Pergamon

Tetrahedron, Vol. 53, No. 43, pp. 14763-14772, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00987-3

Cycloadditions of 3,4-Dihydro-2*H*-pyrrole 1-Oxide to Methylene-γ-butyrolactones

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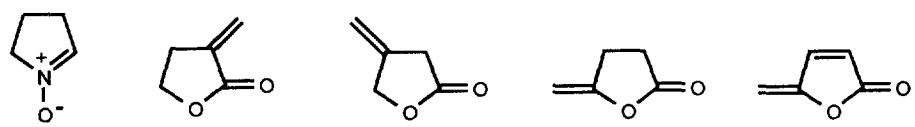
Abstract: In the reactions of nitrone **1** with several methylene-γ-butyrolactones **2-5** we have isolated and identified in all the cases the corresponding [3+2] cycloadducts. In all the adducts the oxygen atom of the dipole has linked to the more substituted carbon atom of the exocyclic double bond of the lactone. For lactone **5** the exocyclic double bond has shown higher reactivity than the endocyclic. Herein three new heterocyclic skeletons are reported. © 1997 Elsevier Science Ltd.

INTRODUCTION

1,3-Dipoles have received much attention, both from the synthetic and the mechanistic points of view, since Huisgen introduced the general concept of these reactive species.[1] During the last years we have been interested in the investigation of the cycloaddition reaction of α,β-unsaturated five, six, and seven membered lactones with cyclic nitrones and, as a result of this research, we have described some new heterocyclic systems.[2] Although the first reaction of a nitrone with an unsaturated lactone was published in 1975,[3] the number of reported examples of this type of 1,3-dipolar cycloaddition is still quite limited and all of them, including our own research,[2,4] have emerged during the last decade. In all these examples the dipolarophilic double bonds are 1,2-disubstituted and incorporated into the lactone ring, hence endocyclic.



1 **2** **3** **4** **5**

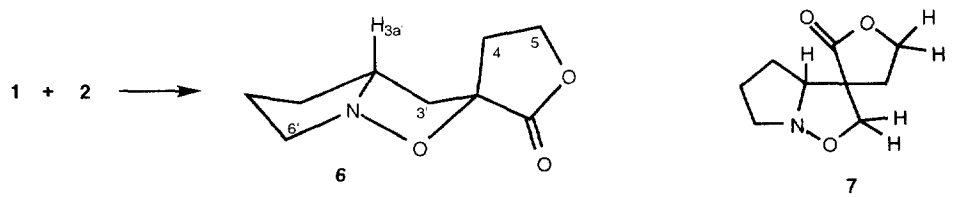
Figure 1

In an effort to extend the study of the reactivity of nitrones to other unsaturated lactones, we decided to investigate the cycloaddition between 3,4-dihydro-2*H*-pyrrole 1-oxide, **1**,[2e,5] and several five membered lactones with a terminal exocyclic double bond (Figure 1). For this purpose we chose α-methylene-γ-butyrolactone, **2**, β-methylene-γ-butyrolactone, **3**,[6] and γ-methylene-γ-butyrolactone, **4**, as representative dipolarophiles and also protoanemonin, **5**,[7] a suitable substrate for chemoselectivity studies whose chemistry

has received already much attention in our laboratories.[8] In the literature, the use of methylene-γ-butyrolactones in 1,3-dipolar processes is limited to scarce examples in which diazo compounds,[9] nitrile oxides,[10] nitrilimines,[11] and azomethine ylides[12] have been employed as dipoles. Herein we describe the 1,3-dipolar cycloaddition of nitrone **1** to lactones **2-5**.

RESULTS AND DISCUSSION

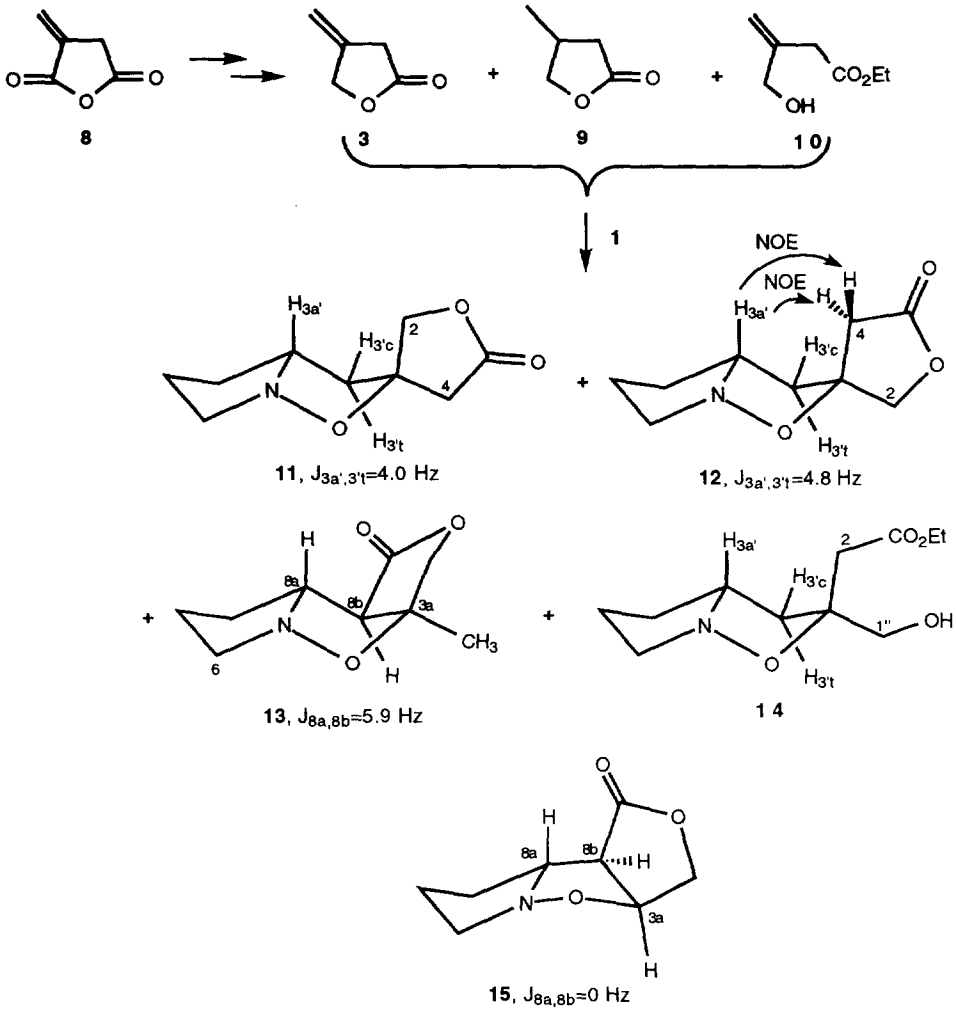
All the cycloadditions were run in chloroform at the reflux temperature. The reaction between nitrone **1** and commercially available lactone **2** was completed after 1 h and afforded a sole cycloadduct **6** as an oil in 96% yield (Scheme 1). This result evidences that lactone **2** presents much greater dipolarophilic activity than 2(5*H*)-furanone, in which the conjugated double bond is endocyclic, since the later requires 50 h to conclude its cycloaddition to **1** under the same reaction conditions.[2e] The regiochemistry of **6** can be deduced from its ^{1}H-NMR spectrum, that shows only two absorptions in the typical region of the protons α to an oxygen atom (δ 4.38 and 4.28) and a false quintuplet for the methinic proton α to nitrogen, $H_{3a'}$, (δ 3.79). These observations allow to discard the structure of the regioisomer **7** and indicate that the less sterically demanding oxygen end of the nitrone has linked to the more crowded carbon atom of the olefin. This fact is in agreement with previous results of nitrone cycloadditions to terminal electron-deficient olefins,[13] where the electronic effects are overwhelmed by steric interactions. The stereochemistry of **6** is assumed to be *endo* based on previous results of cycloadditions of nitrones to terminal conjugated olefins.[13] Compound **6** is the first example of the heterocyclic skeleton spiro[furo-3(2*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole].



Scheme 1

β-Methylene-γ-butyrolactone, **3**, was prepared from itaconic anhydride, **8**, according to a previously described method,[6] but we encountered some problems and **3** could only be obtained in *ca.* 70% purity, along with 25% of 4,5-dihydro-4-methyl-2(3*H*)-furanone, **9**, and 5% of ethyl 4-hydroxy-3-methylenebutyrate, **10**. Treatment of this mixture with excess of nitrone **1** during 16 h yielded a complex reaction crude (tlc analysis). After repeated column chromatographies we were able to isolate four pure compounds, identified as **11-14**, although in very low yields (Scheme 2).

Compounds **11** (16%) and **12** (19%) are positional isomers of **6** containing the same new heterocyclic skeleton. Their regiochemistry was evidenced, as in adduct **6**, by the presence of only two absorptions at δ>4, corresponding to the protons at C_2. In product **12** the irradiation of proton $H_{3a'}$ at δ 3.66 causes a small NOE on both hydrogen atoms at C_4. This result permits us to establish the stereochemistry of **12**, and therefore **11** presents the alternative stereochemistry. A remarkable anisotropy is observed for the pair of diastereotopic protons at C_2 in **11** and those at C_4 in **12**. As it will be seen later these carbon atoms are in pseudoaxial orientation in the preferred conformer of the compounds, as is evidenced by their values of $J_{3a',3'trans}$.



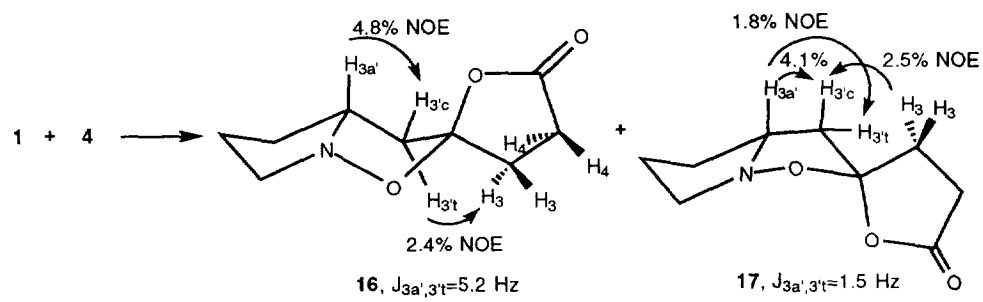
Scheme 2

Compound **13** (18% yield) derives from the reaction between nitrone **1** and 4-methyl-2(5*H*)-furanone, a more stable isomer of lactone **3**, that is presumably formed in the reaction conditions and has a more reactive conjugated double bond. The ^{1}H-NMR spectrum of **13** shows a singlet at δ 1.48, demonstrating the existence of a methyl group attached to a tetrasubstituted carbon atom, and the presence of only two protons in a position α to oxygen. The last fact would be inconsistent with the structure of the other possible regioisomer. The stereochemistry of **13** is assumed to be *exo* considering all our previous results on cycloadditions of cyclic nitrones to α,β-unsaturated lactones.[2] It is worth mention that the value of the coupling constant $J_{8a,8b}$=5.9 Hz is intermediate between those observed for the *exo* adduct **15** ($J_{8a,8b}$=0 Hz), derived from **1** and 2(5*H*)-furanone (Scheme 2), and the corresponding *endo* isomer ($J_{8a,8b}$=9.4 Hz), in which H_{8a} and H_{8b} are *cis* to each other and almost eclipsed.[2e] Obviously, the presence of the methyl group modifies the conformational behaviour of this tricyclic system. An orthogonal arrangement between H_{8a} and H_{8b} ($J_{8a,8b}$=0 Hz) in

compounds **13** and **15** would settle the substituent at C_{3a} in a pseudoaxial position, which may be suitable for a hydrogen atom, but not for a methyl group. A change in the envelope conformation of the isoxazolidine ring in **13** locates the methyl group in a less sterically demanding position with a concomitant increase of the dihedral angle between H_{8a} and H_{8b}.

The remaining isolated adduct **14** presents in its ^{1}H-NMR spectrum a triplet at δ 1.20 and a quadruplet at δ 4.08, which reveal the presence of an ethyl ester and therefore this compound must evolve from **10**, one of the impurities accompanying lactone **3**. The relative stereochemistry of **14** was assured through a chemical correlation experiment: treatment of **14** with a catalytic amount of trifluoroacetic acid in $CDCl_3$ at 50 °C led to the formation of **12**.

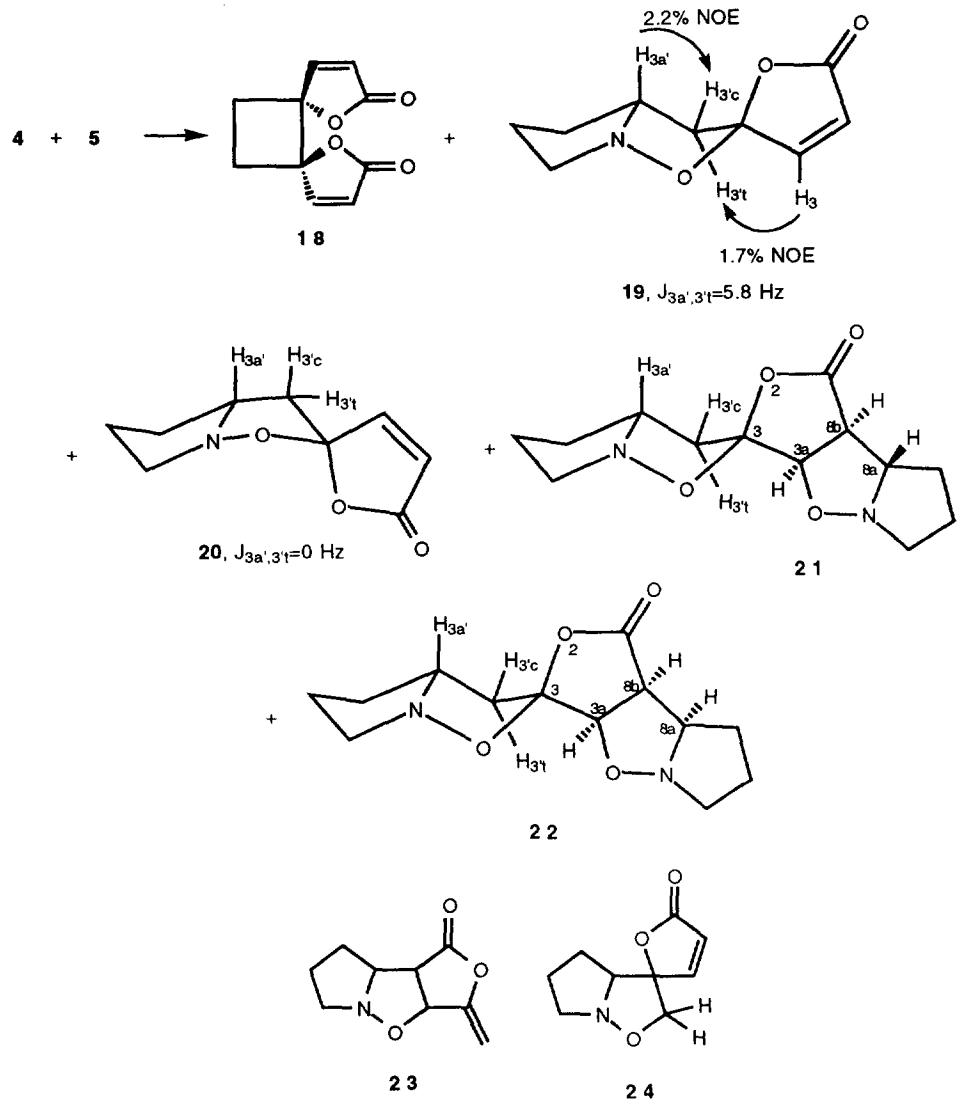
According to previously reported data and in agreement with the FMO theory, the higher electronic density of its double bond compared with the other lactones, makes lactone **4** less reactive towards nitrone **1**. After fourteen days of reaction in the usual conditions, we obtained a *ca.* 3:2 mixture of two cycloadducts, **16** and **17**, in 69% yield (Scheme 3). Successive column chromatographies allowed the isolation of pure samples of both compounds. The spiro[furo-2(3*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole] heterocyclic system present in these adducts had not been described before. The presence of absorptions at δ 113.2 and 114.8 in the ^{13}C-NMR spectra of **16** and **17** respectively, demonstrates the formation of the spiroketal moiety and discards a regioisomeric structure. Both steric and electronic effects favour the observed regioselectivity.



Scheme 3

With the help of COSY, ^{1}H/^{13}C correlation, and HMBC[14] experiments all the signals of the ^{1}H and ^{13}C-NMR spectra of **16** and **17** could be unambiguously associated to the corresponding nuclei. The stereochemical elucidation of the adducts was based on NOE experiments. For compound **16**, presaturation of $H_{3a'}$ (δ 3.92) produces 4.8% enhancement of the signal at δ 2.92, corresponding to one of the hydrogen atoms at $C_{3'}$, that was therefore assigned to $H_{3'cis}$, while irradiation of the signal corresponding to $H_{3'trans}$ (δ 2.14) causes 2.4% NOE on the absorption of the lactonic protons H_3 (δ 2.35). For isomer **17** the irradiation of $H_{3a'}$ produces 4.1% and 1.8% NOE on $H_{3'cis}$ (δ 2.68) and $H_{3'trans}$ (δ 2.55) respectively and presaturation of protons H_3 causes only an enhancement of the signal corresponding to $H_{3'cis}$.

We believe that the preferred conformation of the hexahydropyrrolo[1,2-*b*]isoxazole system in **16** and **17** is that depicted in Scheme 3, with the methylene group at $C_{2'}$ in pseudoequatorial location. This assumption is supported by the values of $J_{3a',3'trans}$ (5.2 and 1.5 Hz in **16** and **17** respectively), which match with the values previously observed for **11** (4.0 Hz), **12** (4.8 Hz), **13** (5.9 Hz), and **15** (0 Hz).



Scheme 4

In the cycloaddition of **1** to **5**, tlc analysis indicated the consumption of protoanemonin after 4 h of reaction. After several purifications by column chromatography we could isolate and identify anemonin, **18**, (15%)[15] the three cycloadducts **19-21** in pure form, and a 2:1 mixture of **21** and **22** (Scheme 4). The structural elucidation of the 1:1 adducts **19** (50%) and **20** (2%) is based on their spectroscopic data. The chemoselectivity of the cycloaddition is evidenced by the presence of a conjugated double bond in both compounds, that show signals at δ 7.04/7.05 and 6.16/6.16 in the ^{1}H-NMR and at δ 149.5/150.7 and 125.1/124.6 in the ^{13}C-NMR spectra, respectively. The regioselectivity is proved by the existence of one acetalic carbon atom in both **19** (δ 112.2) and **20** (δ 113.4). Isomeric adducts with the structure of **23** or **24**

were not detected. The stereochemistry of the major adduct **19** was determined by NOE experiments: when $H_{3a'}$ (δ 4.07) was irradiated a NOE of 2.2% was observed on $H_{3'cis}$ at δ 2.87, while $H_{3'trans}$ (δ 2.36) was not affected, meanwhile presaturation of H_3 produces exclusively enhancement (1.7%) of the signal corresponding to $H_{3'trans}$. Therefore, **19** derives from an *endo* transition state, referred to the endocyclic double bond of **5**, and the stereochemistry of **20** is assigned as *exo* by exclusion. The value of the coupling constant $J_{3a',3'trans}$ of 5.8 Hz for **19** is in agreement with a preference for a butterfly conformation of the azabicyclic system as depicted in Scheme 4. By the contrary, the conformational preference of adduct **20** with $J_{3a',3'trans}$=0 Hz must resemble to that of compounds **15** and **17**.

In the reaction between nitrone **1** and lactone **5** we also obtained 11% yield of a mixture of two products that lacked double bond absorptions in their NMR spectra and were identified as the 2:1 cycloadducts **21** and **22**. Only the major component **21** could be isolated in pure form. Diagnostic observations for the structure of **21** are the signal of the acetal carbon atom (δ 114.8) and the doublet corresponding to H_{3a} (δ 4.58). The relative stereochemistry between $C_{3a'}$ and C_3 must be *endo* as in adduct **19**, since the multiplicity pattern of $H_{3a'}$ is identical for both compounds. On the other hand, H_{8a} and H_{8b} must be *trans* to each other according to their coupling constant $J_{8a,8b}$=0 Hz, as in compound **15** (Scheme 2).[2e] We can therefore conclude that the nitrone has approached in an *endo* mode to the exocyclic double bond of protoanemonin and in an *exo* mode to the endocyclic double bond. The relative stereochemistry at C_{3a} and $C_{3a'}$ remains to be established, but both faces of the double bond of **19** present significantly different steric congestion – an oxygen atom (1') *vs.* a methylene group (3') – and we assume that the second cycloaddition results from the attack of the nitrone to the less hindered face of **19**. The spectroscopic data of **22** are very similar to those of **21**, being the major difference the value of $J_{8a,8b}$=9.5 Hz, indicative of a *cis* relationship between H_{8a} and H_{8b} in **22**. Likely, **22** derives also from the major 1:1 adduct **19** and now the addition of the nitrone has taken place by the same face of the endocyclic double bond through an *endo* transition state.

We can conclude that the exocyclic double bond of **5** is more reactive than the endocyclic towards nitrones. This behaviour is in agreement with the unique reported precedent of a 1,3-dipolar cycloaddition to protoanemonin in which a nitrile oxide was the dipole component[10c] and it also parallels previous findings in Diels-Alder reactions.[8b,8c]

In summary, we have studied the reactivity of unsaturated γ-butyrolactones **2-4** towards nitrone **1**. Through these reactions we have obtained the first examples of the heterocyclic skeletons spiro[furo-3(2*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole] and spiro[furo-2(3*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole]. We have also performed the second case of a 1,3-dipolar cycloaddition to protoanemonin **5**, which reveals the higher reactivity of its exocyclic double bond in this kind of reaction. The isolation of the first cycloadduct derived from a double 1,3-dipolar cycloaddition to **5** permits the description of the new heterocyclic system of spiro[furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-3(3a*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole]. Finally, an accurate conformational analysis of the isoxazolidine ring of several hexahydropyrrolo[1,2-*b*]isoxazole derivatives has been accomplished.

EXPERIMENTAL SECTION

Lactones **2** and **4** are commercially available. The following products were prepared according to previously described methods: **3** (*ca.* 70% purity),[6] **5**,[7] and **1**.[2e,5] Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were

concentrated using a rotary evaporator at 15-20 Torr. Column chromatographies were performed by using Merck silica gel (230-400 mesh) unless otherwise stated. Distillation of small amounts were effected on a Büchi KRV 65/30 rotary distiller (only oven temperature given). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC-250-WB or AM-400-WB instruments in $CDCl_3$ solutions unless otherwise stated. Mass spectra were performed on a Hewlett-Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

(3RS,3a'SR)-Hexahydrospiro[furo-3(2H),2'(3'H)-pyrrolo[1,2-b]isoxazol]-2-one, **6**

A solution of **2** (99 mg, 1.01 mmol) in $CHCl_3$ (5 mL) at room temperature was added to a solution of **1** (185 mg, 2.17 mmol) in the same solvent (5 mL) and the mixture was heated at 70 °C for 1 h. Flash chromatography of the crude material (256 mg) using chloroform-methanol 9:1 as eluent afforded adduct **6** (178 mg, 0.97 mmol, 96% yield) as a brown oil, that was purified by distillation (bp. 115-116 °C/0.02 mm Hg). **6**: IR (film): 2956, 2877, 1783, 1446, 1376, 1245, 1220, 1181, 1090, 1020 cm^{-1}; ^{1}H-NMR (400 MHz): δ 4.38 (dt, $J_{5,5}$=9.0 Hz, $J_{5,4}$=$J_{5,4}$=7.2 Hz, 1H: H_5), 4.28 (ddd, $J_{5,5}$=9.0 Hz, $J_{5,4}$=7.9 Hz, $J_{5,4}$=4.7 Hz, 1H: H_5), 3.79 (br quintuplet, $J_{3a',3'}$≈$J_{3a',3'}$≈$J_{3a',4'}$≈$J_{3a',4'}$≈6.5 Hz, 1H: $H_{3a'}$), 3.40 (ddd, $J_{6',6'}$=12.8 Hz, $J_{6',5'}$=7.7 Hz, $J_{6',5'}$=5.1 Hz, 1H: $H_{6'}$), 3.06 (dt, $J_{6',6'}$=12.8 Hz, $J_{6',5'}$=$J_{6',5'}$=7.6 Hz, 1H: $H_{6'}$), 2.55 (ddd, $J_{4,4}$=13.4 Hz, $J_{4,5}$=7.2 Hz, $J_{4,5}$=4.7 Hz, 1H: H_4), 2.51 (d, $J_{3',3a'}$=6.5 Hz, 2H: 2x$H_{3'}$), 2.23 (dt, $J_{4,4}$=13.4 Hz, $J_{4,5}$=$J_{4,5}$=7.6 Hz, 1H: H_4), 2.13 (m, 1H: $H_{5'}$), 1.95 (m, 2H: 2x$H_{4'}$), 1.76 (m, 1H: $H_{5'}$); ^{13}C-NMR (62.5 MHz): δ 175.8 (C_2), 82.4 (C_3), 66.2 ($C_{3a'}$), 65.7 (C_5), 56.0 ($C_{6'}$), 44.0 ($C_{3'}$), 35.8 (C_4), 29.3 ($C_{4'}$), 23.1 ($C_{5'}$); MS (*m/z*) 183 (M^+, 22), 85 (100), 83 (26), 82 (24), 68 (35), 55 (90), 42 (28), 41 (41). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.04; H, 7.09; N, 7.68.

Cycloaddition of nitrone **1** *to β-methylene-γ-butyrolactone*, **3**

A solution of 200 mg of **3** (*ca.* 70% purity, 1.43 mmol, containing 25% of 4,5-dihydro-4-methyl-2(3*H*)-furanone and 5% of ethyl 4-hydroxy-3-methylenebutyrate) in $CHCl_3$ (1 mL) at room temperature was added to a solution of **1** (326 mg, 3.83 mmol) in the same solvent (4 mL) and the mixture was heated at 70 °C for 16 h. Flash chromatography of the crude material (470 mg) using ethyl acetate as eluent afforded the following fractions: i) 60 mg of a *ca.* 4:1 mixture of **13** and **14**; ii) 40 mg of a *ca.* 1:3 mixture of **14** and **11**; iii) 36 mg of a *ca.* 1:2 mixture of **11** and **12**; iv) 25 mg of pure **12**; and v) 250 mg (77%) of nitrone **1**. Approximate yields for **13**, **11**, and **12** are 18%, 16%, and 19% respectively, based on lactone **3**. Repeated column chromatographies of these fractions using silica gel (Baker) and the same eluent allowed the isolation of analytical samples of **13**, **14** and **11**. (3a*RS*,8a*SR*,8b*SR*)-octahydro-3a-methylfuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **13**: IR (film): 2966, 1771, 1377, 1187, 1145, 1033 cm^{-1}; ^{1}H-NMR (250 MHz): δ 4.25 (d, $J_{3,3}$=10.5 Hz, 1H: H_3), 4.00 (d, $J_{3,3}$=10.5 Hz, 1H: H_3), 3.92 (td, $J_{8a,8}$=$J_{8a,8}$=8.6 Hz, $J_{8a,8b}$=5.9 Hz, 1H: H_{8a}), 3.25 (d, $J_{8b,8a}$=5.9 Hz, 1H: H_{8b}), 3.21 (ddd, $J_{6,6}$=13.7 Hz, $J_{6,7}$=7.0 Hz, $J_{6,7}$=3.8 Hz, 1H: H_6), 2.90 (dt, $J_{6,6}$=13.7 Hz, $J_{6,7}$=$J_{6,7}$=7.7 Hz, 1H: H_6), 2.10-1.60 (m, 4H: 2xH_7, 2xH_8), 1.48 (s, 3H: CH_3); ^{13}C-NMR (62.5 MHz): δ 175.3 (C_1), 85.7 (C_{3a}), 74.7 (C_3), 68.0 (C_{8a}), 57.3/ 55.9 (C_6/C_{8b}), 26.0/24.3 (C_7/C_8), 21.6 (CH_3); MS (*m/z*) 183 (M^+, 19), 182 (25), 124 (35), 99 (46), 86 (35), 85 (100), 84 (53), 83 (50), 82 (39), 55 (64), 43 (89). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.97; H, 7.29; N, 7.31. Ethyl 2-[(2*RS*,3a*SR*)-hexahydro-2-hydroxymethyl[pyrrolo[1,2-*b*]isoxazol-2-yl]acetate, **14**: IR

(film): 3600-3000, 2931, 2868, 1729, 1370, 1335, 1187, 1089, 1060, 1033 cm^{-1}; ^{1}H-NMR (250 MHz): δ 4.08 (q, J=7.1 Hz, 2H: CH_3CH_2O), 3.76-3.56 (m, 3H: $H_{3a'}$, 2x$H_{1''}$), 3.28 (ddd, $J_{6',6'}$=13.4 Hz, $J_{6',5'}$=6.6 Hz, $J_{6',5'}$=3.5 Hz, 1H: $H_{6'}$), 2.87 (ddd, $J_{6',6'}$=13.4 Hz, $J_{6',5'}$=9.3 Hz, $J_{6',5'}$=6.7 Hz, 1H: $H_{6'}$), 2.77 (d, $J_{2,2}$=13.6 Hz, 1H: H_2), 2.66 (d, $J_{2,2}$=13.6 Hz, 1H: H_2), 2.50 (dd, $J_{3',3'}$=12.8 Hz, $J_{3',3a'}$=8.0 Hz, 1H: $H_{3'}$), 1.97 (dd, $J_{3',3'}$=12.8 Hz, $J_{3',3a'}$=4.7 Hz, 1H: $H_{3'}$), 1.98-1.55 (m, 5H: 2x$H_{4'}$, 2x$H_{5'}$, OH), 1.20 (t, J=7.1 Hz, 3H: CH_3); ^{13}C-NMR (62.5 MHz): δ 171.7 (C_1), 83.2 ($C_{2'}$), 65.9 ($C_{3a'}$ and $C_{1''}$), 60.6 (CH_3CH_2O), 56.7 ($C_{6'}$), 42.7/40.4 ($C_2/C_{3'}$), 31.6 ($C_{4'}$), 23.9 ($C_{5'}$), 14.1 (CH_3); ^{13}C-NMR (62.5 MHz, d_6-acetone): δ 171.5 (C_1), 84.1 ($C_{2'}$), 66.5/65.8 ($C_{3a'}/C_{1''}$), 60.4 (CH_3CH_2O), 56.9 ($C_{6'}$), 43.2/40.7 ($C_2/C_{3'}$), 32.2 ($C_{4'}$), 24.5 ($C_{5'}$), 14.4 (CH_3). (3*RS*,3a'*RS*)-Tetrahydrospiro[furo-3(2*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazol]-5(4*H*)-one, **11**: IR (film): 2959, 2924, 2875, 1778, 1462, 1279, 1166, 1019 cm^{-1}; ^{1}H-NMR (250 MHz): δ 4.54 (d, $J_{2,2}$=9.7 Hz, 1H: H_2), 4.02 (d, $J_{2,2}$=9.7 Hz, 1H: H_2), 3.61 (m, 1H: $H_{3a'}$), 3.32 (ddd, $J_{6',6'}$=13.9 Hz, $J_{6',5'}$=7.0 Hz, $J_{6',5'}$=3.0 Hz, 1H: $H_{6'}$), 2.84 (ddd, $J_{6',6'}$=13.9 Hz, $J_{6',5'}$=9.5 Hz, $J_{6',5'}$=7.2 Hz, 1H: $H_{6'}$), 2.63 (s, 2H: 2xH_4), 2.53 (dd, $J_{3',3'}$=13.0 Hz, $J_{3',3a'}$=8.0 Hz, 1H: $H_{3'}$), 2.08 (dd, $J_{3',3'}$=13.0 Hz, $J_{3',3a'}$=4.0 Hz, 1H: $H_{3'}$), 2.08-1.46 (m, 4H: 2x$H_{4'}$, 2x$H_{5'}$); ^{13}C-NMR (62.5 MHz): δ 174.7 (C_5), 83.1 (C_3), 77.7 (C_2), 65.8 ($C_{3a'}$), 56.5 ($C_{6'}$), 43.5 ($C_{3'}$), 37.9 (C_4), 31.9 ($C_{4'}$), 24.3 ($C_{5'}$); MS (*m/z*) 183 (M^+, 22), 86 (100), 85 (53), 55 (46). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.29; H, 7.48; N, 7.16. (3*RS*,3a'*SR*)-Tetrahydrospiro[furo-3(2*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazol]-5(4*H*)-one, **12**: IR (film): 2959, 2924, 2868, 1771, 1173, 1152, 1019 cm^{-1}; ^{1}H-NMR (250 MHz): δ 4.30 (d, $J_{2,2}$=10.1 Hz, 1H: H_2), 4.23 (d, $J_{2,2}$=10.1 Hz, 1H: H_2), 3.66 (tt, $J_{3a',3'}$=$J_{3a',4'}$=8.0 Hz, $J_{3a',3'}$=$J_{3a',4'}$=4.8 Hz, 1H: $H_{3a'}$), 3.30 (ddd, $J_{6',6'}$=13.7 Hz, $J_{6',5'}$=6.8 Hz, $J_{6',5'}$=3.0 Hz, 1H: $H_{6'}$), 2.98 (d, $J_{4,4}$=17.7 Hz, 1H: H_4), 2.87 (ddd, $J_{6',6'}$=13.7 Hz, $J_{6',5'}$=9.5 Hz, $J_{6',5'}$=7.0 Hz, 1H: $H_{6'}$), 2.56 (dd, $J_{3',3'}$=12.8 Hz, $J_{3',3a'}$=8.0 Hz, 1H: $H_{3'}$), 2.46 (d, $J_{4,4}$=17.7 Hz, 1H: H_4), 1.95 (dd, $J_{3',3'}$=12.8 Hz, $J_{3',3a'}$=4.8 Hz, 1H: $H_{3'}$), 2.05-1.46 (m, 4H: 2x$H_{4'}$, 2x$H_{5'}$); ^{13}C-NMR (62.5 MHz): δ 175.0 (C_5), 83.4 (C_3), 74.5 (C_2), 65.4 ($C_{3a'}$), 56.6 ($C_{6'}$), 44.9 ($C_{3'}$), 40.9 (C_4), 32.0 ($C_{4'}$), 24.0 ($C_{5'}$); MS (*m/z*) 183 (M^+, 19), 86 (100), 85 (40), 55 (50).

(2RS,3a'SR)-Tetrahydrospiro[furo-2(3H),2'(3'H)-pyrrolo[1,2-b]isoxazol]-5(4H)-one, **16**, *and its (2RS,3a'RS)-isomer,* **17**

A solution of **4** (355 mg, 3.62 mmol) in $CHCl_3$ (5 mL) at room temperature was added to a solution of **1** (389 mg, 4.57 mmol) in the same solvent (5 mL) and the mixture was heated at 70 °C for 14 d. Flash chromatography of the crude material (713 mg) afforded the following fractions: i) starting lactone **4** (70 mg, 20%) using methylene chloride-ether 9:1 as eluent; ii) a *ca.* 3:2 mixture of adducts **16** and **17**, respectively (366 mg, 2.00 mmol, 55% yield, 69% considering recovered **4**) using chloroform-methanol 9:1 as eluent; and iii) nitrone **1** (77 mg, 20%) with the same eluent. Repeated column chromatography of the second fraction on silica gel (Baker) with chloroform-methanol 9:1 as mobile phase allowed the isolation of pure samples of both adducts. **16**: mp 52-53 °C (hexane); ^{1}H-NMR (400 MHz): δ 3.92 (tt, $J_{3a',3'}$=$J_{3a',4'}$=7.8 Hz, $J_{3a',3'}$=$J_{3a',4'}$=5.0 Hz, 1H: $H_{3a'}$), 3.37 (ddd, $J_{6',6'}$=13.8 Hz, $J_{6',5'}$=6.3 Hz, $J_{6',5'}$=2.6 Hz, 1H: $H_{6'}$), 2.98 (ddd, $J_{6',6'}$=13.8 Hz, $J_{6',5'}$=9.3 Hz, $J_{6',5'}$=6.6 Hz, 1H: $H_{6'}$), 2.92 (dd, $J_{3',3'}$=13.5 Hz, $J_{3',3a'}$=8.1 Hz, 1H: $H_{3'}$), 2.72 (dt, $J_{4,4}$=17.4 Hz, $J_{4,3}$=$J_{4,3}$=9.8 Hz, 1H: H_4), 2.50 (ddd, $J_{4,4}$=17.4 Hz, $J_{4,3}$=8.5 Hz, $J_{4,3}$=3.8 Hz, 1H: H_4), 2.35 (m, 2H, 2xH_3), 2.14 (dd, $J_{3',3'}$=13.5 Hz, $J_{3',3a'}$=5.2 Hz, 1H: $H_{3'}$), 1.95 (m, 2H: $H_{4'}$ and $H_{5'}$), 1.76 (m, 1H: $H_{5'}$), 1.61 (m, 1H: $H_{4'}$); ^{13}C-NMR (62.5 MHz): δ 175.1 (C_5), 113.2 (C_2), 64.6 ($C_{3a'}$), 57.3 ($C_{6'}$), 47.5 ($C_{3'}$), 32.0 ($C_{4'}$), 30.2 (C_3), 29.0 (C_4), 23.8 ($C_{5'}$); MS (*m/z*) 183 (M^+, 21), 86 (100), 85 (21), 82 (26), 68 (44), 55

(43), 41 (21). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.10; H, 7.20; N, 7.63. **17**: ^{1}H-NMR (400 MHz): δ 3.87 (qd, $J_{3a',3a'}=J_{3a',4'}=J_{3a',4'}=7.6$ Hz, $J_{3a',3'}=1.5$ Hz, 1H: $H_{3a'}$), 3.43 (dt, $J_{6',6'}=12.6$ Hz, $J_{6',5'}=J_{6',5'}=6.6$ Hz, 1H: $H_{6'}$), 3.18 (dt, $J_{6',6'}=12.6$ Hz, $J_{6',5'}=J_{6',5'}=7.2$ Hz, 1H: $H_{6'}$), 2.70 (dt, $J_{4,4}=17.3$ Hz, $J_{4,3}=J_{4,3}=9.7$ Hz, 1H: H_4), 2.68 (dd, $J_{3',3'}=13.5$ Hz, $J_{3',3a'}=8.7$ Hz, 1H: $H_{3'}$), 2.55 (dd, $J_{3',3'}=13.5$ Hz, $J_{3',3a'}=1.5$ Hz, 1H: $H_{3'}$), 2.48 (ddd, $J_{4,4}=17.3$ Hz, $J_{4,3}=7.0$ Hz, $J_{4,3}=5.2$ Hz, 1H: H_4), 2.35 (m, 2H, 2xH_3), 2.14 (m, 1H: $H_{5'}$), 1.95 (m, 2H: 2x$H_{4'}$), 1.68 (m, 1H: $H_{5'}$); ^{13}C-NMR (62.5 MHz): δ 175.5 (C_5), 114.8 (C_2), 64.4 ($C_{3a'}$), 58.5 ($C_{6'}$), 46.4 ($C_{3'}$), 31.3 (C_3), 30.7 ($C_{4'}$), 28.4 (C_4), 24.1 ($C_{5'}$).

Cycloaddition of nitrone **1** *to protoanemonin,* **5**

A solution of **5** (166 mg, 1.73 mmol) in $CHCl_3$ (10 mL) at room temperature was added to a solution of **1** (202 mg, 2.37 mmol) in the same solvent (5 mL) and the mixture was heated at 70 °C for 4 h. Flash chromatography of the crude material (368 mg) afforded the following fractions: i) anemonin **18** (25 mg, 15%) using methylene chloride-ether 9:1 as eluent; ii) 156 mg (0.86 mmol, 50% yield) of (2*RS*,3a'*RS*)-3a',4',5',6'-tetrahydrospiro[furo-2(5*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazol]-5-one, **19**, with the same eluent; iii) 7 mg (2% yield) of the (2*RS*,3a'*SR*)-isomer, **20**, with chloroform-methanol 9:1 as mobile phase; and iv) a 4:1 mixture of (3*RS*,3a*RS*,8a*SR*,8b*SR*,3a'*RS*)-spiro[tetrahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-3(3a*H*),2'(3'*H*)-tetrahydropyrrolo[1,2-*b*]isoxazol]-1(8b*H*)-one, **21**, and its (3*RS*,3a*RS*,8a*RS*,8b*SR*,3a'*RS*)-isomer, **22**, (51 mg, 0.19 mmol, 11% yield) with the same eluent. Repeated column chromatography of the last fraction allowed the isolation of 16 mg of pure **21** and a 2:1 mixture of **21** and **22**. **19**: mp 84-85 °C (ethyl acetate-pentane); ^{1}H-NMR (250 MHz): δ 7.04 (d, $J_{3,4}=5.8$ Hz, 1H: H_3), 6.16 (d, $J_{4,3}=5.8$ Hz, 1H: H_4), 4.07 (m, 1H: $H_{3a'}$), 3.44 (ddd, $J_{6',6'}=13.9$ Hz, $J_{6',5'}=6.2$ Hz, $J_{6',5'}=3.3$ Hz, 1H: $H_{6'}$), 3.07 (ddd, $J_{6',6'}=13.9$ Hz, $J_{6',5'}=9.1$ Hz, $J_{6',5'}=6.9$ Hz, 1H: $H_{6'}$), 2.87 (dd, $J_{3',3'}=13.5$ Hz, $J_{3',3a'}=7.7$ Hz, 1H: $H_{3'}$), 2.36 (dd, $J_{3',3'}=13.5$ Hz, $J_{3',3a'}=5.8$ Hz, 1H: $H_{3'}$), 2.01 (m, 2H: $H_{4'}$ and $H_{5'}$), 1.82 (m, 1H: $H_{5'}$), 1.68 (m, 1H: $H_{4'}$); ^{13}C-NMR (62.5 MHz): δ 169.4 (C_5), 149.5 (C_3), 125.1 (C_4), 112.2 (C_2), 65.5 ($C_{3a'}$), 57.4 ($C_{6'}$), 45.7 ($C_{3'}$), 31.5 ($C_{4'}$), 23.7 ($C_{5'}$); MS (*m/z*) 181 (M^+, 13), 85 (100), 68 (24), 55 (84), 41 (21). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.58; H, 6.13; N, 7.71. **20**: IR (film) 2925, 2854, 1770, 1096, 912 cm^{-1}; ^{1}H-NMR (250 MHz): δ 7.05 (d, $J_{3,4}=5.4$ Hz, 1H: H_3), 6.16 (d, $J_{4,3}=5.4$ Hz, 1H: H_4), 3.99 (q, $J_{3a',3'}\approx J_{3a',4'}\approx J_{3a',4'}\approx 7.7$ Hz, 1H: $H_{3a'}$), 3.54 (dt, $J_{6',6'}=13.0$ Hz, $J_{6',5'}=J_{6',5'}=6.0$ Hz, 1H: $H_{6'}$), 3.20 (dt, $J_{6',6'}=13.0$ Hz, $J_{6',5'}=J_{6',5'}=7.0$ Hz, 1H: $H_{6'}$), 2.89 (dd, $J_{3',3'}=13.4$ Hz, $J_{3',3a'}=8.7$ Hz, 1H: $H_{3'}$), 2.46 (d, $J_{3',3'}=13.4$ Hz, 1H: $H_{3'}$), 2.25 (m, 1H: $H_{4'}$), 2.00 (m, 2H), 1.74 (m, 1H); ^{13}C-NMR (62.5 MHz): δ 169.7 (C_5), 150.7 (C_3), 124.6 (C_4), 113.4 (C_2), 65.3 ($C_{3a'}$), 59.0 ($C_{6'}$), 45.6 ($C_{3'}$), 30.7 ($C_{4'}$), 24.2 ($C_{5'}$). **21**: ^{1}H-NMR (250 MHz): δ 4.58 (d, $J_{3a,8b}=7.0$ Hz, 1H: H_{3a}), 3.88 (m, 2H: $H_{3a'}$ and H_{8a}), 3.52 (d, $J_{8b,3a}=7.0$ Hz, 1H: H_{8b}), 3.37 (m, 2H: $H_{6'}$ and H_6), 2.99 (m, 2H: $H_{6'}$ and H_6), 2.86 (dd, $J_{3',3'}=14.2$ Hz, $J_{3',3a'}=7.7$ Hz, 1H: $H_{3'}$), 2.64 (dd, $J_{3',3'}=14.2$ Hz, $J_{3',3a'}=5.1$ Hz, 1H: $H_{3'}$), 2.20-1.50 (m, 8H); ^{13}C-NMR (62.5 MHz): δ 174.2 (C_1), 114.8 (C_3), 80.3 (C_{3a}), 70.5 (C_{8a}), 64.8 ($C_{3a'}$), 57.3/56.4/55.5 (C_6/$C_{6'}$/C_{8a}), 43.1 ($C_{3'}$), 31.5/29.9/24.2/23.9 (C_7/C_8/$C_{4'}$/$C_{5'}$). **22**: ^{1}H-NMR (250 MHz) (observed signals from the 2:1 mixture of **21**/**22**) 4.53 (d, $J_{3a,8b}=6.2$ Hz, 1H: H_{3a}), 3.77 (dd, $J_{8b,8a}=9.5$ Hz, $J_{8b,3a}=6.2$ Hz,1H: H_{8b}); ^{13}C-NMR (62.5 MHz): δ 173.3 (C_1), 111.5 (C_3), 82.5, 68.5, 56.1, 53.3, 31.7, 26.1, 24.3.

Acknowledgements. We gratefully acknowledge the *Ministerio de Educación y Ciencia* for financial support through *DGICYT* (project PB92-0605).

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(*Received in UK* 21 *July* 1997; *revised* 19 *August* 1997; *accepted* 21 *August* 1997)