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Nitroalkylation and nitroalkenylation reactions of γ-lactone enolates. A facile ring switch from polysubstituted γ-lactones to polysubstituted γ-lactams

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Abstract—Michael addition of lithium enolates of γ-butyrolactone **1** and α-methyl-γ-butyrolactone **1′** to (*E*)-1-nitropropene **2**, (*E*)-β-nitrostyrene **3** and (*E*)-2-nitro-1-phenylpropene **4** is described. Reactions of the lithium enolate of **1′** with **2** and **4** occurred with high diasteroselectivity (80 and 92% d.e., respectively). Reactions of the zinc enolate of **1′** with two β-nitroenamines and two methylthio-substituted 1-amino-2-nitro-1,3-dienes were also examined. Catalytic reduction of the nitroalkylated and nitroalkenylated products allowed the achievement of functionalized γ-lactams and/or cyclic hydroxamic acids.
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1. Introduction

Polyfunctionalized γ-lactones are frequently encountered in the literature,[1] owing to the fact that many natural products, in particular those belonging to the sesquiterpene series,[2] contain the γ-lactone ring in their structure. Many examples of α-functionalization and α,α-difunctionalization of γ-lactone rings are present in the literature[3] and among them a new class of anticonvulsant drugs can be mentioned.[4] α-Nitroalkenylation reactions were extensively studied,[5] with the aim of preparing compounds possessing quaternary stereocentres,[6] whereas no examples of nitroalkylation reactions of γ-lactones can be found. On the contrary, Enders and co-workers[7] obtained excellent results in the diastereo- and enantio-selective Michael additions of enolates of γ-lactams to aliphatic and aromatic nitroolefins. Seebach and coworkers[8] investigated the nitroalkylation reactions of lithium enolates of other five-membered ring heterocycles, such as chiral non-racemic 2-*t*-butyl-1,3-dioxolan-4-ones, 2-*t*-butylimidazolidin-4-ones and 2-*t*-butyloxazolidin-5-ones, to verify the 1,3 asymmetric induction on the reaction products. In all cases examined the diastereoselectivity was high, depending however on whether the position α to the carbonyl group was substituted or not.

In this paper we describe the nitroalkylation reactions of the lithium enolates of γ-butyrolactone **1** and α-methyl-γ-butyrolactone **1′** with a few conjugated nitroolefins, such as (*E*)-1-nitropropene **2**, (*E*)-β-nitrostyrene **3** and (*E*)-2-nitro-1-phenylpropene **4**. Nitroalkenylation reactions have also been carried out, by reacting the zinc enolate of compound **1′** with the β-nitroenamines **5**[9] and **6**[10] as well as with the nitrodienes **7**,[11,12] and **7′**[12] (Fig. 1).

2. Results and discussion

2.1. Nitroalkylation reactions

The butanolides **1** and **1′** were enolized with lithium diisopropylamide in THF at −78 °C to the corresponding lithium enolates **8** and **8′**, which reacted with the nitroolefins **2**, **3**, and **4**, to provide the corresponding nitronate salts **9**–**14** (Scheme 1).

No attempt to isolate the lithium nitronate intermediates **9**–**14** was undertaken. Treatment of the crude reaction mixtures with a weak acid afforded the corresponding nitroalkylated lactones **15**–**20**. The nitroalkylated lactones **15**, **16**, **17** and **18**, for which R^2=H, were mixtures of *syn*/

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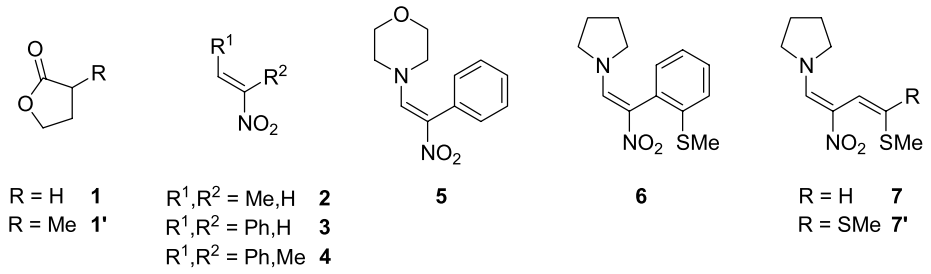


Figure 1.

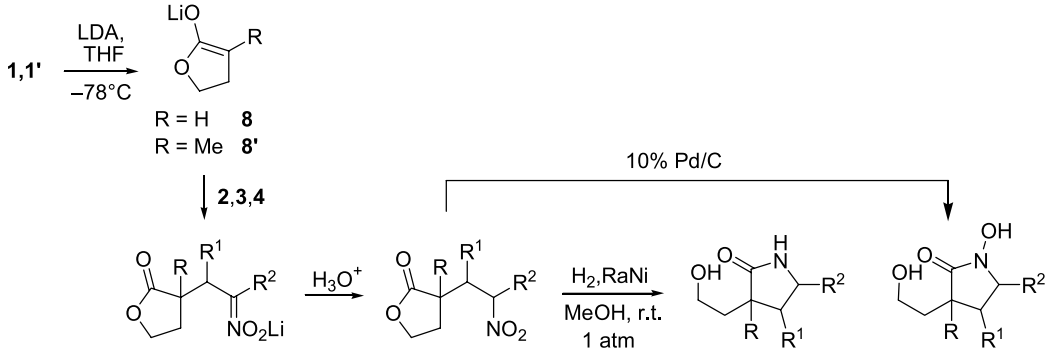
anti diastereomers, **a** and **b** respectively, owing to the presence of two adjacent chiral centres, while **19** was a mixture of four diastereomers and **20** was a mixture of three diastereomers out of the four possible ones. In order to evaluate the diastereoselectivity of the reaction, the *syn* and *anti* descriptors were also used for **19** and **20**, to indicate the relative configurations of the two stereocentres of the newly formed C–C bond.

Since for the nitroalkylated γ-lactones **15**–**20** the *syn*/*anti* stereochemical assignments were not straightforward, a stereochemical correlation was desirable: therefore, such lactones were converted into the corresponding *trans* and *cis* lactam derivatives **21**–**26** to take advantage of the more rigid polysubstituted lactams to determine the configurations of the stereocentres. On the other hand, γ-lactams themselves are attractive targets because they possess a variety of biological activities[13] and have been used to produce γ-aminobutyric acid (GABA) analogues by hydrolysis.[14] Thus, reduction of the nitro group of compounds **15**–**20** with hydrogen on Raney Ni and subsequent cyclization[15] of the corresponding aminoalkyl lactone intermediates, which were not isolated, afforded the corresponding lactam derivatives **21**–**26** (Scheme 1). In this manner, the stereochemical assignments were made on the lactam derivatives **21**–**26** either by a comparison of their ^{13}C NMR spectra or by means of NOE measurements. When this latter method was unsatisfactory, the nitroalkylated γ-lactones **15**–**19** were transformed into the corresponding cyclic hydroxamic acids **27**–**31**,[16] using 10% Pd/C as the catalyst. The latter compounds proved better substrates for NOE measurements, which supported the stereochemical assignments previously made on the lactam derivatives. All resonances of each compound were identified by means of 2D correlated experiments.

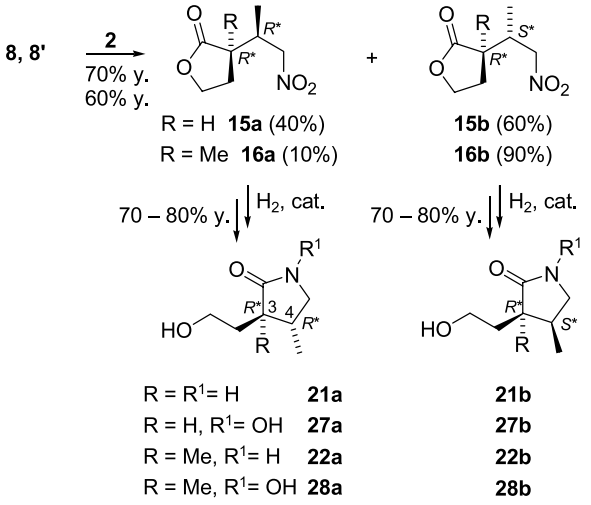
2.2. Reactions of enolates 8 and 8′ with (*E*)-1-nitropropene 2

The reaction of lithium enolate **8** with (*E*)-1-nitropropene **2** led, after acidification with aqueous satd. NH_4Cl, to the formation of two diastereomeric (nitroalkyl)lactones **15a** and **15b** in 2:3 ratio, which were separated by flash chromatography (Scheme 2). They were assigned the *syn* and *anti* configuration, respectively, after transformation into the corresponding lactams **21a** and **21b** whose geometries were demonstrated to be *trans* and *cis*, respectively. In fact the ^{13}C NMR spectrum of **21b** showed an upfield shift for the methyl group with respect to the same resonance in **21a**, thus demonstrating its *cis* relationship with the hydroxyethyl chain (Table 1). The same *trans*/*cis* assignment was made for the corresponding cyclic hydroxamic acids **27a** and **27b** that were obtained in admixture with the corresponding lactams **21a** and **21b** when the reduction was performed using Pd on carbon as the catalyst.

Similarly, the reaction between the enolate **8′** and **2** afforded the corresponding nitroalkylated products **16a** and **16b** in



Scheme 1.



Scheme 2.

1:9 ratio, as determined by HRGC analysis of the crude reaction mixture. However, since in this case the two diastereomers were not separable by flash chromatography, the subsequent reductions of the nitro group were performed on the mixture. When Raney Ni was used as the catalyst, a 1:9 mixture of the corresponding lactams **22a** and **22b** was isolated. They were assigned the (3*R**,4*R**) and (3*R**,4*S**) configurations, respectively, by comparison of their ^{13}C NMR spectra (Table 1): an upfield shift was always observed for those carbon atoms which suffered from steric effects.[17] Thus, the methyl group at C-3 resonated at 15.1 ppm in **22a** and at 20.5 ppm in **22b**, as a consequence of a less constrained situation in the latter diastereomer.

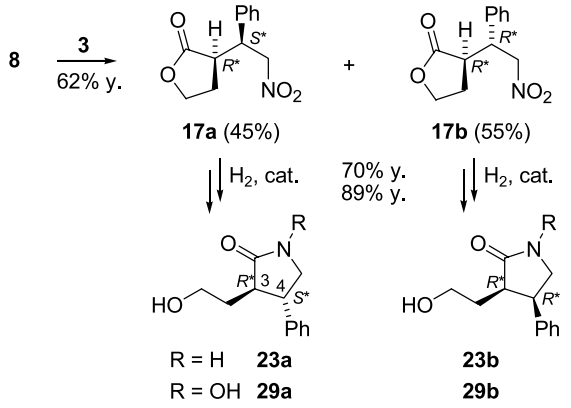
When the reduction of **16a**,**b** was performed using Pd on carbon, two cyclic hydroxamic acids, namely **28a** and **28b**, were obtained in 1:9 ratio (Scheme 2). The relevant configurations were assigned on the basis of NOE measurements performed on the major product **28b**, which was separated in pure form by fractional crystallization. Irradiation of its methyl singlet at 1.18 ppm enhanced the signal of H-4 (5%), while irradiation of the α-methylene hydrogens of the hydroxyethyl chain at 1.74 and 1.50 ppm produced enhancement of the methyl doublet at 1.04 ppm (2%). The NOE enhancement values were low, however this assignment was supported by a comparison of the ^{13}C NMR spectra of the two isomers, whose significant digits are reported in Table 1. Again an upfield shift was observed for those carbon atoms which suffered from steric effects. Thus the methyl group at C-3 is shifted to higher field in **28a**, being *cis* to the methyl group at C-4. The same trend was observed for the α-methylene hydrogens of the hydroxyethyl chain in **28b**. As a consequence, the configuration of the chiral centres in compounds **22a** and **28a** is (3*R**,4*R** or like[18]) and that of **22b** and **28b** is (3*R**,4*S** or unlike[18]). The same configurations can be assigned to the corresponding parent lactones **16a** and **16b**, whose relative configurations are therefore *syn* and *anti* respectively.

2.3. Reactions of enolates 8 and 8′ with (*E*)-β-nitrostyrene 3

The reactions between the nitroalkene **3** and the enolates **8**

Table 1. Selected ^{13}C NMR absorption values (ppm) for the γ-lactams **21–24** and the corresponding cyclic hydroxamic acid derivatives **27–30**

	γ-Lactams						Cyclic hydroxamic acids						
Entry	Me at C-3	Me at C-4	CH_2CH_2OH	C-3	C-4	C-5	Entry	Me at C-3	Me at C-4	CH_2CH_2OH	C-3	C-4	C-5
21a	—	17.3	32.4	49.7	37.1	48.7	**27a**	—	17.6	33.0	47.8	31.5	55.2
21b	—	14.6	28.5	45.5	33.5	48.6	**27b**	—	14.9	28.8	43.4	28.4	55.5
22a	15.1	11.4	38.2	45.9	39.7	47.0	**28a**	16.0	11.5	38.5	44.7	33.8	53.6
22b	20.5	12.6	34.0	44.6	42.0	46.6	**28b**	21.3	12.0	35.0	43.6	37.3	53.6
23a	—	—	32.4	49.0	48.4	48.9	**29a**	—	—	34.1	46.4	43.5	56.3
23b	—	—	29.9	45.3	44.3	48.0	**29b**			30.5	42.6	40.0	55.8
24a	17.4	—	38.5	47.5	51.3	44.5	**30a**	19.5	—	40.1	47.1	45.0	52.5
24b	21.4		35.7	46.5	53.6	44.4	**30b**	23.3		37.0	46.5	45.0	52.4



Scheme 3.

and **8′** were poorly diastereoselective, as the former reaction afforded a ca. 1:1 mixture of diastereomers **17a** and **17b** (Scheme 3), and the latter reaction gave a ca. 2:1 mixture of **18a** and **18b** (Scheme 4). In both cases the diastereomers could not be completely separated: anyway, for an easier stereochemical assignment, different mixtures of **17a**,**b** or **18a**,**b**, enriched in either diastereomer, were converted into the corresponding lactams (**23a**,**b** or **24a**,**b**) or cyclic hydroxamic acids (**29a**,**b** or **30a**,**b**).

The *trans* and *cis* stereochemical assignments for the γ-lactams **23a** and **23b** and for the cyclic hydroxamic acids **29a** and **29b** were based on ^{13}C NMR spectra (Table 1). The carbon resonances for the *cis* diastereomers **23b** and **29b** were shifted upfield with respect to those for the *trans* diastereomers **23a** and **29a**. Furthermore, NOE measurements carried out on **29a** and **29b** confirmed the previous assignments. Irradiation of the H-3 signal at 2.71 ppm in **29a** produced enhancement (4%) of the *ortho* hydrogens of the phenyl ring, while irradiation of the H-3 signal at 2.95 ppm in **29b** enhanced the H-4 signal at 3.64 ppm (5%). Therefore, since the configuration of **23a** and **29a** is ($3R^*$,$4S^*$) and that of **23b** and **29b** is ($3R^*$,$4R^*$), the relative configurations of lactones **17a** and **17b**, from which they are derived, are *syn* and *anti*, respectively.

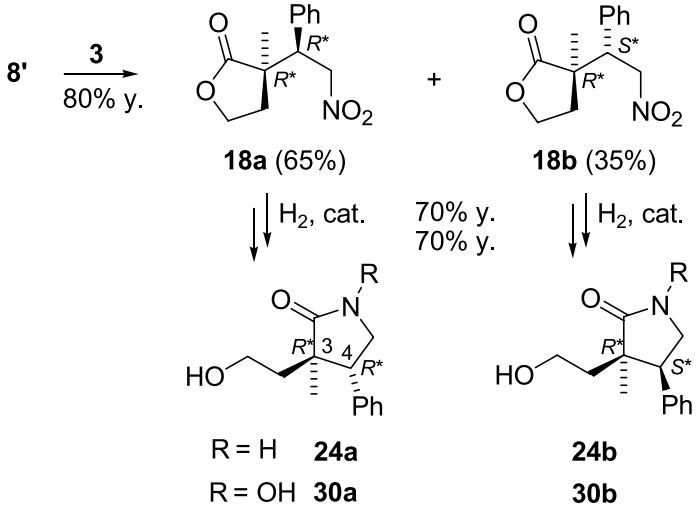
In a similar manner, the NOE experiments performed on the diastereomeric cyclic hydroxamic acids **30a** and **30b**, allowed the correct *syn* and *anti* attributions to the parent lactones **18a** and **18b** to be made. Thus, the configuration of the cyclic hydroxamic acid **30a**, derived from **18a**, was proved to be ($3R^*$,$4R^*$) and that of **30b**, derived from **18b**, was ($3R^*$,$4S^*$). In fact, upon irradiation of the methyl group at 1.30 ppm in **30b**, the H-4 signal was enhanced (10%). On the other hand, irradiation of the H-4 signal at 3.63 ppm in **30a** caused enhancement of the α-methylene protons of the chain (5%), while irradiation of the methyl group at 0.74 ppm enhanced the aromatic *o*-hydrogens (6%). All these assignments were also supported by a comparison of the ^{13}C NMR spectra of each pair of diastereomers, as shown in Table 1.

It should be noted that in spite of the fact that the geometries of the products are the same as those observed for the products of the reaction between **8** or **8′** with 1-nitropropene, the descriptors are different, owing to a different priority of the groups.

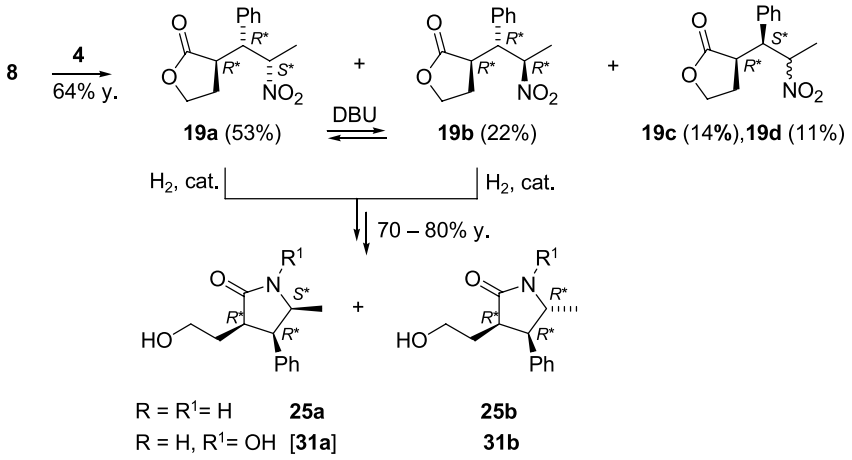
2.4. Reactions of enolates 8 and 8′ with (*E*)-2-nitro-1-phenylpropene 4

In the reaction between the enolate **8** and (*E*)-2-nitro-1-phenylpropene **4** four diastereomers, namely **19a**, **19b**, **19c**, and **19d** were formed, in 53:22:14:11 relative ratio (Scheme 5), as determined by HRGC analysis of the crude reaction mixture. Their separation on chromatographic column allowed the isolation of all stereoisomers as pure compounds with the exception of **19c** which was isolated in admixture with **19a**. Treatment under basic conditions (DBU in chloroform) of the pure diastereomer **19a** afforded a 1:1 mixture of **19a** and **19b**, thus demonstrating that they differed in the configuration of the nitromethine carbon atom. The same was proved for compounds **19c** and **19d**.

As above, the stereochemical assignments for **19a** and **19b** were made on the corresponding lactam **25a** and on the cyclic hydroxamic acid **31b**, respectively. Reduction of **19a** with hydrogen on Raney Ni afforded lactam **25a** as a single



Scheme 4.



Scheme 5.

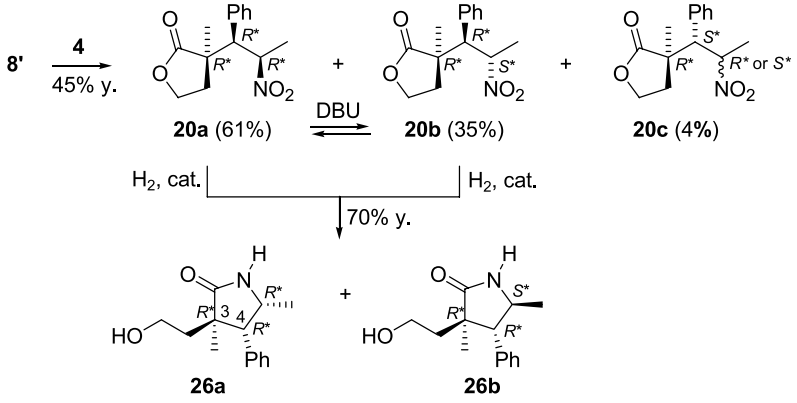
diastereomer, while reduction of **19b** using 10% Pd/C as the catalyst afforded a mixture of lactam **25b** and cyclic hydroxamic acid **31b** in the 1:3 ratio. The stereochemistry of **25a** was established by means of NOE measurements. In fact, irradiation of the H-4 signal enhanced the signals of H-3 (4%) and H-5 (5%). Compound **31b** was less soluble than the corresponding lactam **25b** in ethyl acetate and therefore it could be separated from the mixture in pure state. The NOE experiment carried out on **31b** revealed that the hydroxyalkyl chain was *cis* to the phenyl group which in turn was *trans* to the methyl group. In fact, irradiation of the methyl group enhanced the signal of H-4 (6%) as well as that of H-3 (3%), while irradiation of H-4 enhanced the signals of H-3 (8%) and that of the methyl group (6%). Its configuration was therefore (3*R**,4*R**,5*R**) and, accordingly, the relative configuration of **19b** was assigned as *anti*, *anti*. Since the stereochemical relationship between **19a** and **19b** was known from the previous equilibration reaction, the configuration of **19a** must be *anti*, *syn*.

The reaction between the enolate **8′** and the nitroolefin **4** was somewhat more complicated by the fact that acidification of the nitronate salt intermediate **14** (Scheme 1) required strictly controlled conditions and the use of a weak acid (see Section 4) in order to obtain the nitroalkylated lactones **20**. When glacial acetic acid in THF was used, a 61:35:4 mixture of **20a**, **20b** and **20c** was obtained (Scheme 6), which were isolated by flash chromatography. Equilibration of **20a**, carried out under basic conditions with DBU at room temperature, partially converted it into **20b**, thus demonstrating that **20a** and **20b** differed in the configuration of the nitromethine carbon atom.

Reduction of a 1:1 mixture of lactones **20a** and **20b** using Raney Ni as catalyst furnished a 1:1 mixture of lactams **26a** and **26b**. The stereochemistry of lactam **26a** was assigned by means of NOE measurements: irradiation of the α-methylene hydrogens of the hydroxyethyl chain at 1.90 ppm produced enhancement of the signal of H-4 (5%) as well as that of H-5 (8%) indicating that the hydroxyalkyl chain was *trans* to the phenyl group, which in turn was *cis* to the methyl group at C-5. Its configuration was therefore (3*R**,4*R**,5*R**) and that of **26b** was (3*R**,4*R**,5*S**). Accordingly, the relative configuration of **20a** was assigned as *syn*, *syn* and that of **20b** as *syn*, *anti*, both deriving from the same type of attack of the enolate onto the nitroolefin. The diastereoselective excess of the reaction, with reference to the *syn* configuration around the newly formed C–C bond, was 92%.

2.5. Products of the Nef reaction

The nitronate salt intermediates **13** (R=H) and **14** (R=Me) (Scheme 1) were treated with 3 N HCl,[19] with the aim of obtaining the corresponding Nef products.[20] Thus, a 75:25 diastereomeric mixture of **13** furnished **32a** (isolated in19%



Scheme 6.

yield) and **32b** in a ca. 3:2 ratio, in admixture with the oxime **34** (isolated in 15% yield), the latter most likely resulting from the autoxidation–reduction of the not detected nitronic acid intermediate **36**.[21] Acidic equilibration of the 3:2 mixture of **32a** and **32b** changed its composition to 3:1. The thermodynamically more stable **32a** was tentatively assigned the (3*R**,1′*R**) configuration, by a comparison of the values of the ^{3}J coupling constants between H-3 and the benzylic proton in the two isomers: 7.7 and 5.1 Hz for **32a** and **32b**, respectively.[22] In the ^{13}C NMR spectra, the only significant difference between the two diastereomers was the resonance value of C-3, 42.8 ppm for **32b** and 41.3 ppm for **32a**, suggesting a slightly more crowded situation for the latter compound.

From the nitronic salt intermediates **14** (96:4 diastereomeric ratio) a single Nef product **33** (isolated in 17% yield) and a single oxime **35** (isolated in 10% yield) were obtained by the same acid treatment as above.

Remarkably, when acidification of the crude reaction mixture was performed with a saturated solution of ammonium chloride, followed by separation of the organic phase, the subsequent treatment of the mother liquors with 3 N HCl afforded the nitronic acid **37** (isolated in 10% yield). This latter compound was separated as a white solid, stable at −20 °C. It must be underlined that reduction of the nitronic acid **37** with Raney Ni afforded the same lactams **26a** and **26b**, in the ratio of 7:3, as previously obtained from **20a** and **20b**, thus demonstrating their stereochemistry. The relative configuration reported in Figure 2 for the products of the Nef reaction are correlated with the diastereomeric values of the nitronate lithium salt formation.

2.6. Mechanism of the nitroalkylation reactions

The results relating to the geometry of the products are summarized in Table 2 (the *syn* and *anti* descriptors are also used for **19** and **20**, to indicate the relative configurations of the two stereocentres of the newly formed C–C bond). The diastereoselectivity observed is generally low except for compounds **16**, for which the *anti* diastereomer largely prevailed, and for compound **20**, for which the *syn* diastereomer was formed almost exclusively.

Table 2. Diastereomeric ratios and yields for the nitroalkylated lactones **15–20**

Entry	Product	*syn*/*anti*	Yield (%)
1	**15**	40/60	70
2	**16**	10/90	60
3	**17**	45/55	62
4	**18**	65/35	80
5	**19**	25/75	64
6	**20**	96/4	45

Formation of the *syn* and *anti* diastereomers would involve a different topological approach of the donor and acceptor.[23] Thus the *Re**,*Re** (like) approach of the enolate to the nitroolefin would lead to the *syn* products, while the *Re**,*Si** (unlike) one would give the *anti* products. It appears that the unlike approach was slightly preferred over the like one when the lactone enolate was unsubstituted (R = H) (entries 1, 3, 5). When R was methyl (entries 2, 4, 6) the reactions showed the opposite diastereoselection, with the exception of the reaction of 1-nitropropene. The following simplified model transition states A and B (Fig. 3), in which the pyramidalization of the reacting carbon atoms is ignored as are the role of the solvent and the state of aggregation of the lithium enolates,[24] would account for the different selectivity observed. When R and R^2 are hydrogens no remarkable differences in the transition states exist, and the resulting products *syn* and *anti* **15** and *syn* and *anti* **17** are formed in almost equal amount. Substitution of a hydrogen for a methyl group (R^2 = Me) slightly disfavours the like approach of the reactants and in fact compound *anti*-**19** was formed with 50% d.e. When the lactone bears a methyl group at the α-position, the steric situation seems to be dominated by the presence of the phenyl group (R^1 = Ph), which disfavours the unlike approach and consequently favours the formation of the *syn* products (30% d.e. for **18** and 92% d.e. for **20**).

The prevalent formation of compound **16** in *anti* configuration from 1-nitropropene is not in accordance with the results found for the Michael addition of cyclohexanone lithium enolate to the same nitroolefin[25] which always afforded the *syn*-product under several reaction conditions. Probably this is due to the fact that in our case the presence of the heterocyclic oxygen atom allows the unlike or *endo* orientation of the nitroolefin.

2.7. Nitroolefination and nitrodienylation reactions

The reactivity of lithium enolates of γ- and δ-lactones bearing no substituent at α-position with a few β-nitroenamines has already been reported[26] to lead to the corresponding Nef products[20] and not to the desired nitroolefinated lactones. On the contrary, when the lactone bears a substituent at the α-position, nitroolefination of the lithium enolate by β-nitroenamines proceeds diastereo- and enantio-selectively, as proved by Severin and coworkers.[5a,27] An exchange of the counter ion from lithium to zinc had the

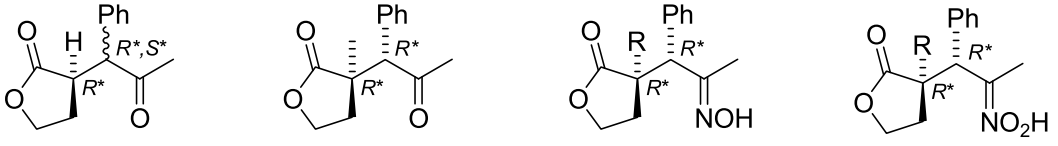


Figure 2.

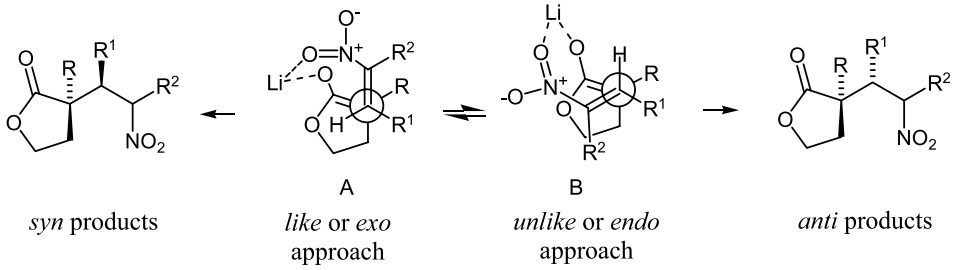


Figure 3.

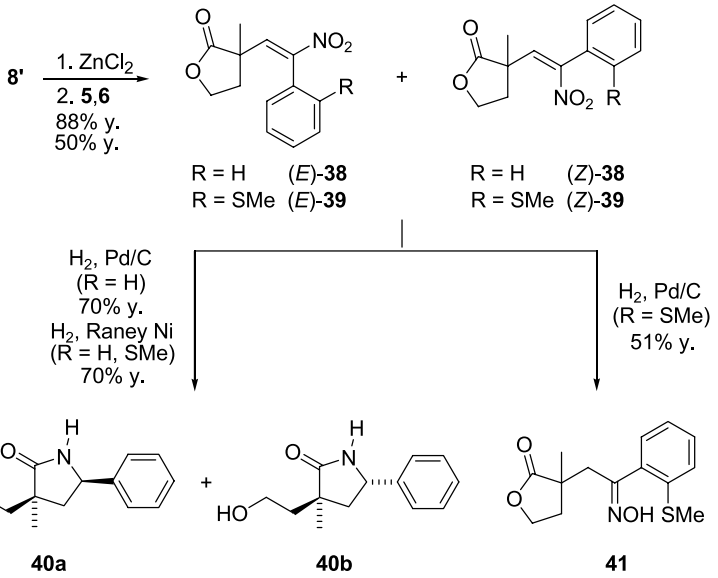
effect of increasing the reactivity and the enantioselectivity of the reactions when a chiral non-racemic β-nitroenamine derived from (*S*)-prolinol was used.[28] In particular, when the zinc enolate[29] of lactone **1′** reacted with (*E*)-1-(1-morpholinyl)-2-nitroethene and (*E*)-1-(1-morpholinyl)-2-nitropropene[5c] the corresponding addition–elimination products in (*E*) configuration were obtained.

Herein an analogous reaction has been carried out on the lithium enolate **8′** with the nitroenamines (*E*)-1-(1-morpholinyl)-2-nitro-2-phenylethene **5** and (*E*)-1-(1-pyrrolidinyl)-2-nitro-2-[2-(methylthio)phenyl]ethene **6** (Scheme 7). The corresponding products, **38** and **39**, were obtained as 85:15 and 65:35 *E*/*Z* mixtures, respectively, as determined by ^{1}H NMR analysis of the crude reaction mixtures. In fact, when the vinyl proton was *cis* to the nitro group, it resonated at lower field (7.75 ppm for **38** and 7.81 ppm for **39**) than in the case it was *trans* to it (6.43 ppm for **38** and 7.73 ppm for **39**).[12,30]

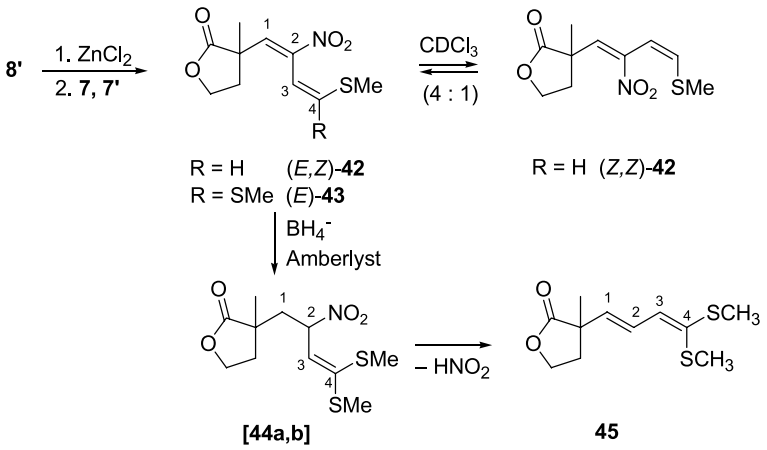
The *E*/*Z* mixtures **38** and **39** were reduced under different conditions. When Pd on carbon was used as the catalyst, lactones **38** afforded a 4:1 mixture of *cis* and *trans* diastereomers of lactam derivatives **40a** and **40b**. Differently from the cases previously reported for the nitroalkylated γ-lactones, no traces of the corresponding cyclic hydroxamic acid derivatives were detected. The geometry of the lactams **40a** and **40b** was established by NOE measurements. Irradiation of the methyl group signal at 1.33 ppm in **40a** caused enhancement of the H-5 signal at 4.75 ppm (6%). On the contrary, under the same conditions, the nitroalkenylated lactones **39** furnished the corresponding oxime **41**. Using Raney Ni as the catalyst, both mixtures **38** and **39** afforded the same diastereomeric mixture of lactams **40a** and **40b**, as a result of the concomitant hydrogenolysis of the methylthio group in **39**. Reduction with sodium borohydride was not satisfactory, even using the reagent supported on Amberlyst® A 26, which is known to reduce regioselectively the carbon–carbon double bond of the nitrovinyl moiety to the corresponding nitroalkane.[31]

The same conditions as above were used for the nitroalkenylation reaction of the enolate **8′** with the dienes **7** and **7′** to afford the corresponding addition–elimination products **42** and **43**, isolated from the respective reaction mixtures in 52 and 70% yield, the former as the (*E*,*Z*) diastereomer, the latter as the (*E*) isomer (Scheme 8).

Interestingly, in deuteriated chloroform, compound **42** slowly equilibrated into a 4:1 mixture of (*E*,*Z*) and (*Z*,*Z*)-diastereomers. This equilibration did not occur in the parent nitrodienamine **7′**. In the major isomer the H-1 vinyl proton resonated at 7.24 ppm, while in the minor isomer it absorbed at 6.29 ppm, values which are consistent with the *cis* and *trans* relationship of the same proton with the nitro group. DIFNOE measurements supported the *Z* geometry for the



Scheme 7.



Scheme 8.

C(3)–C(4) double bond, as it was originally in the reagent. On the contrary, an analogous equilibration between the (*E*) and (*Z*) forms was not observed for compound **43**, under the same conditions.

Reductions with hydrogen and metal, as a catalyst, were unsatisfactory as furnished complex mixtures of products not identified as yet. Treatment of compound **43** with polymer-supported borohydride resulted in the reduction of the sole C(1)–C(2) double bond,[31] affording a 3:2 **44a**,**b** diastereomeric mixture which was assigned the structure indicated in Scheme 8. These compounds however were not stable in $CDCl_3$ solution and were converted into the fully conjugated system **45** in (*E*) configuration. In this manner a conjugated ketene *S*,*S*-acetal was obtained whose reactivity as a precursor of an acyl anion[32] will be further investigated.

3. Conclusions

Differently from the cases of lithium enolates and enamines from cycloalkanones, for which the Michael addition of nitroolefins proceeded with high diastereoselectivity,[24,33] in general the lactone lithium enolates **1** and **1′** showed low to moderate diastereoselectivity, with the exception of the case in which both reactants were substituted by bulky groups. The stereochemical assignments were made either on the lactam derivatives or on the cyclic hydroxamic acids formed by reduction of the nitro group under different reaction conditions. The reduction with Raney Ni however needed milder conditions than those reported in the literature for other heterocyclic nitroalkylated compounds.[8b,15]

The nitroolefination reaction proceeded smoothly and quantitatively on the zinc enolates of **1′** and afforded new α,β-unsaturated nitroderivatives in *E* and *Z* configurations, the percentage of the latter increasing with the size of the substituent on the carbon bearing the nitro group.

4. Experimental

4.1. General

IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 spectrometer (400 MHz for proton, 100.5 MHz for carbon) and on a Jeol EX-270 (270 MHz for proton, 67.9 MHz for carbon), using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Coupling constants are given in Hz. Mass spectra were recorded on a VG 7070 (70 eV) spectrometer and on an ion trap instrument Finnigan GCQ (70 eV). GLC analyses were run on a Carlo Erba GC 8000 instrument, the capillary columns being OV 1701 (25 m×0.32 mm) (carrier gas He, 40 KPa, split 1:50). TLC's were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluant: light petroleum–ethyl acetate). CHN analyses were run on a Carlo Erba 1106 Elemental Analyser. Flash chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). Light petroleum refers to the fraction with bp 40–70 °C and ether to diethyl ether. γ-Butyrolactone **1**, α-methyl-γ-butyrolactone **1′** and (*E*)-2-nitrostyrene **3** were purchased from Aldrich. (*E*)-1-Nitropropene **2**,[34] (*E*)-2-nitro-1-phenylpropene **4**,[35] (*E*)-1-(2-methylthiophenyl)-1-nitro-2-pyrrolidinoethene **6**,[10] (1*E*,3*Z*)-4-methylthio-2-nitro-1-pyrrolidino-1,3-butadiene **7**[11] and 4,4-bis(methylthio)-2-nitro-1-pyrrolidino-1,3-butadiene **7′**[12] were prepared according to the literature.

4.1.1. (*E*)-2-Morpholinyl-1-nitro-1-phenylethene 5.[9] The synthesis was accomplished in accordance with a literature procedure,[36] using phenylnitromethane[37] as the nitroaliphatic component. Thus phenylnitromethane (0.09 mol, 12.3 ml), triethyl orthoformate (0.1 mol, 17 ml), morpholine (0.09 mol, 7.8 ml) and *p*-toluenesulfonic acid (0.09 g, 0.5 mmol) were heated under reflux for 1 h. Then the solvent was evaporated, the residue diluted with dichloromethane and purified through an alumina column (30× 2.5 cm) using dichloromethane as eluting agent. Although the crude reaction mixture contained both diastereomers, the nitroenamine **5** was isolated as pure *E*-isomer and crystallized from ethanol. 21% Yield, mp 150–152 °C, [lit.[9] for a 1:1 mixture of *E*- and Z-isomers, mp 125 °C]; IR (cm^{-1}, nujol): 3056 (=CH), 1626, 1592, 1573, 785, 772, 725, 696 (Ph), 1488, 1377 (NO_2); ^{1}H NMR (δ, ppm): 8.41 (1H, s, H–C=C), 7.42 (3H, m, Ph), 7.26 (2H, m, Ph) 3.59 (4H, s, CH_2–O), 3.14 (4H, s, CH_2–N).

4.2. General procedure for the Michael addition of nitroalkenes to lactone enolates

To a solution of lithium diisopropylamide (3.5 mmol, 2.3 ml of a 1.5 M solution in THF) in THF (16 ml), a solution of the γ-lactone (2.9 mmol) in 2.5 ml of THF was slowly added, at −78 °C. The mixture was stirred at −78 °C for 1 h and the appropriate nitroalkene (3.5 mmol) dissolved in 2.5 ml of THF was added dropwise. The mixture was stirred at −78 °C for 2 h, the temperature was allowed to raise to −40 °C and the reaction mixture was kept at this temperature for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was analysed by HRGC and purified by flash chromatography (light petroleum/ethyl acetate).

4.2.1. Reaction of the lactone 1 with (*E*)-1-nitropropene 2. *syn*- and *anti*-4,5-Dihydro-3-(1-methyl-2-nitroethyl)-2(3*H*)-furanone 15a and 15b. The isomers **15a** and **15b** (70% yield) were only partially separable by column chromatography, yellow oil, IR (cm^{-1}, neat): 1760 (OC=O), 1550, 1380 (NO_2); MS (*m*/*z*): 126 (7), 86 (56), 83 (10), 82 (16), 81 (10), 69 (14), 68 (16), 67 (34), 55 (100). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.4; H, 6.20; N, 7.89.

Compound **15a**. ^{1}H NMR (δ, ppm): 4.73 (1H, dd, J_1= 6.6 Hz, J_2=12.8 Hz, $CHNO_2$), 4.48 (1H, dd, J_1=7.1 Hz, J_2=12.8 Hz, $CHNO_2$), 4.39 (1H, dt, J_1=2.4 Hz, J_2=J_3= 9.0 Hz, H-5), 4.24 (1H, dt, J_1=6.9 Hz, J_2=J_3=9.0 Hz, H-5), 2.74 (2H, m, H-3 and C*H*CH_3), 2.42 (1H, m, H-4), 2.14 (1H, m, H-4), 1.15 (3H, d, *J*=6.6 Hz, CH_3); ^{13}C NMR (δ, ppm): 176.7 (s), 78.5 (t, CH_2NO_2), 66.5 (t, C-5), 41.2 (d, C-3), 32.4 (d, *C*HCH_3), 26.2 (t, C-4), 13.3 (q, CH_3).

Compound **15b**. ^{1}H NMR (δ, ppm): 4.71 (1H, dd, J_1= 6.2 Hz, J_2=12.4 Hz, $CHNO_2$), 4.51 (1H, dd, J_1=7.1 Hz, J_2=12.4 Hz, $CHNO_2$), 4.38 (1H, dt, J_1=1.8 Hz, J_2=J_3= 9.0 Hz, H-5), 4.21 (1H, dt, J_1=6.7 Hz, J_2=J_3=9.0 Hz, H-5), 2.79 (1H, sept, *J*=6.9 Hz, C*H*CH_3), 2.69 (1H, ddd, J_1=11.3 Hz, J_2=8.4 Hz, J_3=6.9 Hz, H-3), 2.36 (1H, m, H-4), 2.10 (1H, m, H-4), 1.08 (3H, d, *J*=6.9 Hz, CH_3); ^{13}C NMR (δ, ppm): 177.1 (s), 78.9 (t, CH_2NO_2), 66.3 (t, C-5), 41.2 (d, C-3), 32.5 (d, *C*HCH_3), 25.3 (t, C-4), 14.5 (q, CH_3).

4.2.2. Reaction of the lactone 1′ with (*E*)-1-nitropropene 2. *syn*- and *anti*-4,5-Dihydro-3-methyl-3-(1-methyl-2-nitroethyl)-2(3*H*)-furanone 16a and 16b. The isomers **16a** and **16b** (60% yield) were obtained as a 1:9 inseparable mixture, yellow oil, IR (cm^{-1}, neat): 1764 (OC=O), 1550, 1380 (NO_2); MS (*m*/*z*): 140 (3), 100 (35), 97 (8), 96 (18), 83 (10), 82 (16), 81 (34), 71 (10), 69 (29), 67 (24), 57 (20), 55 (100). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.4; H, 6.92; N, 7.19.

For clarity sake the NMR values are given separately for each isomer.

Compound **16a**. ^{1}H NMR (δ, ppm): 4.93 (1H, dd, J_1= 4.0 Hz, J_2=12.4 Hz, $CHNO_2$), 4.19 (1H, dd, J_1=9.9 Hz, J_2=12.4 Hz, $CHNO_2$), 1.22 (3H, s, CH_3), 1.05 (3H, d, *J*= 7.0 Hz, CH_3); ^{13}C NMR (δ, ppm): 180.0 (s), 77.6 (t, CH_2NO_2), 64.8 (t, C-5), 44.5 (s, C-3), 36.9 (d, *C*HCH_3), 32.8 (t, C-4), 18.7 (q, CH_3 at C-3), 13.5 (q, CH_3 of the chain).

Compound **16b**. ^{1}H NMR (δ, ppm): 4.53 (1H, dd, J_1= 4.0 Hz, J_2=12.1 Hz, $CHNO_2$), 4.33 (1H, dd, J_1=10.4 Hz, J_2=12.1 Hz, $CHNO_2$), 4.26 (2H, m, 2H-5), 2.63 (1H, m, C*H*CH_3), 2.22 (1H, dt, J_1=13.2 Hz, J_2=J_3=8.8 Hz, H-4), 1.98 (1H, ddd, J_1=4.0 Hz, J_2=7.3 Hz, J_3=13.2 Hz, H-4), 1.31 (3H, s, CH_3), 1.10 (3H, d, *J*=7.0 Hz, CH_3); ^{13}C NMR (δ, ppm): 179.5 (s), 78.2 (t, CH_2NO_2), 65.0 (t, C-5), 44.6 (s, C-3), 37.6 (d, *C*HCH_3), 32.5 (t, C-4), 21.5 (q, CH_3 at C-3), 13.1 (q, CH_3 of the chain).

4.2.3. Reaction of lactone 1 with (*E*)-2-nitrostyrene 3. *syn* and *anti*-4,5-Dihydro-3-(2-nitro-1-phenylethyl)-2(3*H*)-furanone 17a and 17b. The isomers **17a** and **17b** (62% yield) were obtained as a 45:55 inseparable mixture, white solid, mp 65–69 °C, IR (cm^{-1}, nujol): 1762 (OC=O), 1603 (Ph), 1552, 1378 (NO_2); ^{13}C NMR (δ, ppm): 176.9 (s), 176.8 (s), 136.7 (s), 135.4 (s), 129.2 (d), 129.1 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.7 (d), and for **17a**: 77.7 (t, CH_2NO_2), 66.3 (t, C-5), 44.3 (d, CHPh), 41.3 (d, C-3), 27.6 (t, C-4), and for **17b**: 76.6 (t, CH_2NO_2), 66.7 (t, C-5), 43.8 (d, CHPh), 41.7 (d, C-3), 26.1 (t, C-4). MS (*m*/*z*): 235 ($M^{+\cdot}$, 2), 217 (8), 189 (21), 188 (66), 160 (23), 145 (51), 143 (22), 131 (18), 130 (100), 128 (19), 118 (34), 116 (34), 106 (26), 105 (90), 103 (33), 91 (85), 86 (13), 78 (18), 77 (30). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.3; H, 5.50; N, 6.04.

For clarity sake the NMR values are given separately for each isomer.

Compound **17a**. ^{1}H NMR (δ, ppm): 7.30 (5H, m, Ph), 5.44 (1H, dd, J_1=5.5 Hz, J_2=13.2 Hz, $CHNO_2$), 4.80 (1H, dd, J_1=9.9 Hz, J_2=13.2 Hz, $CHNO_2$), 4.25 (1H, dt, J_1= 2.8 Hz, J_2=J_3=8.8 Hz, H-5), 4.12 (1H, m, H-5), 3.80 (1H, m, CHPh), 2.92 (1H, q, *J*=9.8 Hz, H-3), 1.98 (2H, m, 2H-4); ^{1}H NMR (δ, ppm, $CDCl_3$ + drops of C_6D_6): 7.20 (5H, m, Ph), 5.33 (1H, dd, J_1=5.3 Hz, J_2=12.9 Hz, $CHNO_2$), 4.67 (1H, dd, J_1=9.9 Hz, J_2=12.9 Hz, $CHNO_2$), 4.06 (1H, dt, J_1=2.5 Hz, J_2=J_3=8.8 Hz, H-5), 3.93 (1H, m, H-5), 3.63 (1H, m, CHPh), 2.69 (1H, dt, J_1=8.8 Hz, J_2=J_3=10.2 Hz, H-3), 1.84 (1H, m, H-4), 1.71 (1H, m, H-4).

Compound **17b**. ^{1}H NMR (δ, ppm): 7.30 (5H, m, Ph), 5.20 (1H, dd, J_1=7.3 Hz, J_2=13.5 Hz, $CHNO_2$), 5.05 (1H, dd, J_1=8.4 Hz, J_2=13.5 Hz, $CHNO_2$), 4.12 (1H, m, H-5), 3.80 (2H, m, CHPh, H-5), 3.06 (1H, dt, J_1=4.6 Hz, J_2=J_3= 9.4 Hz, H-3), 2.38 (1H, m, H-4), 1.98 (1H, m, H-4); ^{1}H NMR (δ, ppm, $CDCl_3$ + drops of C_6D_6): 7.20 (5H, m, Ph), 5.07 (1H, dd, J_1=6.9 Hz, J_2=13.4 Hz, $CHNO_2$), 4.93 (1H, dd, J_1=8.0 Hz, J_2=13.4 Hz, $CHNO_2$), 3.93 (1H, m, H-5), 3.71 (1H, dt, J_1=4.5 Hz, J_2=J_3=8.0 Hz, CHPh), 3.63 (1H, m, H-5), 2.85 (1H, dt, J_1=4.5 Hz, J_2=J_3=9.3 Hz, H-3), 2.10 (1H, m, H-4), 1.84 (1H, m, H-4).

4.2.4. Reaction of lactone 1′ with (*E*)-2-nitrostyrene 3. *syn*- and *anti*-4,5-Dihydro-3-methyl-3-(2-nitro-1-phenylethyl)-2(3*H*)-furanone 18a and 18b. The isomers **18a** and

18b (80% yield), obtained in the ratio of 65:35 were not separable by flash chromatography, white solid, mp 99–101 °C; IR (cm^{-1}, nujol): 1756 (OC═O), 1602 (Ph), 1548, 1339 (NO_2); MS (*m/z*): 250 (MH^+, 1), 204 (4), 203 (13), 143 (16), 129 (13),128 (10), 116 (14), 114 (13), 106 (26), 105 (100), 104 (18), 101 (85), 100 (10), 98 (10), 92 (40), 85 (15), 83 (11), 78 (13), 77 (26), 71 (23), 69 (20), 57 (40), 56 (12), 55 (34). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.5; H, 6.17; N, 5.81.

For clarity sake the NMR values are given separately for each isomer.

Compound **18a**. ^{1}H NMR (δ, ppm): 7.28 (5H, m, Ph), 5.28 (1H, dd, J_1=4.0 Hz, J_2=13.4 Hz, $CHNO_2$), 4.93 (1H, dd, J_1=11.5 Hz, J_2=13.4 Hz, $CHNO_2$), 4.17 (1H, m, H-5), 4.08 (1H, m, H-5), 3.82 (1H, dd, J_1=4.0 Hz, J_2=11.5 Hz, CHPh), 2.28 (1H, m, H-4), 1.72 (1H, ddd, J_1=5.5 Hz, J_2=7.3 Hz, J_3=13.2 Hz, H-4), 1.29 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 179.8 (s), 135.0 (s), 128.8 (d), 128.5 (d), 128.3 (d), 75.2 (t, CH_2–NO_2), 64.8 (t, C-5), 47.3 (d, CHPh), 44.6 (s, C-3), 34.0 (t, C-4), 19.6 (q, CH_3).

Compound **18b**. ^{1}H NMR (δ, ppm): 7.28 (5H, m, Ph), 5.09 (1H, dd, J_1=11.2 Hz, J_2=13.2 Hz, $CHNO_2$), 4.89 (1H, dd, J_1=4.2 Hz, J_2=13.2 Hz, $CHNO_2$), 4.08 (1H, m, H-5), 3.70 (1H, dd, J_1=4.2 Hz, J_2=11.2 Hz, CHPh), 3.59 (1H, dt, J_1=J_2=9.0 Hz, J_3=4.8 Hz, H-5), 2.28 (1H, m, H-4), 1.98 (1H, ddd, J_1=4.8 Hz, J_2=8.1 Hz, J_3=12.8 Hz, H-4), 1.36 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 179.9 (s), 135.8 (s) 129.0 (d), 128.4 (d), 128.3 (d), 76.5 (t, CH_2–NO_2), 65.5 (t, C-5), 50.2 (d, CHPh), 45.5 (s, C-3), 33.3 (t, C-4), 23.4 (q, CH_3).

4.2.5. Reaction of the lactone 1 with (*E*)-2-nitro-1-phenylpropene 4. 4,5-Dihydro-3-(2-nitro-1-phenylpropyl)-2(3*H*)-furanone 19a,b,c,d. Four isomers **19a**, **19b**, **19c** and **19d** in 53:22:14:11 ratio were identified in the ^{1}H NMR spectrum of the crude reaction mixture. They were separated by flash chromatography.

Compound **19a**. 30% Yield, white solid, mp 125–126 °C, from ether; IR (cm^{-1}, nujol): 1756, (OC═O), 1546, 1377 (NO_2); ^{1}H NMR (δ, ppm): 7.28 (5H, m, Ph), 5.72 (1H, dq, J_1=11.0 Hz, J_2=J_3=J_4=6.6 Hz, $CHNO_2$), 4.09 (1H, q, J=8.2 Hz, H-5), 3.64 (1H, dt, J_1=4.8 Hz, J_2=J_3=8.2 Hz, H-5), 3.45 (1H, dd, J_1=4.8 Hz, J_2=11.0 Hz, CHPh), 3.12 (1H, dt, J_1=4.8 Hz, J_2=J_3=8.2 Hz, H-3), 2.38 (1H, m, H-4), 1.92 (1H, dq, J_1=13.0 Hz, J_2=J_3=J_4=8.2 Hz, H-4), 1.82 (3H, d, J=6.6 Hz, CH_3), ^{13}C NMR (δ, ppm): 177.0 (s), 135.6 (s), 128.9 (d), 128.5 (d), 128.4 (d), 85.4 (d, $CHNO_2$), 66.8 (t, C-5), 50.0 (d, CHPh), 39.9 (d, C-3), 26.1 (t, C-4), 18.6 (q, CH_3); MS (*m/z*): 250 (MH^+, 4), 203 (26), 202 (31), 144 (25), 143 (63), 142 (38), 131 (29), 129 (21), 118 (100), 116 (27), 106 (19), 103 (31), 102 (29), 91 (57), 79 (13), 77 (19). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.5; H, 5.87; N, 5.28.

Compound **19b**. 17% Yield; white solid, mp 95–97 °C, IR (cm^{-1}, nujol): 1762, (OC═O), 1600 (Ph), 1550, 1388 (NO_2); ^{1}H NMR (δ, ppm): 7.36 (3H, m, Ph), 7.26 (2H, m, Ph), 5.89 (1H, dq, J_1=11.1 Hz, J_2=J_3=J_4=6.7 Hz, $CHNO_2$), 4.06 (1H, q, J=8.5 Hz, H-5), 3.70 (1H, dt, J_1=4.3 Hz, J_2=J_3=8.5 Hz, H-5), 3.44 (1H, dd, J_1=4.2 Hz, J_2=11.1 Hz, CHPh), 2.88 (1H, dt, J_1=4.2 Hz, J_2=J_3=8.5 Hz, H-3), 2.46 (1H, m, H-4), 1.91 (1H, dq, J_1=12.8 Hz, J_2=J_3=J_4=8.5 Hz, H-4), 1.33 (3H, d, J=6.7 Hz, CH_3); ^{13}C NMR (δ, ppm): 176.8 (s), 135.0 (s), 129.4 (d), 129.3 (d), 128.6 (d), 83.5 (d, $CHNO_2$), 66.6 (t, C-5), 50.6 (d, CHPh), 40.5 (d, C-3), 26.5 (t, H-4), 19.5 (q, CH_3); MS (*m/z*): 249 ($M^{+\cdot}$, 3), 203 (26), 202 (36), 143 (14), 131 (37), 129 (27), 118 (38), 117 (100), 115 (29), 105 (15), 91 (67), 84 (13), 77 (14). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.9; H, 6.23; N, 5.33.

Compound **19c** (in admixture with **19a**). ^{1}H NMR (δ, ppm): 7.21 (5H, m, Ph), 5.68 (1H, dq, J_1=5.5 Hz, J_2=J_3=J_4=6.6 Hz, $CHNO_2$), 4.13 (2H, m, 2H-5), 3.40 (2H, m, CHPh and H-3), 2.12 (1H, m, H-4), 1.85 (1H, m, H-4), 1.54 (3H, d, J=6.6 Hz, CH_3); ^{13}C NMR (δ, ppm): 177.5 (s), 134.6 (s), 128.7 (d), 128.6 (d), 128.2 (d), 82.5 (d, $CHNO_2$), 66.2 (t, C-5), 50.1 (d, CHPh), 39.7 (d, C-3), 27.2 (t, H-4), 17.5 (q, CH_3).

Compound **19d**. Oil, 6% yield; IR (cm^{-1}, neat): 1766, 1712 (OC═O), 1602 (Ph), 1550, 1390 (NO_2); ^{1}H NMR (δ, ppm): 7.34 (3H, m, Ph), 7.16 (2H, m, Ph), 5.31 (1H, dq, J_1=9.1 Hz, J_2=J_3=J_4=6.6 Hz, $CHNO_2$), 4.13 (2H, m, 2H-5), 3.87 (1H, dd, J_1=6.2 Hz, J_2=9.1 Hz, CHPh), 2.84 (1H, dt, J_1=6.2 Hz, J_2=J_3=9.6 Hz, H-3), 2.34 (1H, m, H-4), 2.09 (1H, m, H-4), 1.45 (3H, d, J=6.6 Hz, CH_3); MS,(*m/z*): 203 (15), 202 (34), 176 (19), 148 (28), 143 (15), 131 (46), 130 (47), 129 (36), 118 (35), 117 (100), 116 (20), 115 (42), 105 (18), 104 (14), 103 (10), 91 (95), 77 (22).

4.2.6. Reaction of the lactone 1′ with (*E*)-2-nitro-1-phenylpropene 4. 4,5-Dihydro-3-methyl-3-(2-nitro-1-phenylpropyl)-2(3*H*)-furanone 20a,b,c. The isomers **20a**, **20b** and **20c** (61%, 35% and 4% relative ratio) were obtained acidifying the reaction mixture with 0.43 ml (7 mmol) of glacial acetic acid in 1.5 ml of THF, at −78 °C. The temperature was allowed to raise to −40 °C and, after 15 min, 25 ml of water was added. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the crude reaction mixture was purified by flash chromatography (light petroleum/ethyl acetate) to give the mixture of lactones **20a**,**b**,**c** (45% yield) which could not be separated. White solid, mp 89–92 °C, IR (cm^{-1}, nujol): 1755 (OC═O), 1602 (Ph), 1545, 1334 (NO_2); MS (*m/z*): 263 ($M^{+\cdot}$, 0.8), 221 (10), 206 (44), 145 (14), 131 (18), 129 (13), 119 (100), 118 (39), 116 (21), 106 (42), 102 (13), 101 (75), 99 (10), 91 (48), 77 (20), 69 (14), 57 (36), 56 (16), 55 (43). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.0; H, 6.74; N, 5.31.

For clarity sake the NMR values are given separately for each isomer.

Compound **20a**. ^{1}H NMR (δ, ppm): 7.31 (3H, m, Ph), 7.23 (2H, m, Ph), 5.31 (1H, quintet, J_1=6.6 Hz, $CHNO_2$), 4.18 (1H, dt, J_1=8.0 Hz, J_2=9.2 Hz, H-5), 4.02 (1H, ddd, J_1=4.8 Hz, J_2=8.0 Hz, J_3=9.2 Hz, H-5), 3.44 (1H, d, J=6.6 Hz, CHPh), 2.44 (1H, dt, J_1=8.0 Hz, J_2=13.2 Hz, H-4), 2.08 (1H, ddd, J_1=4.8 Hz, J_2=8.0 Hz, J_3=13.2 Hz, H-4), 1.59 (3H, d, J=6.6 Hz, CH_3), 1.50 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 180.2 (s), 135.6 (s), 130.0 (d), 128.7 (d),

128.1 (d), 83.2 (d, $CHNO_2$), 64.8 (t, C-5), 54.3 (d, CHPh), 45.7 (s, C-3), 33.3 (t, C-4), 22.2 (q, CH_3), 19.9 (q, CH_3).

Compound **20b**. ^{1}H NMR (δ, ppm): 7.33 (5H, m, Ph), 5.22 (1H, dq, $J_1=9.5$ Hz, $J_2=J_3=6.6$ Hz, $CHNO_2$), 4.18 (1H, m, H-5), 4.10 (1H, ddd, $J_1=4.8$ Hz, $J_2=8.4$ Hz, $J_3=9.5$ Hz, H-5), 3.62 (1H, d, $J=9.5$ Hz, CHPh), 2.47 (1H, m, H-4), 2.05 (1H, m, H-4), 1.34 (3H, d, $J=6.6$ Hz, CH_3), 1.26 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 179.4 (s), 135.3 (s), 129.8 (d), 128.6 (d), 128.2 (d), 83.6 (d, $CHNO_2$), 65.1 (t, H-5), 53.4 (d, CHPh), 45.7 (s, C-3), 33.4 (t, H-4), 22.2 (q, CH_3), 19.9 (q, CH_3).

Compound **20c**. Only a few signals were identified: ^{1}H NMR (δ, ppm): 5.45 (1H, dq, $J_1=6.6$ Hz, $J_2=9.5$ Hz, $CHNO_2$), 3.89 (1H, dt, $J_1=3.9$ Hz, $J_2=9.2$ Hz, H-5), 3.61 (1H, d, $J=9.5$ Hz, CHPh), 2.63 (1H, m, H-4), 1.93 (1H, m, H-4), 1.29 (3H, d, $J=6.6$ Hz, CH_3); ^{13}C NMR (δ, ppm): 129.1 (d), 82.5 (d, $CHNO_2$), 65.7 (t, C-5), 54.8 (d, CHPh), 32.6 (s).

4.3. Acidification of the lithium nitronates 13 and 14 with 3 N HCl

The crude reaction mixture containing the lithium nitronate was acidified with 20 ml of 3 N HCl, the mixture was stirred overnight and extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography (light petroleum/ethyl acetate). In the case of nitronate **13**, from the complex mixture containing the Nef products **32a** and **32b** in 3:2 ratio and the oxime **34**, only **32a** and **34** could be isolated as pure compounds, by flash chromatography. In the case of nitronate **14** the Nef product **33** and the oxime **35** could be isolated by flash chromatography (see text).

4.3.1. 4,5-Dihydro-3-(2-oxo-1-phenylpropyl)-2(3*H*)-furanone 32a. 19% Yield, white solid, mp 87–88 °C from ether; IR (cm^{-1}, nujol): 1753 (OC=O), 1714 (C=O); ^{1}H NMR (δ, ppm): 7.33 (3H, m, Ph), 7.21 (2H, m, Ph), 4.15 (2H, m, 2H-5), 4.08 (1H, d, $J=7.7$ Hz, CHPh), 3.56 (1H, ddd, $J_1=7.7$ Hz, $J_2=8.7$ Hz, $J_3=12.1$ Hz, H-3), 2.20 (3H, s, CH_3), 2.12 (1H, m, H-4), 1.82 (1H, m, H-4); ^{13}C NMR (δ, ppm): 206.1 (s, C=O), 177.9 (s, COO), 134.7 (s), 129.0 (d), 128.8 (d), 128.0 (d), 66.9 (t, C-5), 58.3 (d, CHPh), 41.3 (d, C-3), 29.4 (q, CH_3), 26.4 (t, C-4); MS (*m*/*z*): 218 ($M^{+\cdot}$, 1), 176 (53), 149 (76), 148 (32), 132 (47), 131 (100), 118 (18), 117 (19), 116 (28), 105 (31), 92 (74), 77 (18). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.3; H, 6.39.

4.3.2. 4,5-Dihydro-3-(2-oxo-1-phenylpropyl)-2(3*H*)-furanone 32b. The lactone **19d** was submitted to the Nef reaction conditions according to the literature,[19] furnishing a 3:1 mixture of **32a** and **32b**.

Compound **32b**. ^{1}H NMR (δ, ppm): 7.36 (5H, m, Ph), 4.48 (1H, dt, $J_1=2.3$ Hz, $J_2=J_3=9.0$ Hz, H-5), 4.28 (1H, d, $J=5.1$ Hz, CHPh), 4.16 (1H, m, H-5), 2.89 (1H, ddd, $J_1=5.1$ Hz, $J_2=9.5$ Hz, $J_3=11.0$ Hz, H-3), 2.56 (1H, quintet, $J=10.4$ Hz, H-4), 2.21 (1H, m, H-4), 2.08 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 206.3 (s, C=O), 177.8 (s, COO), 136.3 (s), 129.3 (d), 128.7 (d), 127.9 (d), 66.6 (t, C-5), 58.2 (d, CHPh), 42.8 (d, C-3), 29.1 (q, CH_3), 25.1 (t, C-4).

4.3.3. 4,5-Dihydro-3-methyl-3-(2-oxo-1-phenylpropyl)-2(3*H*)-furanone 33. 17% Yield; white solid, mp 67–70 °C; IR (cm^{-1}, nujol): 1772 (OC=O), 1701(C=O), 1580 (Ph); ^{1}H NMR (δ, ppm): 7.33 (3H, m, Ph), 7.28 (2H, m, Ph), 4.27 (1H, s, CHPh), 4.06 (1H, q, $J_1=8.6$ Hz, H-5), 3.58 (1H, dt, $J_1=5.1$ Hz, $J_2=8.6$ Hz, H-5), 2.63 (1H, m, H-4), 2.23 (1H, m, H-4), 2.12 (3H, s, CH_3–CO), 1.38 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 205.6 (s, C=O), 180.6 (s, COO), 133.4 (s), 130.0 (d), 128.9 (d), 128.2 (d), 65.6 (t, C-5), 62.7 (d, CHPh), 46.1 (s, C-3), 31.1 (q, CH_3–CO), 30.9 (t, C-4), 23.3 (q, CH_3); MS (*m*/*z*): [232 ($M^{+\cdot}$) at 20 eV], 190 (25), 175 (15), 162 (21), 144 (44), 129 (25), 117 (22), 115 (20), 106 (52), 105 (65), 91 (100), 77 (41), 65 (10), 57 (10). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.5; H, 6.80.

4.3.4. 4,5-Dihydro-3-(2-hydroxyimino-1-phenylpropyl)-2(3*H*)-furanone 34. 15% Yield; white solid, mp 127–129 °C from light petroleum/ether; IR (cm^{-1}, nujol): 3329 (OH), 1730 (OC=O), 1655 (C=N), 1600 (Ph); ^{1}H NMR (δ, ppm): 8.00 (1H, bs, OH), 7.27 (5H, m, Ph), 4.40 (1H, dt, $J_1=3.0$ Hz, $J_2=J_3=8.8$ Hz, H-5), 4.16 (1H, q, $J=8.8$ Hz, H-5), 4.10 (1H, d, $J=5.9$ Hz, CHPh), 2.99 (1H, dt, $J_1=5.9$ Hz, $J_2=J_3=8.8$ Hz, H-3), 2.66 (1H, dq, $J_1=12.0$ Hz, $J_2=J_3=J_4=8.8$ Hz, H-4), 1.99 (1H, m, H-4), 1.75 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 178.3 (s, COO), 155.8 (s, C=N), 138.5 (s), 128.8 (d), 128.4 (d), 127.4 (d), 66.7 (t, C-5), 50.4 (d, CHPh), 43.2 (d, C-3), 24.7 (t, C-4), 13.8 (q, CH_3); MS (*m*/*z*): 233 ($M^{+\cdot}$, 15), 216 (79), 185 (20), 175 (22), 174 (40), 173 (32), 172 (18), 170 (26), 157 (26), 156 (17), 149 (41), 148 (49), 147 (20), 132 (32), 130 (49), 128 (22), 121 (26), 118 (30), 116 (65), 92 (100), 89 (29), 81 (39),77 (65). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.2; H, 6.58; N, 6.02.

4.3.5. 4,5-Dihydro-3-methyl-3-(2-hydroxyimino-1-phenylpropyl)-2(3*H*)-furanone 35. 10% Yield, white solid, mp 117–119 °C. IR (cm^{-1}, nujol): 3271 (OH), 1758 (C=O), 1670 (C=N); ^{1}H NMR (δ, ppm): 7.80 (1H, bs, OH), 7.30 (5H, m, Ph), 4.03 (1H, dt, $J_1=7.3$ Hz, $J_2=8.8$ Hz, H-5), 3.89 (1H, s, CHPh), 3.56 (1H, dt, $J_1=5.1$ Hz, $J_2=8.8$ Hz, H-5), 2.65 (1H, ddd, $J_1=7.3$ Hz, $J_2=8.8$ Hz, $J_3=13.6$ Hz, H-4), 2.17 (1H, m, H-4), 1.79 (3H, s, CH_3C=N–OH), 1.45 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 181.4 (s, COO), 156.6 (s, C=N), 136.1 (s), 130.1 (d), 128.5 (d), 127.8 (d), 65.4 (t, C-5), 56.5 (d, CHPh), 46.7 (s, C-3), 31.7 (t, C-4), 24.5 (q, CH_3), 15.5 (q, CH_3); MS (*m*/*z*): 247 ($M^{+\cdot}$,16), 202 (10), 186 (18), 149 (43), 148 (100), 131 (25), 130 (42), 129 (26), 117 (19), 116 (15), 115 (33), 106 (25), 105 (17), 100 (13), 95 (17), 91 (42), 77 (25), 69 (10), 55(13). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.9; H, 7.00; N, 5.56.

4.3.6. 1-(Tetrahydro-3-methyl-2-oxofuryl)-1-phenylpropan-2-ylideneazinic acid 37. The reaction between the lithium enolate of **1′** and (*E*)-2-nitro-1-phenylpropene **4**, carried out in accordance with the general procedure, was quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 three times in order to separate the nitroalkylated lactones. From

the mother liquors, acidified to pH 2 with 3 N HCl, the nitronic acid **37** precipitated as a white solid which was washed with ether. 10% Yield, mp 100–102 °C; IR (cm^{-1}, nujol): 2668 (OH); 1754 (COO), 1658 (C=N); ^1H NMR (DMSO-d_6, δ, ppm) 7.20 (5H, m, Ph), 4.70 (1H, s, CHPh), 4.18 (1H, q, $J=8.4$ Hz, H-5), 3.93 (1H, dt, $J_1=2.7$ Hz, $J_2=J_3=8.4$ Hz, H-5), 2.43 (1H, m, H-4), 2.12 (1H, m, H-4), 2.03 (3H, s, CH_3), 1.23 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm): 180.9 (s), 137.9 (s), 129.3 (d), 129.0 (d), 127.7 (d), 121.2 (s), 65.4 (t), 50.8 (d), 46.4 (t), 31.2 (s), 23.0 (q), 16.6 (q); MS (*m/z*): 262 ($M-H^{\neg+}$, 0.3), 247 (0.4), 216 (1.3), 190 (30), 175 (18), 162 (13), 145 (27), 144 (58), 130 (35), 118 (27), 116 (28), 106 (44), 100 (10), 99 (5), 92 (100), 77 (47), 55 (7), 51 (17). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.7; H, 6.71; N, 5.26.

4.4. General procedure for the reduction with Raney Ni

The nitro compound (0.85 mmol) was dissolved in 1:1 EtOH/ethyl acetate (20 ml) and one teaspoon of Raney Ni (Aldrich) was added. The apparatus was evacuated and flushed with H_2. The mixture was stirred at room temperature under H_2 atmosphere for 16 h, then filtered on Celite and the solvent was evaporated.

4.4.1. (3*R,4*R**)- and (3*R**,4*S**)-3-(2-Hydroxyethyl)-4-methyl-2-pyrrolidinone 21a and 21b.** Reduction of the nitroalkylated lactone **15a** gave the *trans* isomer **21a**: 80% yield, white solid, mp 78–80 °C, IR (cm^{-1}, nujol): 3165 (OH and NH), 1672 (NHC=O); ^1H NMR (δ, ppm): 7.03 (1H, bs, NH), 4.9 (1H, bs, OH), 3.84 (1H, m, CHOH), 3.72 (1H, m, CHOH), 3.49 (1H, t, $J=9.0$ Hz, H-5), 2.99 (1H, t, $J=9.0$ Hz, H-5), 2.18 (1H, m), 2.09 (1H, m), 1.78 (2H, m, CH_2CH_2OH), 1.15 (3H, d, $J=6.9$ Hz, CH_3); ^{13}C NMR (δ, ppm): 181.6 (s), 62.2 (t, CH_2OH), 49.7 (d, C-3), 48.7 (t, C-5), 37.1 (d, C-4), 32.4 (t, CH_2CH_2OH), 17.3 (q, CH_3); MS (*m/z*): 144 (MH^+, 41), 126 (6), 113 (9), 112 (10), 99 (22), 98 (33), 96 (17), 85 (18), 84 (100), 67 (9). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.5; H, 8.90; N, 9.59.

Reduction of nitroalkylated lactone **15b** gave the *cis* isomer **21b**: 80% yield, white solid, mp 62–65 °C, IR (cm^{-1}, nujol): 3165 (OH and NH), 1672 (NHC=O); ^1H NMR (δ, ppm): 6.77 (1H, bs, NH), 4.4 (1H, bs, OH), 3.82 (1H, m, CHOH), 3.70 (1H, m, CHOH), 3.48 (1H, dd, $J_1=6.0$ Hz, $J_2=9.5$ Hz, H-5), 2.94 (1H, bd, $J=9.5$ Hz, H-5), 2.50 (2H, m, H-3 and H-4), 1.70 (2H, m, CH_2CH_2OH), 0.97 (3H, d, $J=6.9$ Hz, CH_3); ^{13}C NMR (δ, ppm): 180.3 (s), 62.2 (t, CH_2OH), 48.6 (t, C-5), 45.5 (d, C-3), 33.5 (d, C-4), 28.5 (t, CH_2CH_2OH), 14.6 (q, CH_3); MS (*m/z*): 144 (MH^+, 49), 126 (14), 112 (22), 99 (27), 98 (69), 96 (23), 85 (23), 84 (100), 67 (22). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58. 5; H, 9.00; N, 9.58.

4.4.2. (3*R,4*R**)- and (3*R**,4*S**)-3-(2-Hydroxyethyl)-3,4-dimethyl-2-pyrrolidinone 22a and 22b.** The two isomers were obtained as a 1:9 inseparable mixture, 80% yield, white solid, mp 88 °C (from light petroleum/ethyl acetate); IR (cm^{-1}, nujol): 3330 (OH and NH), 1680 (NHC=O); MS (*m/z*): 158 ($M+H^{\neg+}$, 13), 113 (40), 112 (54), 98 (100), 84 (17), 67 (11), 55 (22). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.3; H, 9.41; N, 9.14.

For clarity sake the NMR values of the two isomers are given separately.

Compound **22a** in admixture with **22b**. ^1H NMR (δ, ppm) (only few signals were identified): 6.97 (1H, bs, NH), 2.25 (1H, m, H-4), 1.70 (1H, ddd, $J_1=5.8$ Hz, $J_2=10.2$ Hz, $J_3=15.7$ Hz, C*H*CH_2OH), 1.42 (1H, m, C*H*CH_2OH), 0.94 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 184.5 (s), 58.7 (t, CH_2OH), 47.0 (t, C-5), 45.9 (s, C-3), 39.7 (d, C-4), 38.2 (t, *C*H_2CH_2OH), 15.1 (q, CH_3 at C-3), 11.4 (q, CH_3 at C-4).

Compound **22b**. ^1H NMR (δ, ppm). 6.92 (1H, bs, NH), 3.82 (1H, m, C*H*OH), 3.79 (1H, bs, OH), 3.63 (1H, m, C*H*OH), 3.35 (1H, dd, $J_1=8.2$ Hz, $J_2=9.0$ Hz, H-5), 2.92 (1H, dd, $J_1=8.2$ Hz, $J_2=9.7$ Hz, H-5), 2.13 (1H, m, H-4), 1.73 (1H, ddd, $J_1=5.3$ Hz, $J_2=9.0$ Hz, $J_3=14.1$ Hz, C*H*CH_2OH), 1.35 (1H, dt, $J_1=4.7$ Hz, $J_2=14.1$ Hz, C*H*CH_2OH), 1.13 (3H, s, CH_3), 0.96 (3H, d, $J=7.3$ Hz, CH_3); ^{13}C NMR (δ, ppm): 184.0 (s), 58.9 (t, CH_2OH), 46.6 (t, C-5), 44.6 (s, C-3), 42.0 (d, C-4), 34.0 (t, *C*H_2CH_2OH), 20.5 (q, CH_3 at C-3), 12.6 (q, CH_3 at C-4).

4.4.3. (3*R,4*S**)- and (3*R**,4*R**)-3-(2-Hydroxyethyl)-4-phenyl-2-pyrrolidinone 23a and 23b.** Treatment of the crude reaction mixture with light petroleum/ethyl acetate gave a 3:2 mixture of **23a** and **23b** as a white solid (70% yield), mp 90–93 °C, IR (cm^{-1}, nujol): 3366, 3262 (OH and NH), 1693 (NHC=O), 1638 (Ph); MS (*m/z*): 206 (MH^+, 16), 160 (100), 159 (90), 147 (13), 118 (13), 117 (43), 115 (33), 104 (16), 91 (13), 84 (14), 78 (11). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.0; H, 7.11; N, 6.64.

For clarity sake the NMR values of the isomeric mixture are given separately for each isomer.

Compound **23a**. ^1H NMR (δ, ppm): 7.64 (1H, bs, NH), 7.28 (5H, m, Ph), 4.5 (1H, bs, OH), 3.74–3.50 (3H, m, CH_2OH, H-5), 3.41 (1H, t, $J=9.5$ Hz, H-5), 3.27 (1H, q, $J=9.5$ Hz, H-4), 2.70 (1H, dt, $J_1=J_2=9.5$ Hz, $J_3=4.0$ Hz, H-3), 1.85 (1H, m, C*H*CH_2OH), 1.74 (1H, m, C*H*CH_2OH); ^{13}C NMR (δ, ppm): 180.4 (s), 140.0 (s), 129.0 (2d), 128.7 (2d), 127.6 (d), 61.6 (t, CH_2OH), 49.0 (d, C-3), 48.9 (t, C-5), 48.4 (d, C-4), 32.4 (t, *C*H_2CH_2OH).

Compound **23b**. ^1H NMR (δ, ppm): 7.67 (1H, bs, NH), 7.28 (5H, m, Ph), 4.5 (1H, bs, OH), 3.79 (1H, dd, $J_1=7.1$ Hz, $J_2=9.7$ Hz, H-5), 3.74–3.50 (4H, m, CH_2OH, H-5, H-4), 2.92 (1H, dt, $J_1=J_2=8.7$ Hz, $J_3=5.0$ Hz, H-3), 1.48 (1H, m, C*H*CH_2OH), 1.30 (1H, m, C*H*CH_2OH); ^{13}C NMR (δ, ppm): 181.2 (s), 140.4 (s), 127.8 (2d), 127.5 (2d), 127.3 (d), 61.4 (t, CH_2OH), 48.0 (t, C-5), 45.3 (d, C-3), 44. 3 (d, C-4), 29.9 (t, *C*H_2CH_2OH).

4.4.4. (3*R,4*R**)- and (3*R**,4*S**)-3-(2-Hydroxyethyl)-3-methyl-4-phenyl-2-pyrrolidinone 24a and 24b.** The 65:35 crude mixture of **24a** and **24b** (70% overall yield), obtained from the reduction, was purified by flash chromatography. The two isomeric lactams could be separated only partially. Semisolid material, IR (cm^{-1}, neat): 3260 (OH and NH), 1685 (NHC=O); MS (*m/z*): 220 (MH^+, 20), 204 (27), 175 (100), 174 (69), 160 (68), 158 (28), 131 (14), 129 (18), 128 (15), 117 (11), 115 (19), 104 (21), 98 (54), 91 (16), 78 (11).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.0; H, 7.88; N, 6.25.

Compound **24a**. ^{1}H NMR (δ, ppm). 7.33 (3H, m, *m*-, *p*-ArH), 7.23 (2H, m, *o*-ArH), 6.31 (1H, bs, NH), 4.53 (1H, dd, $J_1=8.4$ Hz, $J_2=2.6$ Hz, OH), 3.85–3.60 (4H, m, CH_2OH, 2H-5), 3.48 (1H, dd, $J_1=10.1$ Hz, $J_2=7.8$ Hz, H-4), 1.90 (1H, m, CHCH$_2$OH), 1.72 (1H, m, CHCH$_2$OH), 0.93 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.4 (s), 136.4 (s), 129.1 (2d), 128.5 (2d), 127.7 (d), 58.6 (t, CH_2OH), 51.3 (d, C-4), 47.5 (s, C-3), 44.5 (t, C-5), 38.5 (t, *C*H$_2$CH$_2$OH), 17.4 (q, CH_3).

Compound **24b**. ^{1}H NMR (δ, ppm). 7.33 (3H, m, *m*-, *p*-ArH), 7.21 (2H, m, *o*-ArH), 6.34 (1H, bs, NH), 3.85–3.60 (4H, m, CH_2OH, H-5, H-4), 3.62 (1H, dd, $J_1=2.1$ Hz, $J_2=$ 10.1 Hz, OH), 3.36 (1H, t, $J=7.7$ Hz, H-5), 1.66 (1H, m, CHCH$_2$OH), 1.37 (3H, s, CH_3), 0.98 (1H, m, CHCH$_2$OH); ^{13}C NMR (δ, ppm): 183.6 (s), 137.8 (s), 128.7 (2d), 128.4 (2d), 127.6 (d), 58.7 (t, CH_2OH), 53.6 (d, C-4), 46.5 (s, C-3), 44.4 (t, C-5), 35.7 (t, *C*H$_2$CH$_2$OH), 21.4 (q, CH_3).

4.4.5. (3*R,4*R**,5*S**)-3-(2-Hydroxyethyl)-5-methyl-4-phenyl-2-pyrrolidinone 25a.** The crude reaction mixture obtained from the reduction of **19a** was treated with light petroleum/ethyl acetate to afford **25a** (70% yield) as a white solid, mp 123–125 °C; IR (cm^{-1}, nujol): 3260 (OH and NH), 1690 (NHC=O), 1600 (Ph); ^{1}H NMR (CD_3OD, δ, ppm): 7.27 (3H, m, *m*-, *p*-ArH), 7.12 (2H, bd, *o*-ArH), 4.09 (1H, dq, $J_1=6.6$ Hz, $J_2=5.8$ Hz, H-5), 3.54 (1H, dd, $J_1=$ 7.7 Hz, $J_2=5.8$ Hz, H-4), 3.45 (2H, m, CH_2OH), 3.03 (1H, ddd, $J_1=8.9$ Hz, $J_2=7.7$ Hz, $J_3=5.8$ Hz, H-3), 1.86 (1H, m, CHCH$_2$OH), 1.30 (1H, m, CHCH$_2$OH), 0.83 (3H, d, $J=$ 6.6 Hz, CH_3); ^{13}C NMR (δ, ppm): 183.7 (s), 139.3 (s), 132.5 (2d), 131.3 (2d), 130.4 (d), 65.1 (t, CH_2OH), 56.0 (d), 54.2 (d), 51.2 (d, C-3), 32.4 (t, *C*H$_2$CH$_2$OH), 19.5 (q, CH_3); MS (*m*/*z*): 220 (MH$^+$, 14), 175 (100), 174 (19), 131 (15), 118 (27), 117 (65), 115 (33), 91 (10). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 69.9; H, 7.41; N, 6.14.

4.4.6. (3*R,4*R**,5*R**)- and (3*R**,4*R**,5*S**)-3,5-Dimethyl-3-(2-hydroxyethyl)-4-phenyl-2-pyrrolidinone 26a and 26b.** A 1:1 mixture of nitroalkylated lactones **20a** and **20b** was reduced under the above mentioned conditions to give a 1:1 mixture of the corresponding lactams **26a** and **26b** (70% overall yield). The same compounds were obtained from the reduction with Raney Ni of the nitronic acid **37**, although in a 7:3 molar ratio. The two isomers could not be separated. White solid, mp 94–100 °C, IR (cm^{-1}, $CHCl_3$): 3336 (OH and NH), 1680 (NHC=O), 1602 (Ph); MS (*m*/*z*): 234 (MH$^+$, 14), 218 (49), 203 (16), 190 (27), 189 (100), 188 (82), 174 (62), 162 (28), 161 (14), 160 (15), 132 (28), 131 (87), 129 (42), 128 (20), 118 (28), 117 (55), 116 (22), 115 (37), 112 (35), 91 (46). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.9; H, 8.11; N, 5.89.

For clarity sake the NMR values of the isomeric mixture are given separately for each isomer.

Compound **26a**. ^{1}H NMR (CD_3OD, δ, ppm). 7.25 (3H, m, *m*-, *p*-ArH), 7.12 (2H, bd, *o*-ArH), 4.25 (1H, dq, $J_1=6.2$ Hz, $J_2=6.9$ Hz, H-5), 3.8–3.6 (2H, m, CH_2OH), 3.38 (1H, d, $J_1=6.2$ Hz, H-4), 1.90 (2H, m, CH_2CH$_2$OH), 0.91 (3H, d, $J=6.9$ Hz, CH_3), 0.81 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.0 (s), 136.9 (s), 130.1 (2d), 128.1 (2d), 127.7 (d), 59.2 (t, CH_2OH), 57.4 (d, C-4), 50.6 (d, C-5), 47.7 (s, C-3), 40.5 (t, *C*H$_2$CH$_2$OH), 18.7 (q, CH_3 at C-3), 17.1 (q, CH_3 at C-5).

Compound **26b**. ^{1}H NMR (CD_3OD, δ, ppm). 7.25 (3H, m, *m*-, *p*-ArH), 7.12 (2H, bd, *o*-ArH), 4.12 (1H, dq, $J_1=6.2$ Hz, $J_2=9.9$ Hz, H-5), 3.8–3.6 (2H, m, CH_2OH), 3.07 (1H, d, $J_1=9.9$ Hz, H-4), 1.70 (2H, m, CH_2CH$_2$OH), 1.15 (3H, d, $J=6.2$ Hz, CH_3), 0.85 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 181.9 (s), 134.8 (s), 129.4 (2d), 128.5 (2d), 127.9 (d), 60.7 (d, C-4), 58.3 (t, CH_2OH), 51.7 (d, C-5), 48.8 (s, C-3), 38.4 (t, *C*H$_2$CH$_2$OH), 19.7 (q, CH_3 at C-3), 19.6 (q, CH_3 at C-5).

4.5. Reduction of the nitro group with 10% Pd on carbon

The appropriate nitroalkylated γ-lactone (0.8 mmol) was dissolved in 6 ml of MeOH and 10% Pd on activated carbon (54 mg) was added. The mixture was stirred at room temperature under H_2 for 4 h. The mixture was filtered on Celite and the solvent was evaporated.

4.5.1. (3*R,4*R**)- and (3*R**,4*S**)-1-Hydroxy-3-(2-hydroxyethyl)-4-methyl-2-pyrrolidinone 27a and 27b.** The two isomers were obtained in admixture with the corresponding lactams **21a** and **21b** from the corresponding parent lactones **15a** and **15b**. For clarity sake the NMR values of the isomeric mixture are given separately for each isomer.

Compound **27a**. ^{1}H NMR (δ, ppm): 9.0 (1H, vbs, OH), 4.6 (1H, bs, OH), 3.75 (2H, m, CH_2OH), 3.72 (1H, m, H-5), 3.22 (1H, bd, $J=9.1$ Hz, H-5), 2.14 (2H, m, H-3 and H-4), 1.80 (2H, m, CH_2CH$_2$OH), 1.14 (3H, d, $J=6.2$ Hz, CH_3); ^{13}C NMR (δ, ppm): 172.4 (s), 61.5 (t, CH_2OH), 55.2 (t, C-5), 47.8 (d, C-3), 33.0 (t, *C*H$_2$CH$_2$OH), 31.5 (d, C-4), 17.6 (q, CH_3).

Compound **27b**. ^{1}H NMR (δ, ppm): 9.0 (1H, vbs, OH), 4.6 (1H, bs, OH), 3.75 (2H, m, CH_2OH), 3.73 (1H, m, H-5), 3.21 (1H, dd, $J_1=9.5$ Hz, $J_2=11.0$ Hz, H-5), 2.66 (1H, m, H-3), 2.52 (1H, m, H-4), 1.70 (2H, m, CH_2CH$_2$OH), 1.04 (3H, d, $J=7.0$ Hz, CH_3); ^{13}C NMR (δ, ppm): 172.0 (s), 61.5 (t, CH_2OH), 55.5 (t, C-5), 43.4 (d, C-3), 28.8 (t, *C*H$_2$CH$_2$OH), 28.4 (d, C-4), 14.9 (q, CH_3).

4.5.2. (3*R,4*R**) and (3*R**,4*S**)-1-Hydroxy-3-(2-hydroxyethyl)-3,4-dimethyl-2-pyrrolidinone 28a and 28b.** The two isomers were obtained from the corresponding nitroalkylated lactones **16a** and **16b**.The crude reaction mixture was purified by flash chromatography (eluant: ethyl acetate, 70% yield) and the isomer **28b** crystallized on standing at room temperature.

Compound **28a** (in admixture with **28b**). Oil, only a few signals were identified; ^{1}H NMR (δ, ppm): 3.36 (1H, m), 2.95 (1H, m), 2.23 (1H, m, H-4), 0.94 (3H, s, CH_3), 0.92 (3H, d, $J=7.3$ Hz, CH_3); ^{13}C NMR (δ, ppm): 58.5 (t, CH_2OH), 53.6 (t, C-5), 44.7 (s, C-3), 38.5 (t, *C*H$_2$CH$_2$OH), 33.8 (d, C-4), 16.0 (q, CH_3 at C-3), 11.5 (q, CH_3 at C-4).

Compound **28b**. White solid, mp 90–92 °C, IR (cm^{-1}, neat): 3350 (OH), 1680 (NC=O); ^{1}H NMR (δ, ppm): 10.0 (1H,

vbs, NOH), 5.00 (1H, vbs, OH), 3.82 (1H, m, C*H*OH), 3.66 (2H, m, H-5 and CHOH), 3.29 (1H, t, $J=9.0$ Hz, H-5), 2.18 (1H, sextet, $J=7.3$ Hz, H-4), 1.74 (1H, m, C*H*CH_2OH), 1.50 (1H, dt, $J_1=J_2=5.1$ Hz, $J_3=13.9$ Hz, C*H*CH_2OH), 1.18 (3H, s, CH_3), 1.04 (3H, d, $J=7.3$ Hz, CH_3); ^{13}C NMR (δ, ppm): 174.0 (s), 58.3 (t, CH_2OH), 53.6 (t, C-5), 43.6 (s, C-3), 37.3 (d, C-4), 35.0 (t, *C*H_2CH_2OH), 21.3 (q, CH_3 at C-3), 12.0 (q, CH_3 at C-4). MS (*m*/*z*): 156 ($M-OH^{\neg+}$, 12), 129 (18), 128 (34), 127 (11), 114 (100), 113 (33), 100 (14), 99 (68), 83 (21), 82 (39), 81 (13), 70 (22), 69 (66), 67 (65), 55 (80). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.4; H, 8.29; N, 7.89.

4.5.3. (3*R,4*S**)- and (3*R**,4*R**)-1-Hydroxy-3-(2-hydroxyethyl)-4-phenyl-2-pyrrolidinone 29a and 29b.** Treatment of the crude reaction mixture, obtained by reduction of **17a** and **17b**, with ethyl acetate led to the crystallization of the isomer **29a** (6% yield). The isomer **29b** was recovered in 1:1 admixture with **29a** (89% yield).

Compound **29a**. White solid, mp 171–173 °C; IR (cm^{-1}, nujol): 3210 (OH), 1685 (NC=O); ^{1}H NMR (CD_3OD, δ, ppm): 7.35 (5H, m, Ph), 3.85 (1H, t, $J=8.6$ Hz, H-5), 3.66–3.48 (3H, m, CH_2OH and H-5), 3.25 (1H, q, $J=8.5$ Hz, H-4), 2.71 (1H, m, H-3), 1.94 (1H, sextet, $J=6.9$ Hz, C*H*CH_2OH), 1.73 (1H, sextet, $J=6.9$ Hz, C*H*CH_2OH); ^{13}C NMR (CD_3OD, δ, ppm): 173.3 (s), 141.2 (s), 129.9 (d), 128.6 (d), 128.4 (d), 60.6 (t, CH_2OH), 56.3 (t, C-5), 46.4 (d, C-3), 43.5 (d, C-4), 34.1 (t, *C*H_2CH_2OH); MS (*m*/*z*): 175 (19), 174 (13), 161 (93), 160 (43), 148 (16), 131 (25), 130 (16), 129 (16), 128 (11), 118 (26), 117 (100), 116 (33), 115 (48), 104 (67), 91 (48), 84 (30), 78 (17), 77 (25). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.4; H, 6.71; N, 6.16.

Compound **29b**. ^{1}H NMR (CD_3OD, δ, ppm): 7.35 (5H, m, Ph), 3.99 (1H, t, $J=8.2$ Hz, H-5), 3.64 (2H, m, H-5 and H-4), 3.47 (2H, m, C*H*$_2$OH), 2.95 (1H, q, $J=7.7$ Hz, H-3), 1.59 (1H, sextet, $J=7.2$ Hz, C*H*CH_2OH), 1.25 (1H, m, C*H*CH_2OH); ^{13}C NMR (CD_3OD, δ, ppm): 172.9 (s), 141.6 (s), 129.6 (d), 128.2 (d), 128.1 (d), 60.6 (t, CH_2OH), 55.8 (t, C-5), 42.6 (d, C-3), 40.0 (d, C-4), 30.5 (t, *C*H_2CH_2OH).

4.5.4. (3*R,4*R**)- and (3*R**,4*S**)-1-Hydroxy-3-(2-hydroxyethyl)-3-methyl-4-phenyl-2-pyrrolidinone 30a and 30b.** Treatment of the crude reaction mixture, obtained by reduction of **18a** and **18b**, with ethyl acetate led to the crystallization of the isomer **30a**, while **30b** was obtained by flash chromatography of the mother liquors (eluant: ethyl acetate).

Compound **30a**. 57% Yield, white solid, mp 175–178 °C; IR (cm^{-1}, nujol): 3200 (OH), 1681 (NC=O); ^{1}H NMR (CD_3OD, δ, ppm): 7.31 (5H, m, Ph), 3.90 (1H, dd, $J_1=8.4$ Hz, $J_2=9.1$ Hz, H-5), 3.80 (1H, dd, $J_1=7.8$ Hz, $J_2=9.0$ Hz, H-5), 3.77–3.66 (2H, m, CH_2OH) 3.63 (1H, t, $J=8.1$ Hz, H-4), 1.80 (2H, m, C*H*$_2CH_2$OH), 0.74 (3H, s, CH_3); ^{13}C NMR (CD_3OD, δ, ppm): 175.3 (s), 138.7 (s), 129.9 (d), 129.5 (d), 128.4 (d), 59.3 (t, CH_2OH), 52.5 (t, C-5), 47.1 (s, C-3), 45.0 (d, C-4), 40.1 (t, *C*H_2CH_2OH), 19.5 (q, CH_3); MS (*m*/*z*): 218 ($M-OH^{\neg+}$, 1), 190 (18), 189 (18), 175 (100), 174 (37), 160 (23), 131 (43), 129 (23), 117 (28), 116 (19), 115 (27), 104 (77), 98 (57), 91 (62), 78 (15), 77 (18). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.5; H, 7.31; N, 5.81.

Compound **30b**. 12% Yield; oil, IR (cm^{-1}, film): 3200 (OH), 1681 (NC=O); ^{1}H NMR (CD_3OD, δ, ppm): 7.31 (5H, m, Ph), 3.92 (1H, dd, $J_1=7.9$ Hz, $J_2=9.3$ Hz, H-5), 3.81 (1H, dd, $J_1=7.7$ Hz, $J_2=9.2$ Hz, H-5), 3.55 (1H, m, C*H*OH), 3.35 (2H, m, C*H*OH and H-4), 1.57 (1H, ddd, $J_1=6.4$ Hz, $J_2=9.5$ Hz, $J_3=13.9$ Hz, C*H*CH_2OH), 1.30 (3H, s, CH_3), 1.15 (1H, ddd, $J_1=5.2$ Hz, $J_2=9.4$ Hz, $J_3=14.1$ Hz, C*H*CH_2OH); ^{13}C NMR (CD_3OD, δ, ppm): 175.2 (s), 138.7 (s), 129.7 (d), 129.5 (d), 128.6 (d), 58.9 (t, CH_2OH), 52.4 (t, C-5), 46.5 (s, C-3), 45.0 (d, C-4), 37.0 (t, *C*H_2CH_2OH), 23.3 (q, CH_3).

4.5.5. (3*R,4*R**,5*R**)-1-Hydroxy-3-(2-hydroxyethyl)-5-methyl-4-phenyl-2-pyrrolidinone 31b.** Reduction of **19b** afforded a 1:3 mixture of the lactam **25b** and the cyclic hydroxamic acid **31b** (80% yield), from which **31b** was isolated by treatment with ethyl acetate.

Compound **25b** not separated: ^{1}H NMR ($CDCl_3+CD_3OD$, δ, ppm) (only a few signals were identified): 3.96 (1H, bq, $J=5.7$ Hz, H-5), 3.25 (1H, dd, $J_1=4.6$ Hz, $J_2=8.6$ Hz, H-4), 1.29 (3H, d, $J=6.2$ Hz, CH_3); ^{13}C NMR ($CDCl_3+CD_3OD$, δ, ppm): 180.1 (s), 138.8 (s), 128.6 (2d), 127.9 (2d), 127.1 (d), 61.0 (t, CH_2OH), 54.8 (d, C-5), 52.1 (d, C-4), 44.2 (d, C-3), 29.6 (t, *C*H_2CH_2OH), 20.6 (q, CH_3).

Compound **31b**. White solid, mp 158 °C, 18% yield, IR (cm^{-1}, nujol): 3220 (OH), 1676 (NC=O); ^{1}H NMR ($CDCl_3+CD_3OD$, δ, ppm): 7.24 (3H, m, Ph), 7.14 (2H, m, Ph), 3.94 (1H, dq, $J_1=4.4$ Hz, $J_2=J_3=J_4=6.2$ Hz, H-5), 3.45 (2H, m, C*H*$_2$OH,), 3.20 (1H, dd, $J_1=4.4$ Hz, $J_2=8.8$ Hz, H-4), 2.91 (1H, dt, $J_1=8.8$ Hz, $J_2=J_3=6.2$ Hz, H-3), 1.47 (1H, m, C*H*CH_2OH), 1.33 (3H, d, $J=6.2$ Hz, CH_3), 1.24 (1H, m, C*H*CH_2OH); ^{13}C NMR ($CDCl_3+CD_3OD$, δ, ppm): 171.3 (s), 138.3 (s), 128.7 (2d), 128.0 (2d), 127.3 (d), 60.8 (d, C-5), 60.7 (t, CH_2OH), 47.6 (d, C-4), 41.7 (d, C-3), 30.0 (t, *C*H_2CH_2OH), 17.1 (q, CH_3); MS (*m*/*z*): 217 ($M-H_2O^{\neg+\cdot}$, 1), 216 (1), 176 (28), 175 (32), 148 (13), 133 (11), 132 (25), 131 (13), 119 (51), 118 (100), 117 (29), 116 (38), 92 (35), 77 (14); MS (*m*/*z*, 20 eV): 236 (MH^+, 2), 235 ($M^{+\cdot}$, 2). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.5; H, 7.27; N, 5.90.

4.6. Reactions of α-methyl-γ-butyrolactone 1′ with (*E*)-2-morpholinyl-1-nitro-1-phenylethene (5), (*E*)-1-(2-methylthiophenyl)-2-pyrrolidinyl-1-nitroethene (6), (*Z*,*E*)-1-methylthio-4-pyrrolidinyl-2-nitrobutadiene (7) and (*E*)-1,1-dimethylthio-4-pyrrolidinyl-2-nitrobutadiene (7′). General procedure for the Michael addition of nitroenamines to α-methyl-γ-butyrolactone zinc enolate 8′

To a solution of lithium diisopropylamide (1.5 M solution in THF) (2 mmol, 1.3 ml for the reaction with **5**, **7** and **7′**; 3.5 mmol, 2.3 ml for the reaction with **6**) in THF (1.3 ml), a solution of the lactone **1′** (0.162 g, 1.62 mmol) in 1.3 ml of THF was slowly added, at −78 °C. The mixture was stirred for 1 h at −78 °C. A solution of 1M $ZnCl_2$ (1.62 ml) was then added and the temperature was raised to −40 °C. After 1 h at this temperature, the solution was transferred to the

appropriate aminonitroalkene (0.81 mmol) dissolved in 5.2 ml of THF at −78 °C. The mixture was stirred at −78 °C for 2 h, the temperature was allowed to raise and the solution was kept overnight at room temperature. The reaction mixture was then quenched with 2 N HCl and extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography (light petroleum/ethyl acetate 3:2).

4.6.1. (*E*)- and (*Z*)-4,5-Dihydro-3-methyl-3-(2-nitro-2-phenylethenyl)-2(3*H*)-furanone 38. The crude reaction mixture (88% yield), whose composition was 85:15 in favour of the (*E*)-isomer, was treated with ether and ethanol at 0 °C. The major isomer (*E*)-**38** was isolated as pure compound (30% yield), mp 90–92 °C; IR (cm^{-1}, nujol): 1778 (COO), 1672 (C=C), 1528 (NO_2). ^1H NMR (δ, ppm): 7.75 (1H, s, HC=C), 7.50 (3H, m, Ar–H), 7.32 (2H, m, Ar–H), 4.13 (2H, m, 2H-5), 2.10 (1H, dt, $J_1=9.3$ Hz, $J_2=13.2$ Hz, H-4), 1.60 (1H, ddd, $J_1=2.9$ Hz, $J_2=6.2$ Hz, $J_3=13.2$ Hz, H-4), 1.41 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 177.8 (s, COO), 152.2 (s, C=CNO_2), 137.6 (d, CH=CNO_2), 130.7 (2d, *o*-Ar–H), 130.4 (2d, *m*-Ar–H), 129.1 (s), 128.6 (d, *p*-Ar–H), 65.1 (t, C-5), 43.2 (s, C-3), 34.6 (t, C-4), 23.5 (q, CH_3). MS (*m*/*z*): 247 ($M^{+\cdot}$, 0.01), 201 (72), 174 (15), 173 (100), 171 (14), 170 (13), 156 (13), 155 (10), 145 (23), 143 (20), 142 (43), 141 (38), 130 (12), 129 (65), 128 (67), 127 (25), 117 (17), 115 (49), 105 (58), 104 (18), 103 (52), 102 (31), 99 (10), 91 (40), 84 (32), 77 (73), 76 (28), 75 (15), 69 (17), 65 (10), 63 (17), 56 (11), 55 (29), 51 (66), 53 (13). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.0; H, 5.19; N, 5.90.

The compound (*Z*)-**38** was not isolated as pure isomer.

^1H NMR (δ, ppm): 7.43 (5H, m, Ar–H), 6.43 (1H, s, HC=C), 4.44 (1H, dt, $J_1=1.5$ Hz, $J_2=J_3=9.2$ Hz, H-5), 4.32 (1H, ddd, $J_1=6.3$ Hz, $J_2=9.2$ Hz, $J_3=10.7$ Hz, H-5), 2.51 (1H, ddd, $J_1=9.2$ Hz, $J_2=10.7$ Hz, $J_3=12.8$ Hz, H-4), 2.35 (1H, ddd, $J_1=1.5$ Hz, $J_2=6.3$ Hz, $J_3=12.8$ Hz, H-4), 1.58 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 178.2 (s), 152.2 (s), 137.6 (d), 128.8 (d), 128.5 (d), 128.2 (d), 65.3 (t, C-5), 43.8 (s, C-3), 32.9 (t, C-4), 22.7 (q, CH_3); the singlet relative to C-1 of the phenyl ring was hidden under other signals.

4.6.2. (*E*)- and (*Z*)-4,5-Dihydro-3-methyl-3-[2-(2-methylthiophenyl)-2-nitroethenyl]-2(3*H*)-furanone 39. The crude reaction mixture, whose composition was 67:33 in favour of the (*E*)-isomer, was purified on flash chromatography, 50% yield, yellow oil, IR (cm^{-1}, neat): 1775 (COO), 1520, (C=C–NO_2); ^1H NMR (δ, ppm): 7.81 (0.67H, s, C=CH), 7.73 (0.33H, s, C=CH), 7.47 (1H, m, Ar–H), 7.31 (1H, bd, $J=7.7$ Hz, Ar–H), 7.23 (2H, m, Ar–H), 4.23 (0.67H, dt, $J_1=9.0$ Hz, $J_2=2.6$ Hz, H-5), 4.09 (1.33H, m, H-5), 2.45 (3H, s, SCH_3), 2.26 (0.33H, dt, $J_1=8.9$ Hz, $J_2=13.1$ Hz, H-4), 2.16 (0.67H, dt, $J_1=9.1$ Hz, $J_2=12.8$ Hz, H-4), 1.78 (0.33H, ddd, $J_1=3.7$ Hz, $J_2=6.6$ Hz, $J_3=13.1$ Hz, H-4), 1.48 (0.67H, ddd, $J_1=2.4$ Hz, $J_2=6.6$ Hz, $J_3=12.8$ Hz, H-4), 1.43 (0.90H, s, CH_3), 1.38 (2.1H, s, CH_3); ^{13}C NMR (δ, ppm): (*E*)-**39**: 177.7 (s), 150.8 (s), 140.6 (s), 139.0 (d), 131.6 (d), 131.3 (d), 128.5 (s), 126.0 (d), 125.0 (d), 65.4 (t), 43.6 (s), 33.3 (t), 23.3 (q), 15.7 (q); (*Z*)-**39**: 178.0 (s), 150.2 (s), 140.1 (s), 139.2 (d), 132.2 (d), 131.3 (d), 127.9 (s), 126.1 (d), 125.0 (d), 65.4 (t), 43.3 (s), 34.6 (t), 22.9 (q), 15.8 (q); MS (*m*/*z*): 293 ($M^{+\cdot}$, 28), 248 (12), 247 (49), 220 (16), 219 (100), 201 (12), 194 (36), 191 (12), 189 (17), 186 (14), 174 (15), 173 (36), 161 (14), 151 (41), 149 (25), 148 (13), 147 (28), 129 (14), 128 (12), 115 (18), 83 (11). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 56.4; H, 5.19; N, 4.60.

4.6.3. *cis*- and *trans*-3-(2-Hydroxyethyl)-3-methyl-5-phenyl-2-pyrrolidinone 40a and 40b. The nitroalkenylated lactones **38** and **39** were reduced using Pd on carbon and Raney Nickel as a catalyst as reported in the general procedure.

A 2:3 mixture of lactams **40a** and **40b** were obtained in 70% yield. The two isomers were only partially separable by flash chromatography; yellow oil, IR (cm^{-1}, $CHCl_3$): 3420, 3153 (NH and OH), 1685 (NHC=O); MS (*m*/*z*): 220 (MH^+, 33), 219 ($M^{+\cdot}$, 38), 202 (10), 191 (65), 190 (46), 175 (100), 174 (69), 173 (35), 172 (29), 160 (40), 158 (40), 147 (18), 146 (49), 145 (17), 144 (13), 143 (14), 132 (13), 131 (41), 130 (26), 129 (34), 128 (32), 120 (11), 117 (12), 115 (23), 106 (16), 104 (21), 91 (26), 84 (11), 77 (14). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.5; H, 7.65; N, 6.30.

For sake of clarity the NMR values of the isomeric mixture are given separately for each isomer.

Compound **40a**. ^1H NMR (δ, ppm): 7.33 (5H, m, Ph), 6.23 (1H, bs, NH), 4.75 (1H, t, $J=6.6$ Hz, H-5), 4.09 (1H, bd, $J=6.2$ Hz, OH), 3.92 (1H, m, C*H*OH), 3.70 (1H, m, C*H*OH), 2.30 (1H, dd, $J_1=6.6$ Hz, $J_2=12.6$ Hz, H-4), 1.90 (2H, m, C*H*CH_2OH and H-4), 1.71 (1H, m, C*H*CH_2OH), 1.33 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.3 (s), 141.6 (s), 129.0 (2d), 128.0 (d), 125.7 (2d), 58.7 (t, CH_2OH), 55.8 (d, C-5), 46.6 (t, C-4), 44. 6 (s, C-3), 40.3 (t, *C*H_2CH_2OH), 21.8 (q).

Compound **40b**. ^1H NMR (δ, ppm): 7.38 (2H, m, Ph), 7.31 (3H, m, Ph), 5.94 (1H, bs, NH), 4.77 (1H, t, $J=7.3$ Hz, H-5), 3.94 (1H, m, C*H*OH), 3.75 (1H, m, C*H*OH), 2.97 (1H, bd, OH), 2.55 (1H, dd, $J_1=7.3$ Hz, $J_2=13.0$ Hz, H-4), 2.02 (1H, m, C*H*CH_2OH), 1.90 (1H, dd, $J_1=7.3$ Hz, $J_2=13.0$ Hz, H-4), 1.71 (1H, m, C*H*CH_2OH), 1.28 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.3 (s), 142.2 (s), 129.1 (2d), 128.1 (d), 125.8 (2d), 59.4 (t, CH_2OH), 55.0 (d, C-5), 46.8 (t, C-4), 43. 3 (s, C-3), 40.6 (t, *C*H_2CH_2OH), 23.5 (q).

4.6.4. 4,5-Dihydro-3-(2-(hydroxyimino)-2-(2-methylthiophenyl))ethyl-3-methyl-2(3*H*)-furanone 41. 51% Yield, yellow oil, IR (cm^{-1}) 3350 (OH), 1766 (COO), 1625 (C=N), 1587, 1560 (Ph), ^1H NMR (δ, ppm): 8.8 (1H, vbs, OH), 7.27 (4H, m, Ph), 4.25 (2H, m, 2H-5), 3.21 (2H, AB system, $J=13.2$ Hz, CH_2 of the chain), 2.44 (3H, s, SCH_3), 2.30 (1H, dt, $J_1=J_2=7.6$ Hz, $J_3=12.9$ Hz, H-4), 1.90 (1H, ddd, $J_1=5.1$ Hz, $J_2=7.3$ Hz, $J_3=12.9$ Hz, H-4), 1.17 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 181.0 (s), 156.7 (s), 137.7 (s), 135.7 (s), 129.4 (d), 129.1 (d), 126.6 (d), 124.9 (d), 65.3 (t, C-5), 42.4 (s, C-3), 34.6 (t), 34.3 (t), 22.9 (q, CH_3), 16.5 (q, CH_3); MS (*m*/*z*): 264 ($M-CH_3^{\cdot+}$, 100), 262 (76), 247 (50), 232 (42), 229 (16), 203 (13), 188 (10), 164 (17), 152 (14).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 60.3; H, 6.25; N, 4.96.

4.6.5. (*E*,*Z*)- and (*Z*,*Z*)-4,5-Dihydro-3-methyl-3-(4-methylthio-2-nitrobutadienyl)-2(3*H*)-furanone 42. The product (*E*,*Z*)-**42** was purified on column chromatography (52% yield). Oil, IR (cm^{-1}, $CHCl_3$): 1775 (COO), 1525 (C═C–NO_2); ^1H NMR (δ, ppm): 7.32 (1H, d, $J=1.5$ Hz, H-1 of the chain), 6.64 (1H, d, $J=10.2$ Hz, H-3 of the chain), 6.04 (1H, dd, $J_1=10.2$ Hz, $J_2=1.5$ Hz, H-4 of the chain), 4.32 (2H, m, 2H-5), 2.55 (1H, dt, $J_1=8.5$ Hz, $J_2=13.1$ Hz, H-4), 2.32 (1H, m, H-4), 2.36 (3H, s, SCH_3), 1.52 (3H, s, CH_3); ^{13}C NMR (δ, ppm): (*E*,*Z*)-**42**: 177.7 (s), 148.5 (s), 141.3 (d), 141.2 (d), 113.1 (d), 65.4 (t, C-5), 43.4 (s, C-3), 33.3 (t, C-4), 23.3 (q, SCH_3), 15.7 (q, CH_3); Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 48.8; H, 5.49; N, 5.64. On standing in $CDCl_3$, the (*E*,*Z*)-isomer converted into its (*Z*,*Z*) isomer for an amount of 20%.

Compound (*Z*,*Z*)-**42**. ^1H NMR (δ, ppm) (a few signals were hidden under those of the (*E*)-isomer): 6.54 (1H, d, $J=$ 11.0 Hz, H-3 of the chain), 6.29 (1H, s, H-1 of the chain), 6.09 (1H, d, $J=11.0$ Hz, H-4 of the chain), 4.44 (1H, dt, $J_1=1.5$ Hz, $J_2=9.2$ Hz, H-5), 2.41 (3H, s, SCH_3), 1.57 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 180.6 (s), 147.5 (s), 137.9 (d), 132.6 (d), 115.2 (d), 65.4 (t, C-5), 43.6 (s, C-3), 34.3 (t, C-4), 23.9 (q, SCH_3), 18.9 (q, CH_3).

4.6.6. (*E*)-4,5-Dihydro-3-methyl-3-(4,4-dimethylthio-2-nitro)butadienyl-2(3*H*)-furanone 43. The product (70% yield) was purified by flash chromatography (eluant: light petroleum:ethyl acetate, gradient), mp 82–84 °C; IR (cm^{-1}, film): 1770 (COO), 1666 (C═C), 1528, 1368 (NO_2); ^1H NMR (δ, ppm): 7.24 (1H, d, $J=1.8$ Hz, H-1 of the chain), 5.96 (1H, d, $J=1.8$ Hz, H-3 of the chain), 4.32 (2H, dd, $J_1=$ 6.0 Hz, $J_2=7.7$ Hz, 2H-5), 2.48 (1H, dt, $J_1=7.7$ Hz, $J_2=$ 12.8 Hz, H-4), 2.45 (3H, s, SCH_3), 2.35 (3H, s, SCH_3), 2.30 (1H, dt, $J_1=6.0$ Hz, $J_2=12.8$ Hz, H-4), 1.51 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 177.7 (s), 149.8 (s), 147.9 (s), 137.0 (d, C-1 of the chain), 111.0 (d, C-3 of the chain), 65.3 (t, C-5), 43.2 (s, C-3), 35.9 (t, C-4), 22.6 (q, CH_3), 16.4 (q, SCH_3), 16.2 (q, SCH_3); MS (*m*/*z*): 289 ($M^{+\cdot}$, 3), 243 (100), 215 (48), 195 (11), 167 (22), 139 (11), 91 (11). Anal. Calcd for $C_{11}H_{15}NO_4S_2$: C, 45.66; H, 5.22; N, 4.84; S, 22.16. Found: C, 46.5; H, 5.35; N, 4.76.

4.6.7. 4,5-Dihydro-3-methyl-3-[(4,4-dimethylthio-2-nitro)but-3-enyl]-2(3*H*)-furanone 44a,b. To a solution of the nitrodiene **43** (0.04 g, 0.14 mmol) in MeOH (7 ml), 0.105 g of supported borohydride (2 mmol/g of Amberlyst A26, Aldrich product) was added under stirring and the reaction was monitored by TLC. After 15 min, the polymer was filtered off and washed with MeOH, the filtrated was evaporated and purified by flash chromatography. Compounds **44a** and **44b** (60 and 40%, respectively) were not separable by flash chromatography. For sake of clarity the NMR values of the isomeric mixture are given separately for each isomer.

Compound **44a**. ^1H NMR (δ, ppm): 5.52 (1H, d, $J=8.8$ Hz, H–C═C), 4.50 (1H, dt, $J_1=J_2=8.8$ Hz, $J_3=4.8$ Hz, CH–NO_2), 4.26 (2H, m, 2H-5), 2.44 (1H, m), 2.35 (3H, s, SCH_3), 2.31 (3H, s, SCH_3), 2.03 (2H, m), 1.70 (1H, m), 1.29 (3H, s, CH_3).

Compound **44b**. ^1H NMR (δ, ppm): 5.57 (1H, d, $J=8.4$, H–C═C), 4.58 (1H, ddd, $J_1=3.0$, $J_2=8.4$, $J_3=10.6$, CH–NO_2), 4.26 (2H, m, 2H-5), 2.44 (1H, m), 2.35 (3H, s, SCH_3), 2.30 (3H, s, SCH_3), 2.03 (2H, m), 1.70 (1H, m), 1.30 (3H, s, CH_3).

4.6.8. (*E*)-4,5-Dihydro-3-methyl-3-(4,4-dimethylthio)butadienyl-2(3*H*)-furanone 45. On standing in $CDCl_3$, **44a** and **44b** convert into the diene system **45**. Oil. IR (cm^{-1}, $CHCl_3$): 1770 (COO), 1605, 1558 (C═C); ^1H NMR (δ, ppm): 6.78 (1H, dd, $J_1=15.7$ Hz, $J_2=10.2$ Hz, H-2 of the chain), 6.32 (1H, d, $J=10.2$ Hz, H-3 of the chain), 5.77 (1H, d, $J=15.7$ Hz, H-1 of the chain), 4.29 (2H, m, 2H-5), 2.40 (1H, m, H-4), 2.33 (3H, s, SCH_3), 2.32 (3H, s, SCH_3), 2.17 (1H, m, H-4), 1.40 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 168.0 (s), 133.6 (s), 133.2 (d), 129.4 (d), 126.9 (d), 65.2 (t), 45.3 (s), 35.8 (t), 23.3 (q), 17.4 (q,), 16.7 (q); MS (*m*/*z*): 245 (MH^+, 19), 244 ($M^{+\cdot}$, 21), 231 (19), 230 (24), 229 (100), 213 (13), 212 (15), 201 (36), 185 (12), 183 (43), 155 (10), 138 (10), 137 (13), 123 (10), 91 (19), 77 (12). Anal. Calcd for $C_{11}H_{16}O_2S_2$: C, 54.06; H, 6.60; S, 26.24. Found: C, 55.0; H, 6.67.

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