Tetrahedron Vol. 43, No. 17, pp. 4007 to 4014, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

PSEUDOESTERS AND DERIVATIVES. XXVI.[1] FORMATION OF CYCLOPROPANES AND FIVE MEMBERED HETEROCYCLES BY MICHAEL INITIATED RING CLOSURE REACTIONS OF 2-BROMO-3-FORMYLACRYLIC ACID DERIVATIVES

Francisco Fariña[a], M. Carmen Maestro[b], M. Victoria Martín[a] and M. Luisa Soria[a]

[a]*Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3. 28006 Madrid, Spain.*

[b]*Departamento de Química Orgánica, Universidad Autónoma de Madrid, Canto Blanco, 28049 Madrid, Spain.*

(*Received in UK 6 July* 1987)

Abstract– The reaction of 3-bromo-5-methoxyfuran-2(5*H*)-one (**1**) with the stabilized carbanions derived from **2a-d**, in a solid-liquid two-phase system in the presence of potassium carbonate and tetrabutylammonium bromide, affords the cyclopropane lactones **5a-d**. With the ambident anions generated from **2e** and **2f**, the fused heterocyclic compounds **10** and **11**, respectively, are obtained. The reaction of methyl 2-bromo-4,4-dimethoxy-2-butenoates (**7, 8**) with **2b-f**, under similar conditions, gives rise to mixtures of the functionalized cyclopropanes **12b-f** and **13b-f** as mixtures of diastereoisomers; dihydrofurans **14** and **15** are also formed as minor components using ethyl acetoacetate (**2f**) as nucleophile.

INTRODUCTION

Previous results from our laboratory[2,3,4] have shown that 3-bromo-5-methoxyfuran-2(5*H*)-one (**1**), a cyclic pseudoester of 2-bromo-3-formylacrylic acid, behaves as an excellent Michael acceptor towards several carbon, oxygen, nitrogen and sulphur nucleophiles. Recently we have also reported[5] that bromofuranone **1** reacts with different nucleophiles in acetonitrile, in a solid-liquid two-phase system, in the presence of potassium carbonate and a phase transfer catalyst, to give cyclopropane bis-lactones of the type **6** by addition of the initial enolate anion to a second bromofuranone molecule followed by ring closure.

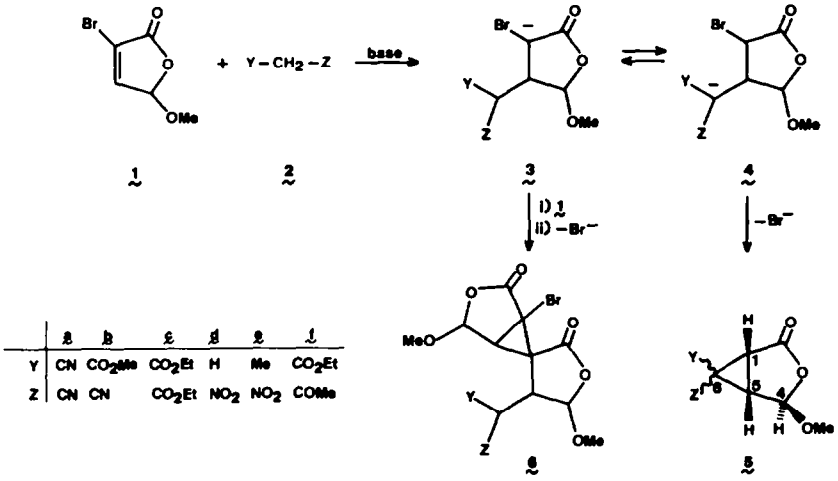
However, when diethyl malonate anion (**2c**) was used as nucleophile, the cyclopropane bis-lactone **6c** was accompanied by minor amounts of the cyclopropane lactone **5c** (Scheme 1). This is presumably due to the presence of an acidic methine proton in the enolate anion **3**, which favours the equilibrium with the carbanionic intermediate **4**, readily converted to the cyclopropane lactone **5c** by intramolecular nucleophilic substitution of the halogen[5]. Compounds of the type **5** as derivatives of caronic acid, are expected to be versatile precursors of chrysanthemic acids used as starting materials for the synthesis of pyrethroids[6].

The present investigation was aimed at extending the study to conjugate additions of carbanions from several methylene derivatives of the type **2** to bromofuranone **1**, which might afford carbanionic intermediates **4**, readily converted to cyclopropane lactones **5** by intramolecular nucleophilic substitution. Furthermore, we have also studied similar reactions using as substrates open-chain derivatives of the type **7** and **8**, which would afford functionalized cyclopropane derivatives with different stereochemistry. Related reactions have been termed Michael initiated ring closure (MIRC) reactions by Little[7] and offer an efficient route for the construction of several carbocycles.

RESULTS AND DISCUSSION

The reactions of the bromofuranone **1** with the nucleophiles **2a-f** (Scheme 1) were conducted under the above mentioned conditions in a solid-liquid two-phase system[8] in the presence of tetra-n-butyl-

Scheme 1



	a	b	c	d	e	f
Y	CN	CO_2Me	CO_2Et	H	Me	CO_2Et
Z	CN	CN	CO_2Et	NO_2	NO_2	COMe

ammonium bromide as a catalyst, using an appropriate base, such as potassium carbonate, which would not alter the functional groups of the substrate. The results are summarized in Table I.

TABLE I

Reaction of 3-bromo-5-methoxyfuran-2(5*H*)-one (**1**) with nucleophiles **2a-f**

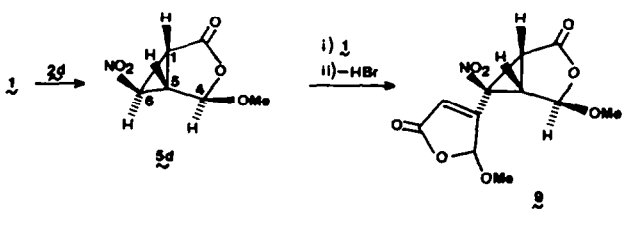
Nucleophile	Temp., °C	Time, h	Products	Yield, %[a]
2a	0	7	**5a**	36
2b	0	7	**5b**	48
2c	r.t.	5	**5c**[b], **6c**[b]	24 , 62
2d	r.t.	30	**5d**[c]	17
2e	r.t.	5	**10**	46[d]
2f	r.t.	6	**11**	45

[a] *Isolated yield.* [b] *From reference*[5]. [c] *A small amount of compound* **9** *was also formed.* [d] *Isolated yield with respect to furanone* **1** *consumed.*

Treatment of bromofuranone **1** with malononitrile (**2a**) or methyl cyanoacetate (**2b**) in acetonitrile at 0°C, in the presence of potassium carbonate and tetra-n-butylammonium bromide, afforded the cyclopropane lactones **5a** and **5b**, respectively, as the sole products. By contrast, as stated above, the reaction with diethyl malonate (**2c**) under similar conditions, provided a mixture of the cyclopropane lactone **5c** and the bis-lactone **6c**, the latter being the major component. These results can be rationalized in terms of acidity of the methine protons in the carbanionic intermediate **3**. Thus, the methine protons of **3a** and **3b** are expected[9] to be more acidic than that of **3c** and the equilibrium in those cases favours the carbanions **4a** and **4b**, which give rise to the cyclopropane lactones **5a** and **5b**.

In a similar manner, bromofuranone **1** reacted with nitromethane (**2d**), under the above conditions, to afford the cyclopropane lactone **5d** as the main product (Scheme 2)[10], although in poor yield. The structure of the bicyclic compound **5d**, with an *exo* arrangement of both nitro and methoxy groups, was supported by the ^{1}H-NMR spectrum. In fact, from the magnitude of the coupling constants $J_{1,6}$ = 2.1 Hz and $J_{5,6}$ = 1.7 Hz a *trans* relationship of the corresponding protons is deduced; furthermore, the absence of a coupling between H-4 and H-5 also suggests a *trans* arrangement, thus indica-

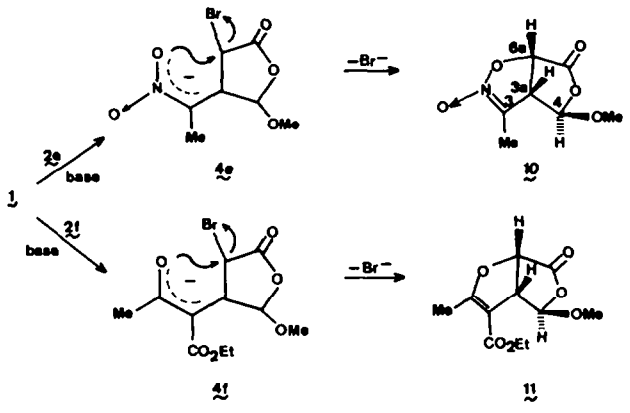
Scheme 2



ting that the initial carbanion attacks from the side opposite to the methoxy group.

From the reaction mixture of **1** with nitromethane, a small amount of a side product was also isolated by chromatography. On the basis of the spectral data it was identified as the bis-lactone **9**, presumably originated by Michael addition of the carbanion from **5d** to the starting bromofuranone **1** followed by dehydrohalogenation.

Scheme 3



Unlike malonic acid derivatives, ethyl acetoacetate (**2f**) did not promote formation of a cyclopropane derivative with bromofuranone **1**. The initial Michael addition occurred normally to give the ambident anion **4f**, but the subsequent ring closure took place on oxygen instead of carbon to yield **11** (Scheme 3), with a new furan ring fused to the initial furanone ring[11]. Nitroethane (**2e**) showed a similar behaviour and the ambident anion **4e**, originated after the conjugate addition to **1**, preferred to undergo intramolecular *O*-alkylation to give the furoisoxazol derivative **10**, in which a new five membered heterocycle is fused to the initial furanone ring[12].

These results broaden the scope of the MIRC-type reactions[7] to the formation of five membered heterocycles by intramolecular ring closure through a heteroatom of an ambident anion originated after the initial Michael addition.

The structures of compounds **10** and **11** have been established on the basis of their IR and NMR spectra. The IR spectra of compounds **10** and **11** showed lactone carbonyl maxima at 1810 and 1790-1805 cm^{-1}, respectively, while the characteristic absorption of the cyclopropane ring was absent; furthermore, in compound **10** lacked also the characteristic band of a nitro group.

The ^{1}H-NMR spectrum of **10** was especially informative. Key features in this regard are: (i) an acetal type proton (singlet at δ 5.47) and a MeO group (δ 3.55), which confirmed the presence of a methoxyfuranone unit; (ii) a doublet (at δ 5.20) assignable to the proton on C-6a coupled (J = 9.0 Hz) to the H-3a proton (δ 4.11); (iii) the long-range coupling (J = 1.9 Hz) between the latter proton and the C-3 methyl protons; (iv) the absence of a coupling between H-4 and H-3a, that would indicate a *trans* relationship. It therefore follows that the initial attack of the carbanion occurs from the side opposite to the OMe group. Analogous data for compound **11** were similarly consistent with the assigned structure.

The ^{13}C-NMR spectra provided further support for these structural assignments. Thus, compound **10** shows signals at 108.3, 53.8, and 69.7 ppm, attributable to C-3, C-3a, and C-6a of the furoisoxazol framework. Similarly, in compound **11** the presence of the furofuran system is confirmed by the signals at 101.9, 51.2, and 78.0 and the absence of a ketone carbonyl carbon around 200 ppm.

We have also studied the behaviour of methyl (*E*)- and (*Z*)-2-bromo-4,4-dimethoxy-2-butenoates (**7** and **8**)[13] as substrates towards the carbon nucleophiles **2a-f** under relatively mild conditions similar to those used for bromofuranone **1**. We have found, however, that the results of the reaction with diethyl malonate are not dependent upon the stereochemistry of the substrate, presumably due to a prior rapid *E* → *Z* isomerization. In fact, we have shown that this isomerization also occurs when the *E*-isomer is treated under similar conditions in absence of the nucleophile. Therefore all the reactions have been carried out with the more readily available *E*-isomer **7**.

The reaction of the acetal **7** with the nucleophiles **2b-f**[14] afforded mixtures of the cyclopropane derivatives **12** and **13** (Scheme 4), in which the ester and acetal groups from the substrate appear in a *cis* or *trans* disposition, respectively. The results of these reactions are summarized in Table II.

The stereochemistry of **12** and **13** has been inferred from the magnitude of the coupling constants $J_{1,2}$ (*ca.* 10-11 Hz for a *cis* and 7-8 Hz for a *trans* arrangement).

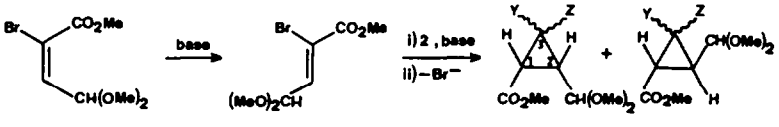
TABLE II

Reaction of methyl (E)-2-bromo-4,4-dimethoxy-2-butenoate (**7**) with nucleophiles **2b-f**

Nucleophile	Temp., °C	Time, h	Products (ratio)[b]	Yield, %[a]
2b	60	96	**12b** (67) **13b** (33)	53
2c	60	120	**12c** (30) **13c** (70)	77
2d	60	96	**12d** (66) **13d** (16), **13'd** (18)	32[c]
2e	60	96	**12e** (50) **13e** (50)	20[c]
2f	60	47	**12f** (32), **12'f** (10) **13f** (32), **13'f** (10) **14** (8) **15** (8)	63

[a] *Isolated yield.* [b] *By GLC.* [c] *Isolated yield with respect to ester 7 consumed.*

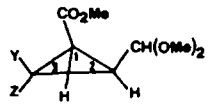
Scheme 4



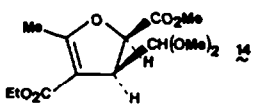
7 **8** **12** **13**

12,13	a	b	c	d	e	f
Y	CN	CO_2Me	CO_2Et	H	Me	CO_2Et
Z	CN	CN	CO_2Et	NO_2	NO_2	COMe

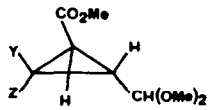
When the substituents Y and Z are different, the cyclopropane derivatives **12** and **13** can appear as epimeric mixtures. Thus, both epimers **13d** and **13'd** have been identified and their stereochemistries assigned on the basis of the respective coupling constants (**13d**: $J_{1,3} = 8.5$, $J_{2,3} = 4.5$; **13'd**: $J_{1,3} = 3.6$, $J_{2,3} = 8.9$). By constrast, **12d** appears as a sole epimer, the ^{1}H-NMR spectrum of which indicates that H-3 has a *trans* relationship to H-1 and H-2; formation of **12d** by lactone ring cleavage of the cyclopropane lactone **5d** corroborates its structure. Moreover, the reaction of **7** with nitroethane afforded only two cyclopropane derivatives **12e** (*cis*, $J_{1,2} = 11.3$ Hz) and **13e** (*trans*, $J_{1,2} = 7.8$ Hz), in which the configuration at C-3 was assigned on the basis of the anisotropy effects of the nitro group. However, the configuration of compounds **12b-13b**, obtained as the sole products from the reactions of **7** with methyl cyanoacetate could not be ascertained from the ^{1}H-NMR data, due to the absence of the H-3 proton.



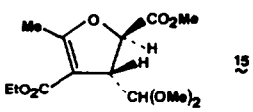
12d	12e
Y	H	Me
Z	NO_2	NO_2



14



13d	13'd	13e
Y	NO_2	H	NO_2
Z	H	NO_2	Me



15

From the above results is deduced that the acetal-esters **7-8** are less active than the furanone **1**, as Michael acceptors, the formation of tandem addition products being therefore not favoured.

A noteworthy feature of the reactions outlined above is the different behaviour of the ambident anions from **2e** and **2f** towards the cyclic pseudoesters **1** and the open-chain esters **7** or **8**. As stated above, the reaction of **2e** and **2f** with the furanone **1** afforded only the compounds **10** and **11**, originated by conjugate addition followed by ring closure *via* intramolecular *O*-alkylation. By contrast, the Michael addition of nitroethane to the acetal-ester **7** was followed by an intramolecular *C*-alkylation to yield the cyclopropane derivatives **12e** and **13e** exclusively. Moreover, the addition product of ethyl acetoacetate to **7** underwent both the *C*-alkylation to give the cyclopropanes **12f** and **13f** and the *O*-alkylation to yield the dihydrofurans **14** and **15**, the former being the major reaction pathway.

EXPERIMENTAL

Melting points have been determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on Perkin-Elmer models 254 and 681 grating spectrophotometers, $\bar{\nu}$ values in cm^{-1}. NMR spectra were obtained in $CDCl_3$ solution on either a Varian EM-390, a Bruker WP-8054 or a WM 200 SY spectrometer. Signals are reported in δ units with TMS = 0 ppm as internal standard. Mass spectra were recorded on either a Hewlett Packard 5985, a 5790 GC-MS System or a Hitachi-Perkin-Elmer RMU-6MG spectrometer. Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh), F_{254} (2 mm layers) and DC-Alufolien 60 F_{254} were used for conventional, flash chromatography, preparative and analytical TLC, respectively. GLC was performed on either a Perkin-Elmer F-11 (4% Reoplex-400 on Chromosorb conventional column) or in a 3920 instrument (SE-30 capillary column) at 150°C, with nitrogen as carrier gas.

Reactions of bromofuranone 1 or bromoester 7 with nucleophiles in the presence of a phase transfer catalyst. General procedure.

Bromofuranone **1** (or bromoester **7**) (10 mmol) is added to a stirred mixture of finely powdered anhydrous potassium carbonate (6.90 g, 50 mmol), tetra-*n*-butylammonium bromide (0.16 g, 0.5 mmol) and the nucleophile (10 mmol) in acetonitrile (20 ml). The mixture is kept with stirring at the temperature indicated in Table I (or Table II) until the starting furanone **1** (or ester **7**) disappears or a practically constant concentration is attained (monitored by TLC or GLC). After addition of acetonitrile or ethyl acetate (100 ml) the reaction mixture is filtered and the salts washed with the same solvent (40 ml). The solvent is removed under reduced pressure to yield the crude mixture.

Reaction of 1 with malononitrile

The crude mixture obtained following the general procedure, in dichloromethane (150 ml), is washed with water (3 x 15 ml), and dried (Na_2SO_4). The solvent is removed under reduced pressure and the crude product (1.38 g), after flash chromatography (petroleum ether-ethyl acetate 6:1), affords **6,6-dicyano-4-*exo*-methoxy-3-oxabicyclo[3.1.0]hexan-2-one (5a)** (36%) as a colourless oil. IR (film): 3100, 3080 (=C-H); 2260 (C≡N); 1810-1785 (C=O). ^{1}H-NMR: 5.47 (s, 1H, H-4); 3.64 (s, 3H, OCH_3); 3.28 (s, 2H, H-1, H-5). ^{13}C-NMR: 165.3 (C=O); 111.0 (C≡N); 102.0 (C-4); 57.9 (OCH_3); 35.9 (C-1); 31.7 (C-5). MS, *m/z*: 179 $(M+1)^+$, 177 $(M-1)^+$, 147, 134 (100), 103, 91. Attempts to obtain analytical samples were unsuccessful because it decomposes readily.

Reaction of 1 with methyl cyanoacetate

The crude mixture obtained following the general procedure in dichloromethane (150 ml) is washed with water and dried (Na_2SO_4). The solvent is removed under reduced pressure and the residue (1.76 g) is chromatographed under pressure (petroleum ether-ethyl acetate 4:1) to yield **6-cyano-4-*exo*-methoxy-6-methoxycarbonyl-3-oxabicyclo[3.1.0]hexan-2-one (5b)** (48%) as a white solid, m.p. 98-102°C (from cyclohexane-benzene). (Found: C, 50.80; H, 4.27; N, 6.45. Calcd. for $C_9H_9O_5N$: C, 51.19; H, 4.30; N, 6.63). IR (nujol): 3120, 3100 (=C-H); 2260 (C≡N); 1805, 1780, 1755 (C=O). ^{1}H-NMR: 5.43 (s, 1H, H-4); 3.89 (s, 3H, CO_2CH_3); 3.60 (s, 3H, OCH_3); 3.07 (s, 2H, H-1, H-5). ^{13}C-NMR: 167.3; 163.5; (C=O); 112.1 (C≡N); 102.3 (C-4); 57.4, 54.6 (OCH_3); 36.1 (C-1); 32.1 (C-5); 23.6 (C-6). MS, *m/z*: 212 $(M+1)^+$, 210 $(M-1)^+$, 180, 167, 152, 136 (100).

Reaction of 1 with diethyl malonate

The crude mixture obtained following the general procedure contains 6,6-bis(ethoxycarbonyl)-4-*exo*-methoxy-3-oxabicyclo[3.1.0]hexan-2-one (**5c**)[5] and the cyclopropane bis-lactone **4c**[5] in a 30:70 ratio (^{1}H-NMR).

Reaction of 1 with nitromethane

The crude mixture obtained following the general procedure is separated by column chromatography on silica gel (chloroform-hexane-acetone 5:4:1) to afford unreacted bromofuranone **1** (0.12 g), **5d** (0.27 g, 17%) and bis-lactone **9** (0.09 g).

4-*exo*-Methoxy-6-*exo*-nitro-3-oxabiciclo[3.1.0]hexan-2-one (5d).- M.p. 101-103°C (sublim.). (Found: C, 42.01; H, 4.03; N, 8.18. Calcd. for $C_6H_7O_5N$: C, 41.62; H, 4.05; N, 8.09). IR (nujol): 3100 (⟩C-H), 1800, 1780 (C=O),1560 (NO_2). ^{1}H-NMR: 5.31 (s, 1H, H-4); 4.26 (dd, 1H, H-6, $J_{1,6}$ = 2.1, $J_{5,6}$ = 1.7); 3.50 (s, 3H, OCH_3); 3.14 (dd, 1H, H-1, $J_{1,5}$ = 6.8); 3.10 (br, dd, 1H, H-5). ^{13}C-NMR: 168.2 (C=O), 102.2 (C-4); 58.4 (C-6); 57.0 (OCH_3); 31.0 (C-1); 26.2 (C-5). MS, *m/z*: 173 (M^+), 172 (M-1)$^+$, 142, 95, 83 (100).

4-*exo*-Methoxy-6(5'-methoxy-2'-oxo-2',5'-dihydrofuran-4'-yl)-6-*exo*-nitro-3-oxabicyclo[3.1.0]hexan-2-one (9).- IR (film): 3120 (⟩C-H), 1800 (br, C=O); 1650 (C=C); 1560 (NO_2). ^{1}H-NMR: 6.24 (d, 1H, H-3', $J_{3',5'}$ = 0.9); 5.78 (d, 1H, H-5'); 5.40 (d, 1H, H-4, $J_{4,5}$ = 0.9); 3.63 (s, 3H, OCH_3); 3.61 (s, 3H, OCH_3); 3.22 (d, 1H, H-1, $J_{1,5}$ = 6.1); 3.11 (dd, 1H, H-5). MS, *m/z*: 142 (M-143)$^+$, 112, 95, 83 (100).

Reaction of 1 with nitroethane

The crude mixture obtained following the general procedure is chromatographed on silica gel (toluene-acetone 5:1) to remove unreacted bromofuranone (Table 1; longer reaction times must be avoided to prevent decomposition). After chromatography, **4-*exo*-methoxy-3-methyl-3a,6a-dihydrofuro[3,4-*d*]isoxazol-6(4*H*)-one *N*-oxide** (**10**) is obtained in 46% yield, m.p. 100-102°C (from ethanol). (Found: C, 44.99; H, 4.91; N, 7.42. Calcd. for $C_7H_8O_5N$: C, 44.92; H, 4.81; N, 7.48). IR (KBr): 1810 (C=O); 1670 (C=N). ^{1}H-NMR: 5.47 (s, 1H, H-4); 5.20 (d, 1H, H-6a, J_{3a-6a} = 9.0); 4.11 (dq, 1H, H-3a), 3.55 (s, 3H, OCH_3); 2.05 (d, 3H, CH_3, J^4 = 1.9). ^{13}C-NMR: 171.0 (C=O); 108.3 (C=N); 103.3 (C-4); 69.7 (C-6a); 57.0 (OCH_3); 53.8 (C-3a); 10.6 (CH_3). MS (C.I. CH_4), *m/z*: 188 (M+2)$^+$, 170 (100).

Reaction of 1 with ethyl acetoacetate

The crude mixture in dichloromethane (150 ml) is washed with water (3 x 15 ml) and dried (Na_2SO_4). The solvent is removed *in vacuo* and the crude product is purified by flash column chromatography (petroleum ether-ethyl acetate 5:1) to yield **3-ethoxycarbonyl-4-*exo*-methoxy-2-methyl-3a,6a-dihydrofuro[3,4-*b*]furan-6(4*H*)-one** (**11**) as a white solid, m.p. 70-71°C (from cyclohexane-benzene). (Found: C, 54.85; H, 5.98. Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83). IR (nujol): 1805, 1790, 1700 (C=O); 1640 (C=C). ^{1}H-NMR: 5.46 (s, 1H, H-4); 5.14 (d, 1H, H-6a, J = 9.1); 4.22 (q, 2H, $CO_2CH_2CH_3$, J = 7.2); 3.90 (dq, 1H, H-3a); 3.51 (s, 3H, OCH_3); 2.21 (d, 3H, CH_3, J^5 = 1.8); 1.30 (t, 3H, $CO_2CH_2CH_3$). ^{13}C-NMR: 172.6, 169.5 (C=O);164.3 (C-2); 107.7 (C-4); 101.9 (C-3); 78.0 (C-6a); 60.3 ($CO_2CH_2CH_3$); 57.2 (OCH_3); 51.2 (C-3a); 14.4, 14.1 ($CO_2CH_2CH_3$, CH_3). MS, *m/z*: 242 (M^+), 211, 197, 154 (100), 126, 125.

Reaction of bromoester 7 with methyl cyanoacetate

The crude product obtained following the general procedure is a 67:33 mixture of compounds **12b** and **13b** (by GLC), which can be separated by short column chromatography (petroleum ether-ethyl acetate 6:1).

Dimethyl 3-cyano-*c*-2-dimethoxymethyl-*r*-1,3-cyclopropanedicarboxylate (**12b**).- (Found: C, 51.23; H, 6.12; N, 5.48. Calcd. for $C_{11}H_{15}O_6N$: C, 51.36; H, 5.88; N, 5.44). IR (film): 3055, 3005 (⟩C-H); 2260 (C≡N); 1745 (C=O). ^{1}H-NMR: 4.93 [d, 1H, $CH(OCH_3)_2$, J = 7.6]; 3.86, 3.80 (2s, 6H, CO_2CH_3); 3.50, 3.39 (2s, 6H, OCH_3); 2.72 (d, 1H, H-1 , $J_{1,2}$ = 10.0); 2.49 (dd, 1H, H-2). ^{13}C-NMR: 166.1 (C=O); 113.0 (C≡N). 99.6 [$CH(OCH_3)_2$]; 55.4; 54.2, 53.9, 52.9 (OCH_3); 35.4, 31.9 (C-1, C-2); 24.2 (C-3). MS, *m/z*: 258 (M+1)$^+$, 256, 226, 166 (100), 88, 75.

Dimethyl 3-cyano-*t*-2-dimethoxymethyl-*r*-1,3-cyclopropanedicarboxylate (**13b**).- (Found: C, 51.53; H, 6.15; N, 5.51. Calcd. for $C_{11}H_{15}O_6N$: C, 51.36; H, 5.88; N, 5.44). IR (film): 3055, 3015 (⟩C-H), 2255 (C≡N); 1750 (C=O); ^{1}H-NMR: 4.55 [d, 1H, $CH(OCH_3)_2$, J = 4.0]; 3.82, 3.73 (2s, 6H, CO_2CH_3); 3.43, 3.42 (2s, 6H, OCH_3); 2.89 (d, 1H, H-1, $J_{1,2}$ = 8.1); 2.67 (dd, 1H, H-2), ^{13}C-NMR: 165.7; 164.5 (C=O); 114.8 (C≡N); 99.7 [$CH(OCH_3)_2$]; 54.0, 52.9, 52.8 (OCH_3); 33.8, 33.1 (C-1, C-2); 22.9 (C-3), MS, *m/z*: 258 (M+1)$^+$, 256, 226, 194, 88, 75 (100).

Reaction of bromoester 7 with diethyl malonate

The crude product is a 30:70 mixture of compounds **12c** and **13c** (by GLC). Partial separation is effected by flash column chromatography on silica gel.

Methyl 3,3-bis(ethoxycarbonyl)-c-2-dimethoxymethyl-*r*-1-cyclopropanecarboxylate (**12c**).- (Found: C, 52.85; H, 7.02. Calcd. for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97). IR (film): 1735 (C=O); ^{1}H-NMR: 4.93 [d, 1H, $CH(OCH_3)_2$, J = 8.0]; 4.24, 4.19 (2q, 4H, $CO_2CH_2CH_3$, J = 7.2), 3.70 (s, 3H, CO_2CH_3); 3.49, 3.33 (2s, 6H, OCH_3); 2.62 (d, 1H, H-1, $J_{1,2}$ = 10.0); 2.23 (dd, 1H, H-2); 1.27, 1.25 (2t, 6H, $CO_2CH_2CH_3$). ^{13}C-NMR: 168.6, 168.5, 164.6 (C=O); 99.6 [$CH(OCH_3)_2$]; 62.7, 61.8 ($CO_2CH_2CH_3$); 55.3, 52.9, 52.4 (OCH_3); 39.3 (C-3), 33.8, 29.2 (C-1, C-2); 14.1 ($CO_2CH_2CH_3$). MS, *m/z*: 287 (M-31)$^+$, 227, 213, 181, 88 (100), 75.

Methyl 3,3-bis(ethoxycarbonyl)-*t*-2-dimethoxymethyl-*r*-1-cyclopropanecarboxylate (**13c**).- (Found: C, 52.72; H, 7.24. Calcd. for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97). IR (film): 1740 (C=O). ^{1}H-NMR: 4.34 [d, 1H, $CH(OCH_3)_2$, J = 6.6]; 4.20, 4.18 (2q, 4H, $CO_2CH_2CH_3$, J = 7.2); 3.68 (s, 3H, CO_2CH_3); 3.33 (s, 6H, OCH_3), 2.85 (d, 1H, H-1, $J_{1,2}$ = 6.9); 2.65 (dd, 1H, H-2); 1.26, 1.24 (2t, 6H, $CO_2CH_2CH_3$). ^{13}C-NMR: 168.9, 166.3, 165.4 (C=O); 100.3 [$CH(OCH_3)_2$]; 62.3, 62.0 ($CO_2CH_2CH_3$); 54.0, 52.3, 50.9 (OCH_3); 40.2 (C-3); 33.1, 30.6 (C-1, C-2); 14.0 (CO_2CH_3). MS, *m/z*: 287 (M-31)$^+$, 227, 213, 167 (100), 139, 88, 75.

Reaction of bromoester 7 with nitromethane

The crude product, obtained following the general procedure, after removal of recovered bromoester **7** by chromatography, is a 66:16:18 diastereoisomeric mixture of **12d, 13d** and **13'd** (32% yield). Diastereoisomers are partially separated by TLC (hexane-acetone 10:1) to give **12d** in analytical pure state.

Methyl c-2-dimethoxymethyl-*t*-3-nitro-*r*-1-cyclopropanecarboxylate (12d).- (Found: C, 44.11; H, 5.90; N, 6.23. Calcd. for $C_8H_{13}O_6N$: C, 43.84; H, 5.94; N, 6.39). IR (film): 3090, 3005 ([C-H), 1740 (C=O), 1555 (NO_2). ^{1}H-NMR: 4.82 (dd, 1H, H-3, $J_{1,3} = J_{2,3} = 3.7$); 4.50 [d, 1H, $CH(OCH_3)_2$, $J = 7.1$], 3.77 (s, 3H, CO_2CH_3), 3.38, 3.33 (2s, 6H, OCH_3); 2.93 (dd, 1H, H-1, $J_{1,2} = 11.3$), 2.71 (ddd, 1H, H-2). ^{13}C-NMR: 167.2 (C=O); 98.9 [$CH(OCH_3)_2$], 61.4 (C-3), 53.6, 52.6, 52.5 (OCH_3), 31.8, 27.7 (C-1, C-2). MS, *m/z*: 218 $(M-1)^+$, 188, 141, 75 (100).

Compound **12d** is also obtained by lactone ring cleavage of 4-*exo*-methoxy-6-*exo*-nitro-3-oxabiciclo [3.1.0] hexan-2-one (**5d**) as follows: A solution of **5d** (236 mg) in methanol (10 ml) and sulfuric acid (0.06 ml) is stirred 12 h at room temperature. The reaction mixture is neutralized with sodium acetate and the methanol removed *in vacuo*. The residue is treated with water and the mixture extracted with ether. The ethereal solution is evaporated under reduced pressure and the acetic acid is removed in a vacuum desiccator under sodium hydroxide to afford **12d** in 85% yield, identical with the compound described above.

Methyl *t*-2-dimethoxymethyl-c-3-nitro-*r*-1-cyclopropanecarboxylate (13d).- The following spectral data are unambigously assigned from a relatively pure sample, obtained by repeated TLC. IR (film): 3005 ([C-H), 1745 (C=O), 1550 (NO_2). ^{1}H-NMR: 4.69 [d, 1H, $CH(OCH_3)_2$, $J = 2.3$]; 4.49 (dd, 1H, H-3, $J_{1,3} = 8.5$, $J_{2,3} = 4.5$); 3.75 (s, 3H, CO_2CH_3); 3.37, 3.36 (2s, 6H, OCH_3); 2.80 (ddd, 1H, H-2, $_{1,2} = 7.9$); 2.54 (dd, 1H, H-1). MS, *m/z*: 188 $(M-31)^+$, 141, 75 (100).

Methyl *t*-2-dimethoxymethyl-*t*-3-nitro-*r*-1-cyclopropanecarboxylate (13'd).- The following ^{1}H-NMR signals are assigned from the spectrum of a mixture of **13d** and **13'd**: 4.65 (dd, 1H, H-3, $J_{1,3} = 3.6$, $J_{2,3} = 8.9$; 4.57 [d, 1H, $CH(OCH_3)$, $J = 7.1$]; 3.70 (s, 3H, CO_2CH_3); 3.40, 3.41 (2s, 6H, OCH_3); 3.06 (dd, 1H, H-1, $J_{1,2} = 7.4$); 2.35 (ddd, 1H, H-2).

Reaction of bromoester 7 with nitroethane

The crude product, after removal of recovered bromoester **7** by chromatography, is a diastereoisomeric mixture of the cyclopropanes **12e** and **13e** in an approximate 1:1 ratio (by ^{1}H-NMR and GLC). Yield 20%. (Found: C, 46.59; H, 6.19; N, 5.73. Calcd. for $C_9H_{15}O_6N$: C, 46.35; H, 6.43; N, 6.00. Separation of the diastereoisomers is effected by conventional column chromatography on silica gel (toluene-hexane-ethyl acetate 10:5:2).

Methyl c-2-dimethoxymethyl-c-3-methyl-*t*-3-nitro-*r*-1-cyclopropanecarboxylate (12e).- IR (film): 3000 ([C-H); 1740 (C=O); 1550 (NO_2). ^{1}H-NMR: 4.81 [d, 1H, $CH(OCH_3)_2$, $J = 8.1$], 3.75 (s, 3H, CO_2CH_3); 3.38, 3.36 (2s, 6H, OCH_3); 2.97 (d, 1H, H-1, $J_{1,2} = 11.3$); 2.76 (dd, 1H, H-2); 1.94 (s, 3H, CH_3). ^{13}C-NMR: 167.7 (C=O); 98.0 [$CH(OCH_3)_2$]; 67.9 (C-3); 53.6; 52.7; 52.4 (OCH_3); 33.9, 30.7 (C-1, C-2); 10.5 (CH_3). MS (10 eV), *m/z*: 202 $(M-31)^+$, 155 (100), 88, 75.

Methyl *t*-2-dimethoxymethyl-*t*-3-methyl-c-3-nitro-*r*-1-cyclopropanecarboxylate (13e).- IR (film): 3000 ([C-H); 1745 (C=O); 1550 (NO_2). ^{1}H-NMR: 4.45 [d, 1H, $CH(OCH_3)_2$, $J = 4.6$]; 3.72 (s, 3H, CO_2CH_3); 3.38 (s, 6H, OCH_3); 2.91 (dd, 1H, H-2, $J_{1,2} = 7.8$); 2,29 (d, 1H, H-1); 1.85 (s, 3H, CH_3). ^{13}C-NMR: 167.3 (C=O); 99.5 [$CH(OCH_3)_2$]; 69.2 (C-3); 53.6, 52.7,52.0 (OCH_3); 32.7, 32.3 (C-1, C-2); 16.5 (CH_3). MS, *m/z*: 202 $(M-31)^+$, 155, 88, 75 (100).

Reaction of bromoester 7 with ethyl acetoacetate

The crude product (63% yield) is a mixture of the cyclopropanes **12f, 12'f, 13f, 13'f** and the dihydrofurans **14** and **15** in a ratio 32:10:32:10:8:8, respectively (by GLC). Partial separation is effected by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give the following fractions: **15/13f, 13f, 12'f/13f/12f, 12f, 14.** Compounds **12f, 13f** and **14** are obtained in analytical pure state. The unresolved mixtures are analyzed by ^{1}H-NMR and/or GLC/MS.

Methyl 3-acetyl-c-2-dimethoxymethyl-3-ethoxycarbonyl-*r*-1-cyclopropanecarboxylate

Isomer **12f**: (Found: C, 53.97; H, 7.17. Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99). IR (film): 1750, 1710 (C=O); ^{1}H-NMR: 4.94 [d, 1H, $CH(OCH_3)_2$, $J = 8.4$]; 4.29 (q, 2H, $CO_2CH_2CH_3$, $J = 7.2$); 3.70 (s, 3H, CO_2CH_3); 3.45, 3.33 (2s, 6H, OCH_3); 2.62 (d, 1H, H-1, $J_{1,2} = 9.9$); 2.33 (s, 3H, $COCH_3$); 2.17 (dd, 1H, H-2); 1.31 (t, 3H, $CO_2CH_2CH_3$). ^{13}C-NMR: 199.5 ($COCH_3$); 168.5, 166.5 (C=O); 99.3 [$CH(OCH_3)_2$]; 62.0 ($CO_2CH_2CH_3$); 54.6, 52.7, 52.2 (OCH_3); 45.8 (C-3); 35.0, 30.5 (C-1, C-2); 28.3 ($COCH_3$); 14.0 ($CO_2CH_2CH_3$). MS, *m/z*: 257 $(M-31)^+$, 197, 183, 88, 75 (100).

Isomer **12'f**: ^{1}H-NMR: 4.78 [d, 1H, $CH(OCH_3)_2$, $J = 8.4$]; 4.22 (q, 2H, $CO_2CH_2CH_3$, $J = 7.2$); 3.71 (s, 3H, CO_2CH_3); 3.43, 3.33 (2s, 6H, OCH_3); 2.61 (d, 1H, H-1); 2.33 (dd, 1H, H-2); 2.30 (s, 3H, $COCH_3$), 1.26 (t, 3H, $CO_2CH_2CH_3$).

Methyl-3-acetyl-*t*-2-dimethoxymethyl-3-ethoxycarbonyl-*r*-1-cyclopropanecarboxylate

Isomer **13f**: (Found: C, 54.22; H, 7.25. Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99; IR (film): 1740 (C=O). ^{1}H-NMR: 4.34 |d, 1H,CH(OCH$_3$)$_2$, J = 6.8|; 4.24 (q, 2H, $CO_2CH_2CH_3$, J = 7.2); 3.68 (s, 3H, CO_2CH_3), 3.33, 3.30 (2s, 6H, OCH_3); 2.88 (d, 1H, H-1, $J_{1,2}$ = 6.9); 2.62 (dd, 1H, H-2); 2.25 (s, 3H, $COCH_3$); 1.28 (t, 3H, $CO_2CH_2CH_3$). ^{13}C-NMR: 197.5 ($COCH_3$); 168.9, 167.0 (C=O); 100.6 |CH(OCH$_3$)$_2$|; 62.3 ($CO_2CH_2CH_3$); 53.8, 52.4, 51.4 (OCH_3); 45.6 (C-3); 32.8, 31.6 (C-1, C-2); 29.0 ($COCH_3$); 14.0 ($CO_2CH_2CH_3$). MS, *m/z*: 257 $(M-31)^+$, 225, 183, 88, 75 (100).

Isomer **13'f**: ^{1}H-NMR: 4.24 (q, 2H, $CO_2CH_2CH_3$, J = 7.2); 4.07 |d, 1H, CH(OCH$_3$)$_2$, J = 7.0|; 3.68 (s, 3H, CO_2CH_3); 3.31, 3.30 (2s, 6H, OCH_3); 2.98 (d, 1H, H-1, $J_{1,2}$ = 6.9); 2.72 (dd, 1H, H-2); 2.30 (s, 3H, $COCH_3$); 1.28 (t, 3H, $CO_2CH_2CH_3$). MS, *m/z*: 257 $(M-31)^+$, 197, 183 (100), 165, 88, 75.

Methyl *cis*-3-dimethoxymethyl-4-ethoxycarbonyl-5-methyl-2,3-dihydrofuran-2-carboxylate (14).- (Found: C, 53.94; H, 7.30. Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99). IR (film): 1760, 1710 (C=O), 1650 (C=C). ^{1}H-NMR: 4.96 (d, 1H, H-2, $J_{2,3}$ = 8.8); 4.41 |d, 1H, CH(OCH$_3$)$_2$, J = 6.2|; 4.18 (q, 2H, $CO_2CH_2CH_3$, J = 7.2); 3.78 (s, 3H, CO_2CH_3); 3.60 (m, 1H, H-3); 3.29, 3.27 (2s, 6H, OCH_3); 2.23 (d, 3H, CH_3, J^5 = 1.0); 1.28 (t, 3H, $CO_2CH_2CH_3$). MS, *m/z*: 257 $(M-31)^+$, 211, 197, 167, 75 (100).

Methyl *trans*-3-dimethoxymethyl-4-ethoxycarbonyl-5-methyl-2,3-dihydrofuran-2-carboxylate (15).- (Found: C, 54.11; H, 7.20. Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99). IR (film): 1750, 1710, 1700 (C=O), 1645 (C=C). ^{1}H-NMR: 5.15 (d, 1H, H-2, $J_{2,3}$ = 4.5); 4.57 |d, 1H CH(OCH$_3$)$_2$, J = 2.6|; 4.20 (q, 2H, $CO_2CH_2CH_3$, J = 7.2); 3.77 (s, 3H, CO_2CH_3); 3.60 (m, 1H, H-3); 3.42, 3.40 (2s, 6H, OCH_3); 2.27 (d, 3H, CH_3, J^5 = 1.2); 1.28 (t, 3H, $CO_2CH_2CH_3$). MS, *m/z*: 257 $(M-31)^+$, 137, 109, 75 (100).

Acknowledgements. Financial support from Comisión Asesora de Investigación Científica y Técnica is gratefully acknowledged. We also thank the C.S.I.C. for a postgraduate fellowship (to M.L.S.).

REFERENCES AND NOTES

1. Part XXV: F. Fariña, M. V. Martín, M.C. Paredes and A. Tito, *J. Heterocyclic Chem.*, in press.
2. F. Fariña, M. C. Maestro, M. R. Martín, M. V. Martín and F. Sánchez, *J. Chem. Research, (S)* 188; *(M)* 2662 (1980).
3. F. Fariña, M. C. Maestro, M. R. Martín, M. V. Martín and F. Sánchez, *Heterocycles*, **20**, 1761 (1983).
4. F. Fariña, M. C. Maestro, M. R. Martín, M. V. Martín and F. Sánchez, *J. Chem. Research, (S)* **44**; *(M)* 0534 (1984).
5. F. Fariña, M. C. Maestro, M. R. Martín, M. V. Martín, F. Sánchez and M. L. Soria, *Tetrahedron*, **42**, 3715 (1986).
6. D. Arlt, M. Jautelat and R. Lantzsch, *Angew. Chem. Int. Ed. Engl.*, **20**, 703 (1981).
7. R. D. Little and J. R. Dawson, *Tetrahedron Lett.*, **21**, 2609 (1980).
8. M. Fedorynski, K. Wojciechowski, Z. Matacz and M. Makosza, *J. Org. Chem.*, **43**, 4682 (1978).
9. R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).
10. A referable nitrocyclopropanation of steroidic α-bromoenones has been reported by M. Kocór and W. Kroszczyński, *Synthesis*, 813 (1976).
11. Formation of a furan ring by conjugate addition of acetoacetates to a nitroolefin followed by ring closure has been described by F. Boberg, M. Ruhr and A. Garming, *Liebigs Ann. Chem.*, 223 (1984).
12. Formation of an isoxazoline *N*-oxide by internal nucleophilic substitution in 3-halo-1-nitroalkanes and 1,3-dinitroalkanes (Kohler synthesis) has been previously reported. See, for example, A. T. Nielsen and T. G. Archibad, *J. Org. Chem.*, **34**, 984 (1969), and references cited therein.
13. F. Fariña, M. R. Martín and M. V. Martín, *Ann. Quím.*, **75**, 144 (1979).
14. Attempts to react malononitrile with the ester **7**, under different conditions, led to complex mixtures in which the presence of the expected cyclopropanes **12a** and **13a** was only detected by NMR.