Tetrahedron Vol. 47, No. 41, pp. 8775-8786, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

5-Ylidene-2(5H)-furanones as Dienophiles in Diels-Alder Cycloadditions: Effect of the Substituents on the Site-Selectivity

V. Branchadell, J.Font, A. Oliva,* J. Ortí, and R.M. Ortuño*
Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain.

S. Rafel, N. Terris, and M. Ventura
Unitat de Química, Estudi General de Girona, UAB, Plaça de l'Hospital, 6; 17071 Girona, Spain.

(*Received in UK* 19 *August* 1991)

Abstract. Diels-Alder cycloadditions of dienes to some 5-ylidene-2(5H)-furanones have been examined from experimental and theoretical points of view. The role that different substituents play on directing the observed site-selectivity (endocyclic or exocyclic double bond at the dienophile counterpart) is discussed. Several new potential synthetic building blocks have been prepared in good yields.

INTRODUCTION

5-Ylidene-2(5H)-furanones are widely distributed among natural products.[1] Many of them, e.g. patulin,[2] protoanemonin,[3] tetrenolin,[4] and penicillic acid[5] have strong antibiotic activity, and the more recently discovered fimbrolides possess antifungal and antimicrobial properties.[6] Some studies on the reactivity of these compounds have been carried out, mainly towards nucleophiles, in order to explain the interactions with the specific receptors, allowing us to understand their biological behaviour.[7] This kind of compound has also been used in the synthesis of other natural products.[8]

However, their cycloaddition reactions had been scarcely investigated, and only the spontaneous (2+2) dimerization of some of these molecules, giving cyclobutane derivatives,[9] were known until our recent work showing that 5-methylene-2(5H)-furanone (protoanemonin) **(5)** (Chart I) is a good dienophile in Diels-Alder cycloadditions. Lactone **5** reacts, exclusively at the exocyclic C-C double bond, with different dienes at temperatures between 120-150 °C (Table I) affording adducts with a spiro ring junction, in good yields.[10,11,12] This excellent site-selectivity has been

interpreted on the basis of theoretical calculations, and both electronic and steric factors have been invoked.[10,11] The regioselectivity with unsymmetrically substituted dienes[10a] and the endo/exo selectivity with cyclic dienes[12] have been also studied and rationalized. This peculiar reactivity of protoanemonin has allowed the development of synthetic approaches to a wide variety of functionalized 1-oxaspiro(4.5)-decanes.[10c,11]

We present in this paper the results obtained in the extension of our investigation to other 5-ylidene-2(5H)-furanones. The purpose of this work is to study the influence of the substituents, placed at the endocyclic or at the exocyclic double bond, on the site-selectivity involved in the Diels-Alder cycloadditions of these compounds.

RESULTS AND DISCUSSION

Lactones **1**,[13] **2**,[14] **3**,[15] and **4**,[16] (Chart I) were chosen as representative dienophiles, which were synthesized according to the methods previously described in the literature. Lactone **1** possesses an electron-withdrawing group directly attached to the exocyclic C-C double bond, therefore extending the conjugation, while compounds **2** and **3** have an electron-donor group that, moreover, could hinder the attack of the diene to that bond, either in the endo or in the exo orientations. Finally, product **4** possesses an acetoxy group bonded to the endocyclic double bond. This substituent could exert an electronic and steric influence on the site-selectivity.

Chart I

	R^1	R^2	R^3
1:	CO_2Me	H	H
2:	Me	H	H
3:	H	Me	H
4:	H	H	AcO
5:	H	H	H
1a:	CHO	H	H
4a:	H	H	OCHO

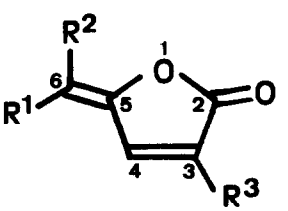


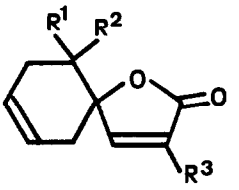
Table I. Diels-Alder reactions of furanones **1**, **2**, **3**, **4** and **5** with dienes.

Entry	Dienophile	Diene	Temp[a]	Time[b]	Adduct(s) (% ratio)	% Total yield
1	**1**	Butadiene	120	5	**10** (100)	51
2	**1**	Butadiene	120	16	**6** (9), **10** (91)	85
3	**1**	Butadiene	150	4	**6** (12), **10** (88)	93
4	**1**	Isoprene	120	16	**13** (6), **16** (94)[c]	94
5	**1**	Cyclopentadiene	120	16	**18** (100)	94
6	**2**	Isoprene	120	16	**14** (100)[d]	21
7	**3**	Butadiene	120	16	**7** (80), **12** (20)	9
8	**3**	Isoprene	120	16	**14** (89)[d], **17** (11)[c]	33
9	**4**	Butadiene	155	4	**8** (100)	72
10	**4**	Cyclopentadiene	90	2.2	**19** (67), **21** (33)	70
11	**4**	Cyclopentadiene	155	2.2	**19** (67), **21** (33)	88
12	**5**[e]	Butadiene	155	4	**9** (100)	85
13	**5**[e]	Isoprene	120	4	**15** (100)[f]	64
14	**5**[g]	Cyclopentadiene	135	7	**20** (70), **22** (30)	80

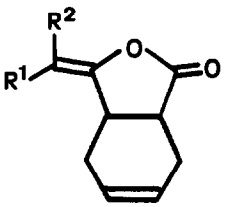
[a] °C. [b] Hours. [c] 1:1 Mixture of regioisomers. [d] 70:30 Mixture of regioisomers. [e] Ref. 10a. [f] 90:10 Mixture of regioisomers. [g] Ref. 12.

The lactones were reacted with some of the most usual dienes: 1,3-butadiene, isoprene, and cyclopentadiene. The reaction conditions and the results obtained in each case are listed in Table I. The nature of the adducts produced (Chart II) was easily monitored by ^{1}H NMR, through observation of disappearance or persistence of the characteristic signals due to the protons linked to each C-C double bond; i.e. δ 5.7-5.9 for the exocyclic protons, and δ 6.1-6.5, and 7.6-8.4 for the endocyclic protons, in compounds **1**, **2**, and **3**; δ 4.9 and 5.2 for the exocyclic protons, and 7.3 for the endocyclic proton in compound **4**.

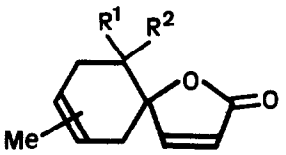
Chart II



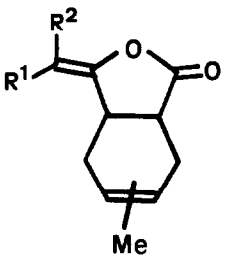
6: $R^1 = MeO_2C$, $R^2 = R^3 = H$
7: $R^1 = Me$, $R^2 = R^3 = H$
8: $R^1 = R^2 = H$, $R^3 = AcO$
9: $R^1 = R^2 = R^3 = H$



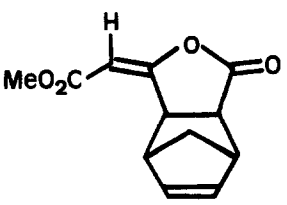
10: $R^1 = MeO_2C$, $R^2 = H$
11: $R^1 = Me$, $R^2 = H$
12: $R^1 = H$, $R^2 = Me$



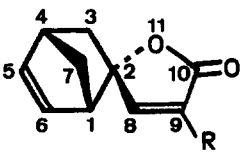
13: $R^1 = MeO_2C$, $R^2 = H$
14: $R^1 = Me$, $R^2 = H$
15: $R^1 = R^2 = H$



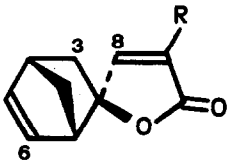
16: $R^1 = MeO_2C$, $R^2 = H$
17: $R^1 = H$, $R^2 = Me$



18



19: R = AcO
20: R = H



21: R = AcO
22: R = H

Table II. Results of the AM1 and MNDO theoretical calculations for the reactions of butadiene with **1a**, **2**, and **4a**.[a]

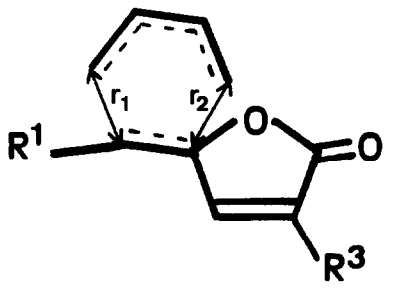
Dienophile	Site-isomer	Stereoisomer	r_1		r_2		$\Delta H^{\neq}$	
			AM1	MNDO	AM1	MNDO	AM1	MNDO
1a	endocyclic	endo	2.149	1.800	2.164	3.579	22.9	42.0
		exo	2.145	1.794	2.161	3.607	21.4	42.1
	exocyclic	endo	2.131	1.801	2.151	3.742	26.2	43.2
		exo	2.094	1.816	2.198	3.593	25.6	44.6
2	endocyclic	endo	2.149	1.783	2.151	3.582	24.7	43.7
		exo	2.145	1.778	2.148	3.605	23.0	43.7
	exocyclic	endo	2.052	1.803	2.245	3.766	29.6	45.8
		exo	2.079	1.813	2.215	3.778	30.9	45.6
4a	endocyclic	endo	2.191	3.691	2.139	1.787	26.8	42.3
		exo	2.199	3.757	2.134	1.791	25.7	42.4
	exocyclic	endo	2.015	1.838	2.300	3.860	25.5	34.5
		exo	2.040	1.825	2.267	3.819	26.9	35.1

[a] Lengths of the two forming bonds at the transition states, r_1 (A), and enthalpy barriers, $\Delta H^{\neq}$ (kcal/mol) are presented in all cases for the two possible site-isomers. See Chart III for the definition of r_1 and r_2.

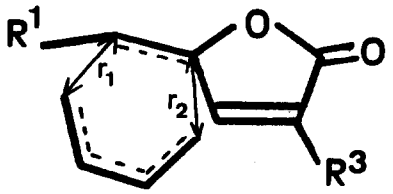
Theoretical calculations were made throughout this work, using the MNDO and AM1 methods, with the aim of rationalizing the results obtained and to afford more information on the mechanism of such cycloadditions. Molecules **1a** and **4a** were used as models of lactones **1** and **4**, respectively, to simplify the calculations. Butadiene was the diene considered in all cases. The results obtained are presented in Table II. The possible endo and exo orientations[12] of the diene have been taken into account for the respective simulated reactions at the endocyclic and at the exocyclic double bonds of the dienophiles. Chart III illustrates these features for the theoretically examined cycloadditions.

Chart III

Exocyclic reaction:

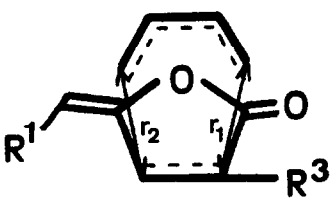


endo orientation

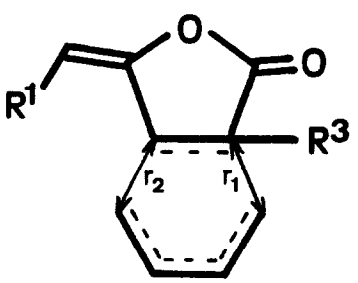


exo orientation

Endocyclic reaction:



endo orientation



exo orientation

5-Methoxycarbonylmethylene-2(5H)-furanone **(1)** reacted with butadiene at 120 °C for 5 hours giving exclusively adduct **10** in 51% yield. However, some compound **6** was obtained along with **10**, when the reaction was prolonged for 16 hours. The best preparative conditions correspond to reaction at 150 °C for 4 hours, affording a 12:88 mixture of adducts **6** and **10** in 93% total yield. These products were isolated by column chromatography and fully characterized.

Similarly, cycloaddition of **1** to isoprene at 120 °C for 16 hours led to a 6:94 mixture of adducts **13** and **16**, in 94% total yield. Column chromatography of the reaction crude allowed the isolation and identification of these compounds. Capillary G.L.C. revealed the presence of a 1:1 mixture of the para and meta regioisomers in **16**, while one sole peak was observed for adduct **13**, presumably the para regioisomer.[10a]

On the other hand, reaction of **1** and cyclopentadiene, under the same conditions than above, gave only product **18** in 94% yield, as a result of the exclusive reaction at the endocyclic double bond. The relative endo/exo stereochemistry was not assigned.

Cycloadditions were not so clean when lactones **2** and **3** were used as dienophiles, as it is shown in Table I. These compounds were much less reactive than **1** and than protoanemonin **(5)**. This lack of reactivity can be attributed to the steric hindrance in the attack of dienes at the exocyclic double bond. Thus, reaction of isoprene with (E)-5-ethylidene-2(5H)-furanone **(2)** gave exclusively adduct **14** (21% yield), resulting of the reaction at the exocyclic double bond, while reaction of this diene with the (Z)-isomer **3**, under the same conditions, afforded a 89:11 mixture of adducts **14** and **17** in a slightly higher total yield (compare entries 6 and 8 in Table I). Moreover, a mixture of adducts **7** and **12** was obtained in very low yield (9%) from cycloaddition of **3** and butadiene (Table I). Purification and characterization of these compounds was very hard work since they were obtained along with much polymeric unidentified material and, furthermore, adducts **14** and **17** contain a mixture of the possible regio- and diastereoisomers. Column chromatography of the respective reaction crudes yielded several fractions in which detection and identification of the isomers was realized by means of GLC and ^{1}H NMR spectroscopy (see Experimental Section).

An excellent site-selectivity was observed when 3-acetoxy-5-methylene-2(5H)-furanone, **4**, was reacted with butadiene and cyclopentadiene, always providing adducts that result from the attack of dienes at the exocyclic double bond, as in the case of protoanemonin **(5)**. Reactivity was also similar for both dienophiles as can be seen from Table I. Thus, reaction of

4 with butadiene at 155 °C for 4 hours afforded adduct **8** in 72% yield. Cycloaddition of **4** to cyclopentadiene carried out at 90 °C for 2.2 hours gave a 2:1 mixture of endo/exo stereoisomers in 70% yield, along with some recovered starting material. When reaction was performed at 155 °C, for the same period of time, the yield was increased to 88%, without recovery of the dienophile. The endo and exo stereoisomers, **19** and **21**, respectively, were isolated by column chromatography and fully characterized. The endo/exo stereochemistry[12] was assigned through differential NOE experiments performed on these products. Thus, 4.5% NOE on $H's_7$ (δ 1.65) and 2.6% NOE on H_{3exo} (δ 2.10) was observed from H_8 (δ 7.40) in the major adduct **19**, which was identified to be the endo isomer. Moreover, 2.8% NOE on H_{3endo} (δ 1.60) and 2.6% NOE on H_6 (δ 5.90) was observed from H_8 (δ 6.85) in the mino adduct **21**, allowing its unambigous assignment as the exo isomer.

The good site-selectivity observed in the cycloadditions of **1** and **4** to dienes is in excellent accordance with the results of the theoretical calculations (Table II). For the reaction of **1a** and butadiene the endocyclic reaction is predicted to be the most favourable process, being the difference in the enthalpy barriers calculated by MNDO and AM1 methods $\Delta\Delta H^{\#}$ = 1.2 and 4.2 kcal/mol, respectively. In the same way, the difference between the enthalpy barriers calculated by the MNDO method for the reaction of **4a** with butadiene is 7.8 kcal/mol, favouring the exocylic reaction. In this case AM1 calculations also confirm this preference, but in fact the computed difference in enthalpy barriers is much smaller (0.2 kcal/mol).

The site-selectivity in cycloaddition processes involving the parent lactone **5** has been rationalized in terms of the stability of the hypothetical biradical intermediates, if a biradical mechanism is assumed for these reactions.[10b] This can be estimated by calculating the relative energies of the species resulting from the attack of a hydrogen atom at the different possible sites which could be involved in the formation of the first bond.[17]

We can apply this model to the reactions studied in this paper. Table III presents the computed heats of formation of the above mentioned radicals. One can observe that the results obtained are again in agreement with the experimentally found site-selectivity for **1a** and **4a**.

Nevertheless, theoretical calculations seem to fail in the prediction of the experimentally observed site-selectivity in the Diels-Alder reactions of **2** and **3**. This discrepancy could be attributed to the fact that reactions of **2** and **3** with butadiene and isoprene (Table I) take place in

small yields due to a considerable extent of polymerization, and the polymers and by-products could have arisen from an initial adduct.

Table III. AM1 computed heat values for the formation of radical species.

Dienophile	1a	1a	2	2	4a	4a
Site[a]	C_3	C_6	C_3	C_6	C_4	C_6
ΔH[b]	-60.9	-60.4	-39.9	-38.3	-99.8	-103.0

[a] See Chart I for the numeration of the carbon atoms. These sites correspond to the carbon atoms for which the lengths of the forming bonds at the transition states are shorter (see Table II). [b] In kcal/mol.

We can conclude that dienes react selectively, in Diels-Alder cycloadditions, with furanone **1** at the endocyclic double bond and with furanone **4** at the exocyclic double bond, affording adducts in good yields. The new compounds **8**, **10**, **16**, **18**, **19** and **20**, owing to their functionalization, are potential synthetic building blocks to be used in the preparation of natural products.

EXPERIMENTAL SECTION

Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts was effected on a rotary distillation apparatus (only the oven temperature is given). The electron-impact mass spectra were recorded at 70 eV.

General procedures for theoretical calculations. The calculations have been performed by using the MNDO[18] and the AM1[19] methods, implemented in the AMPAC program.[20] Full geometry optimization has been carried out throughout. Stationary points of the potential energy hypersurface have been located by minimizing the root-mean-square gradient of the energy second derivative (force constant) matrix.[21] Calculations were performed at the restricted open Hartree-Fock (ROHF) level of theory in the case of radicals.

General procedures for the Diels-Alder cycloadditions. The dienophile (2-4 mmol), the diene (10-20) mL, and a trace of hydroquinone were introduced into a glass reactor fitted with a teflon stopper, and heated in an oil bath (see Table I for the specific reaction temperature and time conditions). The reaction mixture was cooled, diluted with CH_2Cl_2 and filtered to remove hydroquinone and polymeric materials. The solvent and excess of diene were evaporated under reduced pressure. The residue was chromatographed on silica gel (mixtures of hexane-ether as eluents) to afford the corresponding adducts. The relative proportions of regioisomers and stereoisomers in the reactions with isoprene and cyclopentadiene, respectively, were determined by means of capillary GLC analysis. The adducts resulting from the reactions involving lactones **2** and **3** could not been isolated satisfactorily; their proportions and yields were estimated from chromatographic fractions by means of capillary GLC and/or ^1H NMR integration of significant signals. These products were often contaminated

with unidentified polymeric material that made them unsuitable for microanalysis.

7-(2-Methoxycarbonylethylidene)-8-oxabicyclo[4.3.0]non-3-en-9-one (6): entry 2, Table I; yield, 334 mg (77%); oil, oven temperature 145 °C (0.05 Torr); IR (film) 1750, 1695, 1642 cm^{-1}; MS, m/e (relative intensity) 209 (M+1, 26.9), 177 (24.1), 79 (70.0), 77 (100), 69 (95.6), 41 (25.1); 80 MHz ^1H NMR ($CDCl_3$) δ 1.73-2.83 (4H, complex absorption), 3.00 (1 H, dt, J = 8.0 Hz, J' = 2.7 Hz), 3.67 (3 H, s), 3.97 (1 H, q, J = 8.0 Hz), 5.60 (1 H, s), 5.83 (2 H, m); 20 MHz ^{13}C NMR ($CDCl_3$) δ 126.2, 125.9, 96.8, 78.6, 77.0, 75.4, 51.2, 37.4, 35.9, 25.6, 21.7. Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.34; H, 5.67.

(Z)-(7-Ethylidene-8-oxabicyclo[4.3.0]non-3-en-9-one) (7): entry 7, Table I; yield 13 mg (3%); oil; 60 MHz ^1H NMR ($CDCl_3$) δ 1.67 (3 H, d, J = 6 Hz), 0.73-3.1 (6 H, complex absorption), 5.23 (1 H, m), 5.5 (1 H, m), 5.66 (1 H, m). This compound could not be purified for microanalysis.

10-Methoxycarbonyl-1-oxaspiro[4.5]deca-3,7-dien-2-one (10): entry 2, Table I; yield, 45 mg (10%); oil, bath temperature 170 °C (0.05 Torr); MS, m/e (relative intensity) 209, (M+1, 22.7), 208 (M, 25.8), 176 (15.2), 148 (100), 131 (25.8), 123 (37.9); 80 MHz ^1H NMR ($CDCl_3$) δ 2.26 (2 H, dd, J = 4.0 Hz, J' = 2.0 Hz), 2.40 (2 H, dd, J = 5.8 Hz, J' = 2.0 Hz), 3.30-3.38 (1 H, complex absorption), 3.65 (3 H, s), 5.00 (1 H, m), 5.20 (1 H, m), 6,13 (1 H, d, J = 5.33 Hz), 7.66 (1 H, d, J = 5.33 Hz). Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.54; H, 6.06.

3-Methyl- and 4-methyl-7-(2-methoxycarbonylethylidene)-8-oxabicyclo-[4.3.0]non-3-en-2-one (13): entry 4, Table I; 1:1 mixture of regioisomers (capillary GLC); yield, 310 mg (88%); oil, oven temperature 160 °C (0.03 Torr); IR (film) 1790, 1712, 1692, 1639 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) δ 1.70 (3 H, complex absorption), 1.47-4.23 (6 H, complex absorption), 3.75 (s) and 3.76 (s) (3H), 5.53 (1 H, m), 5.63 (1 H, s). Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64,89; H, 6.35. Found: C, 64.91; H, 6.31.

In the same reaction, **8-methyl-10-methoxycarbonyl-1-oxaspiro[4.5]deca-3,7-dien-2-one (13)** was also obtained as a minor product, which was identified from their ^1H NMR data; yield, 20 mg (6%); 80 MHz ^1H NMR ($CDCl_3$) δ 0.66-2.60 (7 H, complex absorption), 2.90 (1 H, q, J = 4.0 Hz), 3.63 (3 H, s), 5.28 (1 H, m), 6.00 (1 H, d, J = 5.3 Hz), 7.67 (1 H, d, J = 5.3 Hz).

8,10-Dimethyl-8-oxaspiro[4.5]deca-3,7-dien-2-one (14a): entry 6, Table I; mixture of diastereoisomers; yield, 44 mg (14%); oil; IR (film) 1762, 1742 cm^{-1}; 80-MHz ^1H NMR ($CDCl_3$) δ 0.77 (3 H, d, J = 6.13 Hz), 1.72 (5 H, complex absorption), 1.90-2.80 (3 H, complex absorption), 5.37 (1 H, m), 6.13 (1 H, d, J = 5.4 Hz), 7.48 (1 H, d, J = 5.4 Hz). This compound could not be purified for microanalysis.

7,10-Dimethyl-8-oxaspiro[4.5]deca-3,7-dien-2-one (14b): entry 6, Table I; mixture of diastereoisomers; yield, 19 mg (7%); oil; IR (film) 1762, 1742 cm^{-1}; 80 MHz-^1H NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 6.1 Hz), 1.53-2.45 (8 H, m), 5.37 (1 H, m), 6.10 (1 H, d J = 5.4 Hz), 7.42 (1 H, d, J = 5.4 Hz). This compound could not be purified for microanalysis.

Mixture of (Z)-(3-methyl- and 4-methyl-7-ethylidene-8-oxabicyclo-[4.3.0]non-3-en-9-one) (17): entry 8, Table I; yield, 46 mg (4%); oil; 80-MHz ^1H NMR ($CDCl_3$) δ 1.10-3.45 (6 H, complex absorption), 1.65 (3 H, d, J = 6.9 Hz), 1.72 (3 H, s), 4.67 (q, J = 6.9 Hz) and 5.21 (q, J = 6.9 Hz) (1 H), 5.53 (1 H, m). This compound could not be purified for microanalysis.

5-(2-methoxycarbonylethylidene)-4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (18): entry 5, Table I; yield, 330 mg (94%); oil, oven temperature 150 °C

(0.05 Torr); IR (film) 1800, 1715, 1660 cm^{-1}; 60-MHz ^1H NMR ($CDCl_3$) δ 1.53 (2 H, broad s), 3.00-4.20 (4 H, complex absorption), 3.58 (3H, s), 5.31 (1 H, m), 6.05 (2 H, broad s). Anal. Calcd. for $C_{12}H_{10}O_4$: C, 65.45; H, 5.45. Found: C, 65.51; H, 5.63.

3-Acetoxy-1-oxaspiro[4.5]deca-3,7-dien-2-one (8): entry 9, Table I; yield, 714 mg (88%); crystals, m.p. 54-55 °C (CH_2Cl_2); IR (KBr) 1781, 1643, 1603 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.77 (1H, m), 1.90 (1 H, m), 2.11-2.42 (4 H, complex absorption), 2.25 (3 H, s), 5.60 (1 H, m), 5.79 (1 H, m), 7.25 (1 H, s); 100 MHz ^{13}C NMR ($CDCl_3$)δ 20.89, 23.25, 31.52, 34.53, 83.27, 122.53, 126.55, 137.07, 137.16, 166.36, 167.13. Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.52; H, 5.82. Found: C, 63.48; H, 5.82.

(1R*,2S*,4R*)-2-Acetoxy-3-(hydroxybicyclo[2.2.1]hept-5-en-2-yl)prop-2-enoic acid lactone (19): entry 11, Table I; yield, 460 mg (59%); crystals, m.p. 64-65 °C (CH_2Cl_2); IR (KBr) 1752. 1650 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) 1.40 (1 H, m), 1.65 (2 H, m), 2.10 (1 H, dd, J = 14.2 Hz, J' = 4.4 Hz), 2.25 (3 H, s), 2.80 (1 H, m), 3.05 (1 H, m), 6.15 (1 H, J = 5.3 Hz, J' = 3.0 Hz), 6.45 (1 H, J = 5.6 Hz, J' = 3.4 Hz), 7.40 (1 H, s); 100-MHz ^{13}C NMR ($CDCl_3$) δ 20.86, 38.26, 42.09, 48.53, 91.99, 132.15, 136.43, 137.70, 142.24, 166.73, 167.13. Anal. Calcd. for $C_{12}H_{12}O_4$: C, 66.52; H, 5.50. Found: C, 65.50; H, 5.49.

(1R*,2R*,4R*)-2-Acetoxy-3-(hydroxybicyclo[2.2.1]hept-5-en-2-yl)prop-2-enoic acid lactone (21): entry 11, Table I; yield, 221 mg (29%); crystals, m.p. 55-56 °C (CH_2Cl_2); IR (KBr) 1757, 1650 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.60 (1 H, dd, J = 12.5 Hz, J' = 2.9 Hz), 1.70 (1 H, dd, J = 9.3 Hz, J' = 1.5 Hz), 1.95 (1 H, m), 2.06 (1 H, m), 2.2 (3 H, s), 2.75 (1 H, m), 2.95 (1 H, m), 5.9 (1 H, dd, J = 5.5 Hz, J' = 2.8 Hz), 6.30 (1 H, dd, J = 5.5 Hz, J' = 2.8 Hz), 6.30 (1 H, dd, J = 5.5 Hz, J' = 2.7 Hz), 6.85 (1 H,s); 100-MHz ^{13}C NMR ($CDCl_3$) δ 20.86, 38.52, 43.11, 47.89, 51.85, 91.39, 132.99, 135.86, 138.16, 139.27, 166.79, 167.21. Anal. Calcd. for $C_{12}H_{12}O_4$: C, 66.52; H, 5.50. Found: C, 65.59; H, 5.54.

Acknowledgements. We thank Mr. T. Parella for helpful advice in the performance of NOE experiments. Financial support from the Dirección General de Investigación Científica y Técnica, DGICYT, through the Project PB88-0241, is gratefully acknowledged.

REFERENCES AND NOTES

1. Pattenden, G. Fortschritte der Chemie Organisher Naturstoffe, vol. 35, pp 133-198; Springer Verlag: New York, 1978.
2. Woodward, R. B.; Singh, G. J. Amer. Chem. Soc. **1949**, 71, 758.
3. Caltrider, P. J. Antibiotics, **1967**, 1, 671.
4. Gallo, G. G.; Coronelli, C.; Vigerani, A.; Lancini, G. C. Tetrahedron **1969**, 25, 5677.
5. Bentley, R.; Keil, J. G. J. Biol. Chem. **1962**, 237, 867.
6. (a) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J. Wells, R. J. Tetrahedron Lett. **1977**, 37. (b) Pettus, J. A. Jr.; Wing, R. M.; Sims, J. J. Ibid **1977**, 41.

7. (a) Jones, J. B.; Young, J. M. Can. J. Chem. **1970**, 48, 1566. (b) Calderón, A.; Font, J.; Ortuño, R. M. Tetrahedron **1984**, 40, 3787. (c) Bigorra, J.; Font, J.; Jaime, C,; Ortuño, R. M.; Sánchez-Ferrando, F. Ibid **1985**, 41, 5577.
8. See for instance: (a) Clemo, N. G.; Pattenden, G. Tetrahedron Lett. **1982**, 23, 581. (b) Begley, M. J.; Clemo, N. G.; Pattenden, G. J. Chem. Soc. Perkin Trans. I **1985**, 2393.
9. (a) Asahina, Y.; Fujita, A. Acta Phytochim. **1922**, 1, 1. (b) Moriarty, R. M.; Romain, C. R.; Karle, J. J. Am. Chem. Soc. **1965**, 87, 3251. (c) Lustig, E.; Moriarty, R. M. Ibid **1965**, 87, 3252. (d) McCombs, J. D.; Blunt, J. W.; Chambers, M. V.; Munro, M. H. G.; Robinson, W. T. Tetrahedron **1988**, 44, 1489.
10. (a) Alonso, D.; Ortí, J.; Branchadell, V.; Oliva, A.; Ortuño, R. M.; Bertrán, J.; Font, J. J. Org. Chem. **1990**, 55, 3060. (b) Branchadell, V.; Ortí, J.; Ortuño, R. M.; Oliva, A.; Font, J.; Bertrán, J.; Dannenberg, J. J. Ibid **1991**, 56, 2190. (c) Alonso, D.; Font, J.; Ortuño, R. M.; d'Angelo, J.; Guingant, A.; Bois, C. Tetrahedron, **1991**, 47, in press.
11. Alonso, D.; Font, J.; Ortuño, R. M. J. Org. Chem. **1991**, 56, in press.
12. Alonso, D.; Branchadell, V.; Font, J.; Oliva, A.; Ortuño, R. M.; Sánchez-Ferrando, F. Tetrahedron, **1990**, 46, 4371. In this paper, cycloaddition of protoanemonin to cyclopentadiene is described. The endo stereoisomer is defined as that compound in which the lactone ring oxygen occupies the endo position of the norbornene system.
13. Ingham, C. F.; Massy-Westropp, R.; Reynolds, G. D.; Thorpe, W. D. Aust. J. Chem. **1975**, 28, 2499.
14. Jones, J. B.; Young, J. M.; J. Med. Chem. **1968**, 11, 1176.
15. Font, J.; Ortuño, R. M.; Sánchez-Ferrando, F.; Segura, C.; Terris, N. Synthetic Commun. **1989**, 19, 2977.
16. Barrett, A. G. M.; Sheth, H. G. J. Org. Chem. **1983**, 48, 5017.
17. Dannenberg, J. J.; Franck, R. W. J. Org. Chem. **1985**, 50, 2635.
18. Dewar, M. J. S.; Thiel, W. J. J. Am. Chem. Soc. **1977**, 99, 4899.
19. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. J. Am. Chem. Soc. **1985**, 107, 3902.
20. Dewar, M. J. S.; Stewart, J. J. P. Quantum Chem. Prog. Exchange Bull. **1986**, 6, 24, QCPE Program 506.
21. McIver, J. W., Jr.; Komornicki, A. J. Am. Chem. Soc. **1972**, 94, 2625.