and **2b** (153 mg, 54%). **2b** : Mp 113.0-113.5 ℃ (benzene-hexane). IR(KBr, cm^{-1}); 1725 (ester CO), 1670(CO). MS(*m/z*, rel%); 287/285(M^+, 4/12), 172/170(M^+-115, 34/100). Anal; Found C 50.43, H 4.19, N 4.76, Cl 12.29, Calcd for $C_{12}H_{12}NO_4Cl$ C 50.45, H 4.23, N 4.90, Cl 12.41. **6b** : oil. IR(film, cm^{-1}) : 1730 (ester CO), 1660(CO). MS(*m/z*, rel%) : 287/285(M^+, 1.9/7.0), 250(100), 172/170(M^+ -115, 12/34). HRFABMS : *m/z*, 288.0465/

286.0487, Calcd for $C_{12}H_{13}NO_5Cl$: MH^++2/MH^+, 288.0453/286.0482. ^1H NMR(400MHz, $CDCl_3$, δ) : 1.38(3H, t, *J*=7.0Hz, CH_3), 3.84(3H, s, OCH_3), 4.39(2H, q, *J*= 7.0Hz, OCH_2), 5.37(1H, d, *J*=2.0Hz, H-7), 5.51(1H, s, H-4), 6.35(1H, dd, *J*=10.0 and 2.0 Hz, H-9), 6.56 (1H, d, *J*=10.0Hz, H-10). ^{13}C NMR (100MHz , $CDCl_3$, δ) : 14.0(CH_3), 56.6(OCH_3), 62.7(OCH_2), 64.2 (C-4), 87.0 (C-5), 96.8(C-7), 127.1(C-9), 133.8(C-10), 150.7(C-3), 158.0(COO), 170.7(C-8), 192.4(CO).

(4α,5β)-Ethyl 4-chloro-6-methyl-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2c): Mp 86-87℃. IR(KBr, cm^{-1}) : 1735(ester CO), 1670(CO), 1640(CN). MS(*m/z*, rel%) : 271/269(M^+, 8/24), 156/154(M^+-115, 34/100). HRMS : *m/z*, 271.0427/269.0461 Calcd for $C_{12}H_{12}ClNO_4$: M+2/M, 271.0430/ 269.0455.

(4α,5β)-Ethyl 4,6-dichloro-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2d) : Mp 73.0-73.5 ℃(ethanol). IR(film, cm^{-1}) : 1730(ester CO), 1670(CO). MS(*m/z*, rel%) : 291/289(M^+, 17/25), 176/174(M^+-115, 77/100). HRMS : *m/z*, 292.9854/ 290.9880/ 288.9897, Calcd for $C_{11}H_9NO_4Cl_2$: M+4/M+2/M, 292.9857/ 290.9881/ 288.9909.

(4α,5β)-Ethyl 4-bromo-6-chloro-, 9-bromo-4,6-dichloro- and **4,9-dibromo-6-chloro-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2'd, 2d'** and **2'd')**, The crude product obtained from **1e** was chromatographed on silica gel (toluene: ethyl acetate 10:1) to give a mixture of **2d'** and **2'd'** (47.5 mg, 8% and 2%, respectively) and a mixture of **2d** and **2'd** (224 mg, 47% and 26%, respectively). **2'd** from the mixture of **2d** and **2'd** : MS(*m/z*, rel%); 337/335/333(M^+, 9/35/27), 222/220/218(M^+-115, 27/100/77). HRMS: *m/z*, 336.9326/ 334.9373/ 332.9407, Calcd for $C_{11}H_9NO_4BrCl$: M+4/M+2/M, 336.9358/ 334.9382/ 332.9403. **2d'**: MS(*m/z*, rel%) : 371/369/367(M^+, 9/21/13), 256/254/252(M^+-115, 45/100/ 59), HRMS : *m/z*, 370.8966/ 368.9027/ 366.9048, Calcd for $C_{11}H_8NO_4BrCl_2$: M+4/M+2/M, 370.8965/ 368.8990/ 366.9014 and **2'd'** : MS(*m/z*, rel%): 415/413/411(M^+, 11/15/8), 300/298/296(M^+-115, 69/100/43). HRMS: *m/z*, 414.8445/ 412.8465/ 410.8522, Calcd for $C_{11}H_8NO_4Br_2Cl$: M+4/M+2/M, 414.8466/ 412.8487/ 410.8509.

(4α,5β)-Ethyl 4-chloro-7-methyl-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2f) and **(*E*)-Ethyl 3-chloro-3-(2'-chloro-4'-methoxy-5'-methylphenyl)-2-hydroxyiminopropionate (3f)**. A solution of hexane and ethyl acetate (8:1) was added to the crude product obtained from **1f**. The precipitates were filtered to give **3f** (74 mg, 24%). Evaporation of the filtrate gave a residue, which was chromatographed on silica gel (toluene:ethyl acetate 10:1) to give **2f** (113 mg, 42%), and 2-hydroxy-4-methoxy-5-methylbenzaldehyde (**4f**)(23 mg, 14%). **2f** : oil. IR(film, cm^{-1}) : 1735(ester CO), 1680(CO), 1655(CN). MS(*m/z*, rel%); 271/269(M^+, 2/5), 156/154(M^+-115, 35/100). HRMS : *m/z*, 271.0438/269.0485, Calcd for $C_{12}H_{12}ClNO_4$: M+2/M, 271.0426/ 269.0455. **3f** : Mp 125.0-125.5℃(ethyl acetate-hexane). ^1H NMR (400MHz, $CDCl_3$, δ) : 1.29(3H, t, *J*=7.1Hz, ester CH_3), 2.21(3H, s, C_7-CH_3), 3.81(3H, s, OCH_3), 4.25 and 4.29(each 1H, dq, *J*=10.5 and 7.1Hz, OCH), 6.60(1H, s, H-3), 6.76(1H, s, H-3'), 7.73(1H, brs, H-6'), 9.88(1H, brs, OH). ^{13}CNMR(100MHz, $CDCl_3$, δ) : 13.9(ester CH_3), 16.0(C_5-CH_3), 47.9(C-3), 55.6(OCH_3), 62.2(ester OCH_2), 110.6(C-3'), 124.6(C-1'), 125.6(C-5'), 130.1(C-2'), 132.3(C-6'), 148.4(C-2), 158.2(C-4'), 161.1(COO). IR(KBr, cm^{-1}) ; 3280(OH), 1745(ester CO), 1610(C=N). MS(*m/z*, rel%) : 321/ 319(M^+, 21/27), 286/284 (69/100). HRFABMS : *m/z*, 321.0365/ 319.0372, Calcd for $C_{13}H_{15}NO_4Cl_2$: M+2/M, 321.0351/ 319.0378.

(4α,5β)-Ethyl 7-bromo-4-chloro-8-oxo-1-oxa-2-azaspiro[4,5]-2,6,9-triene-3-carboxylate (2g) and **(*E*)-Ethyl 3-chloro-3-(5'-bromo-2'-chloro-4'-methoxyphenyl)-2-hydroxyiminopropionate (3g)**. The same

procedure as for **1f**, afforded **2g** (37 mg, 11 %), **3g** (239.5mg, 62%) and 5-bromo-2-hydroxy-4-methoxybenzaldehyde (**4g**)(39 mg, 17%). **2g**: oil. IR(film, cm^{-1}) : 1730(ester CO), 1680(CO). MS(*m/z*, rel%); 335/333(M^+, 2/5), 220/218(M^+-115, 73/100). HRFABMS : *m/z*, 359.9295/357.9279/355.9314, Calcd for $C_{11}H_9NO_4BrClNa$: MNa^++4/ MNa^++2/ MNa^+, 359.9251/ 357.9281/ 355.9301. **3g** : Mp 119.0-120.0℃(ethyl acetate-hexane). ^1H NMR (400MHz, $CDCl_3$, δ) : 1.31(3H, t, *J*=7.1Hz, ester CH_3), 3.89(3H, s, OCH_3), 4.26 and 4.30(each 1H, dq, *J*=3.5 and 7.1Hz, OCH), 6.55(1H, s, H-3), 6.84(1H, s, H-3'), 8.16(1H, s, H-6'). ^{13}C NMR (100MHz, $CDCl_3$, δ) : 13.9(ester CH_3), 47.1(C-3), 56.6(OCH_3), 62.4 (ester OCH_2), 110.1(C-5'), 112.3(C-3'), 126.8(C-1'), 131.9(C-2'), 135.2(C-6'), 147.6(C-2), 156.3(C-4'), 160.9(COO). IR(KBr, cm^{-1}) : 3300(OH), 1740 (ester CO). MS(*m/z*, rel%) : 387/ 385/ 383 (M^+, 0.8/1.5/ 0.6), 250/248(100/95). Anal. Found : C 37.44, H 3.17, N 3.64, Br 20.64, Cl 18.71, Calcd for $C_{12}H_{12}NO_4BrCl_2$: C 37.43, H 3.14, N 3.64, Br 20.75, Cl 18.41.

Ethyl 3-chloro-3-(2'-chloro-4',5'-dimethoxyphenyl)-2-hydroxyiminopropionate (3h). The same procedure as for **1f**, afforded **3h**, 2-hydroxy-4,5-dimethoxybenzaldehyde (**4h**)(77mg, 44%) and **1h** (36mg, 13%). **3h** could not be isolated. **3h** in the crude product : ^1H NMR(400MHz, $CDCl_3$, δ); 1.28(3H, t, *J*=7.1Hz, CH_3), 3.85(3H, s, C_5-OCH_3), 3.91(3H, s, C_4-OCH_3), 4.24 and 4.28(each 1H, dq, *J*=10.5 and 7.1Hz, OCH), 6.62(1H, s, H-3), 6.89(1H, s, H-3'), 7.55(1H, s, H-6'). ^{13}C NMR(100MHz, $CDCl_3$, δ); 13.9(ester CH_3), 48.1(C-3), 56.1(2 x OCH_3), 62.1(ester OCH_2), 111.8(C-3'), 113.4(C-6'), 123.8(C-1'), 125.3(C-2'), 147.7(C-4'), 148.4(C-2), 149.6(C-4'), 161.2(COO). HRFABMS : *m/z*, 337.0304/ 335.0349, Calcd for $C_{13}H_{15}NO_5Cl_2$: M+2/M, 337.0300/ 335.0327.

(4α,5β)-Ethyl 4-chloro-6,7-dimethyl-8-oxo-1-oxa-2azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2i) : Mp 77.5-78.0 ℃ (dichloromethane-hexane). IR (film, cm^{-1}); 1730 (esterCO), 1675(CO) . MS(*m/z*, rel%): 285/ 283(M^+, 4/12), 170/168(M^+-115, 35/100). HRMS : *m/z*, 285.0592/283.0592, Calcd for $C_{13}H_{14}NO_5Cl$: M+2/M, 285.0587/ 283.0611.

(4α,5β)-Ethyl 4-chloro-6,7-dimethoxy-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2j) : Mp 67.5-69.0℃(dichloromethane-hexane). IR(KBr, cm^{-1}) : 1730 (ester CO), 1675(CO). MS(*m/z*, rel%) : 317 /315(M^+, 17/46), 202/200(M^+-115, 35/100). HRMS : *m/z*, 317.0477/315.0513, Calcd for $C_{13}H_{14}NO_6Cl$: M+2/M, 317.0486/ 315.0510.

(4α,5β)-Ethyl 4-chloro-6,9-dimethoxy-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2k): Mp 130.0-131.0℃(dichloromethane-hexane). IR(KBr, cm^{-1}) :1720 (ester CO), 1680(CO). FABMS (*m/z*, rel%) : 318/316(MH^+, 31/88), 203/201(MH^+-115, 34/100). HRFABMS : *m/z*, 318.0567/ 316.0583, Calcd for $C_{13}H_{15}NO_6Cl$: MH^++2/MH^+, 318.0559/ 316.0597.

(4α,5β)-Ethyl 4,6,10-trichloro- and 4,6,7,10-tetrachloro-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2l and 2l') and **Ethyl 5-chloro-4-hydroxy-7-methoxy-4*H*-1,2-benzoxazine-3-carboxylat (10l)**. The crude product obtained from **1l** was chromatographed on silica gel (toluene: ethyl acetate 10:1) to give **1l** (57 mg, 18%), **2l'** (42 mg, 12%), **2l** (116mg, 36%) and **10l** (50 mg, 17%). **2l** : Mp 112.0℃(ethyl ether - hexane). IR(KBr, cm^{-1}) : 1725 (ester CO), 1665(CO), 1590(CN). MS(*m/z*, rel%) : 327/325/323(M^+, 32/91/93), 21/216(66/100), 212/210/208(M^+-115, 36/76/84). HRMS : *m/z*, 326.9446/ 324.9535/ 322.9538, Calcd for $C_{11}H_8NO_4Cl_3$: M+4/M+2/M, 326.9464/ 324.9491/ 322.9519. **2l'** : Mp 141.0-142.0℃(ethyl ether - hexane). IR (KBr, cm^{-1}) : 1735 (ester CO), 1680(CO), 1590(CN). MS(*m/z*, rel%) : 361/359/357(M^+, 39/80/62), 246/244/242 (M^+-115, 49/ 100/78). HRMS: *m/z*, 360.9106/358.9127/ 356.9127, Calcd for $C_{11}H_7NO_4Cl_4$: M+4/M+2/M,

360.9173/ 358.9101/ 356.9129 . **10l** : Mp 130 - 131℃(ethyl acetate-hexane). ^{1}H NMR(δ, $CDCl_3$, 400Hz) : 1.43 (3H, t, *J*= 7.0Hz), 3.12(1H, dd, *J*=5.0 and 0.5Hz, OH), 3.82(3H, s, CH_3O), 4.46(2H, q, *J*=7.0Hz, OCH_2), 5.75(1H, d, *J*= 5.0Hz, H-4), 6.64(1H, d, *J*=2.5Hz, H-8), 6.87(1H, *J*=2.3 and 0.5Hz, H-6). ^{13}C NMR(δ, $CDCl_3$, 100Mz) : 14.1 (CH_3), 52.2(C-4), 55.9(CH_3O), 62.9(OCH_2), 97.5(C-8), 108.0(C-4a), 113.9(C-6), 135.1(C-5), 148.5(C-3), 154.1(C-8a), 160.7(C-7), 162.8(COO). IR(KBr, cm^{-1}) : 3480 and 3440(OH), 1710(COO). MS(*m/z*, rel%) : 287/285(M^+, 8/21), 185(100). HRMS : *m/z*, 287.0375/285.0382, Calcd for $C_{12}H_{12}NO_5Cl$: M+2/M, 287.0379/ 285.0404. **10l** was determined by IR, HRMS and NMR. 4*H*-1,2-benzoxazines have been obtained by the acid-catalyzed reactions of nitro olefin with benzene,[18] the ring transformation of 4-aryl-2-isoxazoline 2-oxides,[19] and the reaction of *m*-methoxyphenyl nitroacrylate with toluene in the presence of titanium tetrachloride.[3]

(4α,5β)-Ethyl 4-chloro-4'-oxospiro[isoxazole-(4*H*)5,1'(4'*H*)-naphthalene]-3-carboxylate (2m) : Mp 112.0 -113.0℃(ethyl ether-petroleum ether). ^{1}H NMR (400MHz, CDCl, δ) : 1.43(3H, t, *J*=7.1Hz, ester CH_3), 4.45 (2H, q, *J*= 7.1Hz, OCH_2), 5.46(1H, s, H-4), 6.60(1H, d, *J*=10.0Hz, H-3'), 7.13(1H, d, *J*=10.5Hz, H-2'), 7.25(1H, dd, *J*=7.5 and 1.2Hz, H-8'), 7.56(1H, td, *J*=7.5 and 1.2Hz, H-6'), 7.62(1H, td, *J*=7.5 and 1.2Hz, H-7'), 8.14(1H, dd, *J*=7.5 and 1.2Hz, H-5'). ^{13}C NMR (100MHz, CDCl, δ) : 14.1(ester CH_3), 63.1(OCH_2), 67.8(C-4), 87.3(C-5), 124.4(C-8'), 127.4(C-5'), 129.1(C-4a'), 130.1(C-6'), 130.8(C-3'), 134.1(C-7'), 139.5(C-8a'), 141.5(C-2'), 151.1(C-3), 158.2(COO), 183.0(C-4'). IR(KBr, cm^{-1}) : 1730(ester CO), 1675(CO). MS(*m/z*, rel%) : 307/305(M^+, 17/42), 192/190(M^+-115, 34/100). Anal. Found : C 59.09, H 3.93, N 4.68, Cl 11.39, Calcd for $C_{15}H_{12}NO_4Cl$: C 58.93, H 3.96, N 4.58, Cl 11.60. The stereochemistry was determined by NOE experiments (H-4 and H-8', 5%).

Ethyl 4'-chloro-2',10-dioxospiro[anthracene-(10*H*)9,5'(4'*H*)-isoxazole]-3-carboxylate (7n), and **Ethyl 2-nitro-3-(10'-oxo-9'-anthrylidene) propionate (8n)** . Titanium tetrachloride (0.22 ml, 2 mmol) was added to a solution of **1n** (351 mg, 1 mmol) in dichloromethane (10 ml) at 0℃. Ethyl ether was added to the crude product and the precipitate was filtered to give **8n** (48 mg, 14%). Evaporation of the filtrate gave a residue, which was chromatographed on silica gel (toluene) to give **1n** (98 mg, 28%), and **7n** (78 mg, 21%). **7n** : Mp 166.5-168.0 ℃ (dichloromethane-hexane). IR(KBr, cm^{-1}): 1740(ester CO), 1670(CO). 1635(CN), FABMS(*m/z*, rel%) : 374/372(MH^+, 0.8/2.1), 208(76), 165/163 (CHClC(NO)COOEt, 34/100). HRFABMS : *m/z*, 374.0641/ 372.0637 Calcd for $C_{19}H_{15}NO_5Cl$: MH^++2/MH^+, 374.0609/ 372.0639. ^{1}H and ^{13}C NMR data is listed Table 4.

The structure of **7n** was determined by comparison of the NMR spectra of **2n** and **7n** as showed in Table 4. The ^{13}C NMR spectrum of **7n** lacked the signal for C-3'(δ 150.6 ppm) found in **2n** and displayed an additional signal at δ 108.7 ppm. The characteristic ^{13}C signal(δ 108.7 ppm) agreed with the value reported[9] for C-3 of an isoxazoline *N*-oxide ring. The ^{1}H NMR signals for *peri* protons(H-1, H-8) to isoxazoline *N*-oxide ring in **7n** were deshielded by 0.18-0.19 ppm in comparison with those in **2n**. Since all the other ^{1}H and ^{13}C signals showed virtually identical chemical shifts and patterns with those for **2n**, these supported the structure of spiroisoxazoline *N*-oxide.

Table 4 ^{1}H and ^{13}C NMR (δ, $CDCl_3$)data

	2n		**7n**	
3'	150.6	-	108.7	-
4'	68.5	5.24	70.0	5.41
5'	91.2	-	81.9	-
1	128.1	7.71	127.5	7.89
2	132.8	7.70	132.8	7.72
3	129.9	7.60	130.0	7.62
4	127.4	8.24	127.8	8.24
4a	131.1	-	131.3	-
10	182.4	-	182.8	-
10a	130.1	-	130.2	-
5	128.6	8.28	129.0	8.28
6	129.8	7.58	130.0	7.61
7	134.0	7.64	134.0	7.69
8	123.7	7.39	122.8	7.58
8a	140.1	-	140.2	-
9a	136.8	-	136.4	-

8n : Mp 134.5-135.5℃(benzene-hexane). IR(KBr, cm^{-1}) : 1760(ester CO), 1665(CO), 1565 and 1380 (NO_2). ^1H NMR (400MHz, CDCl, δ): 1.36(3H, t, *J*=7.1Hz, ester CH_3), 4.36 and 4.40(2H, dq, *J*= 10.5 and 7.1Hz, OCH_2), 6.26(1H, d, *J*=10.7Hz, H-2'), 6.70(1H, d, *J*=10.7Hz, H-3), 7.57(1H, td, *J*=7.5 and 1.1Hz, H-6'), 7.64(1H, td, *J*=7.5 and 1.5Hz, H-3'), 7.68(1H, td, *J*=7.5 and 1.8Hz, H-7'), 7.74(1H, dd, *J*=8.0 and 1.5Hz, H-1'), 7.87(1H, d, *J*=8.0Hz, H-8'), 8.23(1H, dd, *J*=8.0 and 1.2Hz, H-5'), 8.32(1H, dd, *J*=7.5 and 1.2Hz, H-4'). ^{13}C NMR (100MHz, CDCl, δ) : 13.9(ester CH_3), 63.9(OCH_2), 86.5(C-2), 119.0(C-3), 124.1(C-8'), 127.0(C-1'), 127.2(C-5'), 128.2(C-4'), 129.4(C-6'), 130.0(C-3'), 130.8(C-10a'), 132.4(C-4a'), 132.6(C-2'), 133.4(C-7'), 134.7(C-8a'), 139.3(C-9'), 140.9(C-9'), 163.4 (COO), 183.0(C-10'). HRHABMS : *m/z*, 336.0905, Calcd for $C_{19}H_{13}NO_5$: MH^+, 336.0872

Ethyl 4'-chloro-10-oxospiro[anthracene-(10*H*)9,5'(4'*H*)-isoxazole]-3-carboxylate (2n). Titanium tetrachlo ride (0.22 ml, 2 mmol) was added to a solution of **1n** (351 mg, 1 mmol) in dichloromethane (10 ml) at 0℃. The reaction mixture was stirred at room temperature during 3 hours. **1n**, **2n** and **7n** were isolated in 26%, 21% and 6%. **2n** : Mp 149.0-153.0(dichloromethane-hexane). IR(KBr, cm^{-1}) :1730(ester CO), 1670(CO). MS(*m/z*, rel%) : 357/355(M^+, 8/23), 242/240(M^+-115, 25/72), 208(100). Anal. Found : C 64.15, H 3.96, N 3.82, Cl 9.92, Calcd for $C_{19}H_{14}NO_4Cl$: C 64.14, H 3 .97, N 3.94, Cl 9.96. ^1H and ^{13}CNMR data is listed Table 4. An 1% NOE was obtained between H-4' and H-8.

The reaction of ethyl 3-aryl-2-nitroacrylate with titanium tetrabromide

(4α,5β)-Ethyl 4,7-dibromo-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2'a'), and **Ehyl 3-(2'-bromo-4'-methoxypheny, 3'-bromo-4'-methoxyphenyl and 4'-methoxyphenyl)-3-hydroxy-2-hydroxyiminopropionates (3'aa, 3'a' and 3'a)**. Titanium tetrabromide (0.74 mg, 2 mmol) was added to a solution of **1a** (251 mg, 1 mmol) in dichloromethane (20 ml) at 0℃. The reaction mixture was stirred for 2 hours. Water(20 ml) was added and the resulting solution was extracted with dichloromethane (3 x 40 ml), washed with water (4 x 60 ml) , dried over Na_2SO_4, and evaporated. The residue was chromatographed (hexane: ethyl acetate 10:1→1:1 gradient) to give 78 mg(21% yield) of **2'a'** and 103 mg mixture of oximes (**3'aa**: **3'a'**: **3'a** = 7:6:7). **2'a'**: oil. IR(KBr, cm^{-1}) : 1740 (ester CO), 1690(CO). MS(*m/z*, rel%) : 381/379/377(M^+, 0.7/1.1/0.5), 266/264/262 (M^+-115, 26/55/27), 152/150 (100/94). HRFABMS : *m/z*, 381.8940/ 379.8947/ 377.8997, Calcd for $C_{11}H_{10}NO_4Br_2$: MH^++4/ MH^++2/ MH^+, 381.8935/ 379.8956/ 377.8977. the mixture of **3'aa** **3'a'** and **3a** : ^1H NMR(400MHz, $CDCl_3$, δ) : 1.31, 1.32 and 1.32(3H, t, *J*=7.1Hz, ester CH_3), 4.22-4.34(3 x OCH_2), 3.78 and 3.79(each 3H, s, OCH_3), 3.87(3H, s, OCH_3 of **3'aa**), **3'aa**; 6.24(1H, s, H-3), 6.86(1H, dd, *J*=8.5 and 2.5Hz, H-5'), 7.12(1H, d, *J*=2.5Hz, H-3'), 7.39(1H, d, *J*=8.5Hz, H-6'), **3'a'**; 6.10(1H, s, H-3), 6.83(1H, dd, *J*=8.5 and 2.5Hz, H-5'), 7.32(1H, ddd, *J*=8.8, 2.5 and 0.8Hz, H-6'), 7.61(1H, dd, *J*=2.5 and 0.8Hz, H-2'), **3'a**; 6.12(1H, s, H-3), 6.88(2H, d, *J*=8.8Hz, H-3' and H-5'), 7.34 (2H, d, *J*=8.8Hz, H-2' and H-6'). ^{13}C NMR(100MHz, $CDCl_3$, δ): 13.8 , 13.9 and 13.9(ester CH_3), 62.3, 62.4 and 62.4(ester OCH_2), 55.2 and 55.5(OCH_3), 56.3(OCH_3 of **3'a'**), 163.0, 163.1 and 163.2 (COO), **3'aa**; 68.4(C-3), 113.5(C-5'), 118.4(C-3'), 123.9(C-2'), 126.0(C-6'), 130.7(C-1'), 151.7(C-2), 159.9 (C-4'), **3'a'**; 67.0(C-3), 110.7(C-3'), 111.8(C-5'), 125.9(C-6'), 130.8(C-2'), 133.1(C-1'), 151.1(C-2), 155.5(C-4'), **3'a**; 67.8(C-3), 114.0(C-3' and C-5'), 127.1(C-2' and C-6'), 131.5(C-1'), 151.5(C-2), 159.3(C-4'). HRFABMS : **3'aa** and **3'a'** *m/z*, 331.9992/ 329.9957, Calcd for $C_{12}H_{13}NO_5Br$: MH^++2/MH^+ 331.9958/ 329.9977, **3'a** *m/z*, 252.0864, Calcd for $C_{12}H_{14}NO_5$: MH^+, 252.0872.

(4α,5β)-Ethyl 4,6-dibromo- and 4,6,9-tribromo-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (2'e and 2'e'). The crude product obtained from **1e** (330 mg 1 mmol) in a similar way as described above

for **1a** was chromatographed (toluene) to give **2'e'**(54 mg, 12%), and **2'e** (14.6mg, 4%) and 5-bromo-2-hydroxy-4-methoxybenzaldehyde (**4g**) (53.6 mg, 23%). **2'e** : oil. IR(KBr, cm^{-1}) : 1730(ester CO), 1670(CO). MS(*m/z*, rel%) : 381/379/377(M^+, 20/38/20), 266/264/262(M^+-115, 63/100/50). HRMS: *m/z*, 381.8940/ 379.8963/ 377.98998, Calcd for $C_{11}H_{10}NO_4Br_2$: MH^++4/MH^++2/ MH^+, 381.8938/ 379.8957/ 377.8977.
2'e': Mp 102.5-103.0℃(dichloromethane-hexane). IR(KBr, cm^{-1}) : 1725(ester CO), 1680(CO). MS(*m/z*, rel%): 459/457/455 (M^+, 13/13/5), 346/344/342/340(M^+-115, 33/100/95/33). HRMS : *m/z*, 458.7972/ 456.7981. Calcd for $C_{11}H_8NO_4Br_3$: M+4/M+2, 458.7964/ 456.7983.

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