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1,3-Dipolar Cycloaddition of *C*-(2-Thiazolyl)Nitrones to Chiral Acrylates. Synthesis of Enantiopure α-Amino-2-alkylthiazoles and 5-Formylpyrrolidin-2-ones.

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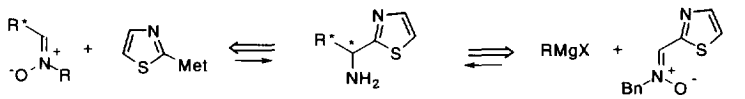
Abstract: The 1,3-dipolar cycloaddition of thiazolyl nitrones with chiral acrylates has been studied. The use of the Oppolzer's camphor sultam as chiral inductor provided isoxazolidines with excellent regio- and diastereoselectivities and good asymmetric induction. The cycloadducts were converted into homochiral α-amino-2-alkylthiazoles and 5-(2-thiazolyl)-3-hydroxy-2-pyrrolidinones. The latter compounds were precursors of highly functionalized pyrrolidines by the aldehyde unmasking from the thiazole ring and subsequent reactions of the formyl group.

Among the nitrogen derivatives of carbonyls, nitrones represent a synthetically useful and versatile class of compounds since they are of easy preparation and enough reactive towards nucleophile, radical, and unsaturated reagents. Their role as partners in 1,3-dipolar cycloaddition reactions is well recognized in natural product synthesis.[1] We have recently been using nitrones in two synthetic approaches to α-amino-2-alkylthiazoles. In one route chiral nitrones were reacted with metalated thiazoles,[2] whereas in the other route[3] Grignard reagents were added to *N*-benzyl-*C*-(2-thiazolyl)nitrone **1** in the presence of chiral additives (Figure 1). The importance of α-amino-2-alkylthiazoles stems from their presence in natural products endowed with antineoplastic activity[4] and from their use as precursors to α-amino aldehydes through the thiazolyl-to-formyl equivalence.[5]

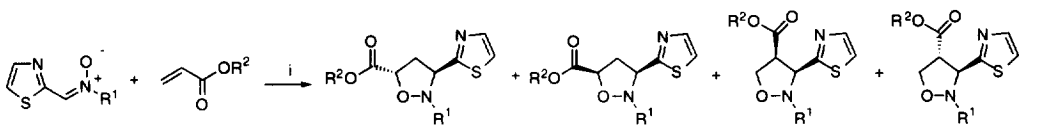


1a

Figure 1

We wish to report here the use of *N*-benzyl nitrone **1a** and its *p*-methoxy derivative **1b** in the synthesis of α-amino-2-alkylthiazoles through their 1,3-dipolar cycloaddition with activated alkenes followed by the cleavage of the resulting isoxazolidines. The reaction of **1** with alkyl acrylates is described first. Then, the asymmetric version of the method employing acrylates bearing a chiral auxiliary will be illustrated together with its implementation in the synthesis of chiral formyl pyrrolidinones.

The reactions of both **1a** and **1b** with methyl and ethyl acrylates **2** and **3** (Scheme 1) were sluggish and required several hours in refluxing toluene or CH_2Cl_2 to go to completion. The ratios of the resulting isoxazolidines **4-7** were determined by ^1H NMR of the crude reaction mixtures (Table 1) and then in most of the cases, individual products were isolated by column chromatography. The regiochemistry of these compounds was readily deduced from their NMR spectra since the H_3 signal of 3,5-disubstituted isomers **4** and **5** appeared as a doublet of doublets at 4.60-4.78 ppm while the same signal of the 3,4-regioisomers **6** and **7** was a doublet at 4.78-4.83 ppm.



4-7	R^1	R^2
a	Bn	Me
b	Bn	Et
c	PMB	Et

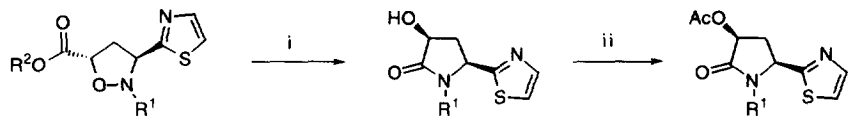
Scheme 1: i: Toluene or CH_2Cl_2, reflux

Table 1: Cycloaddition of nitrones **1** to alkyl acrylates **2** and **3**.

Nitrone	Acrylate	Solvent	T (°C)	time (hour)	Yield (%)[a]	**4**[b] (%)	**5**[b] (%)	**6**[b] (%)	**7**[b] (%)	**4+5/ 6+7**	**4/5**
1a	**2**	Toluene	110	12	92	76	9	11	4	85/15	89/11
1a	**2**	CH_2Cl_2	40	72	91	76	13	8	3	89/11	85/15
1a	**3**	Toluene	110	12	92	81	8	11	-[c]	89/11	91/9
1a	**3**	Toluene	110	12	90	83	7	10	-[c]	90/10	92/8

a) Isolated overall yield.
b) Normalised ratio deriving from the ^1H NMR analysis of the crude reaction mixture
c) Isomer not detected in the ^1H NMR spectrum

The cis relationship of the substituents in compounds **6a-c** was assigned by NOE difference spectroscopy.[6] A representative example is given in Figure 2. On the other hand, due to overlapping of signals in the NMR spectrum of compounds **4a-c**, the relative streochemistry of the substituents at C-3 and C-5 was established following their conversion into pyrrolidinones **9** (Scheme 2). These compounds were obtained by acetylation of 3-hydroxy pyrrolidinones **8** that in turn were formed by reductive cleavage of the nitrogen-oxygen bond of **4** and recyclization by nitrogen-carbon bond formation through alkoxide displacement from the ester group.[7] The NOE data for compounds **9** (Figure 2) indicated a cis relationship between the C-3 acetoxy group and the thiazole ring. Hence considering the mechanism of the above rearrangement, a trans relationship was deduced for the same thiazole ring and the C-5 ester group in in the precursor isoxazolidine **4**.



4a-c **8a** R^1 = Bn; **8b** R^1 = PMB; **9a** R^1 = Bn; **9b** R^1 = PMB

Scheme 2: i) Zn, AcOH, H_2O, THF, 60 °C, 5h. ii) Ac_2O, TEA, CH_2Cl_2, 12h

6b **9a**

Figure 2: Selected NOE data for compounds **6b** and **9a**. η_{obs} values, recorded as percent of η_{max}.

The results of Table 1 indicate that the above cycloaddition occurs with good levels of regio- and diastereoselectivity favouring the formation of the trans 3,5-disubstituted isoxazolidine **4**. The regioselectivity can be rationalized by considering the calculated coefficients (AM1, MOPAC6) for the nitrone **1a** and the acrylate **3** in the frontier molecular orbitals corresponding to the most favoured interaction, in this case HOMO(dipole)-LUMO(dipolarophile) (Figure 3). An alternative explanation has been proposed[8] in which the reactivity is controlled by the interaction HOMO(dipole)-LUMO(dipolarophile), whilst the regioselectivity is determined by the reverse interaction, LUMO(dipole)-HOMO(dipolarophile). Furthermore, the diastereoselectivity can be explained by an endo approach of the olefin to the *Z*-nitrone (*Z*-endo approach) (Figure 4) due to secondary orbital interactions between the *p* orbitals of the nitrone nitrogen and the carbonyl group of the dipolarophile.

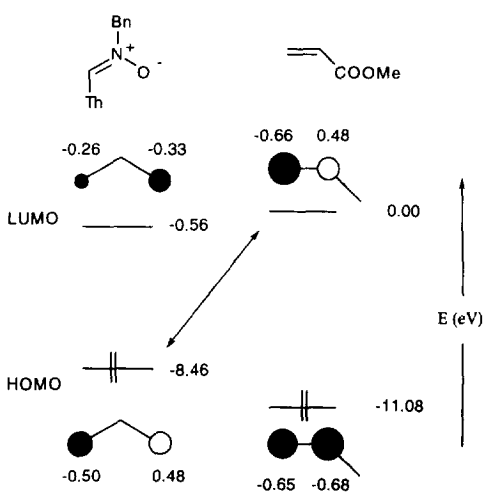


Figure 3: Calculated energies and atomic coefficients for the FMO.

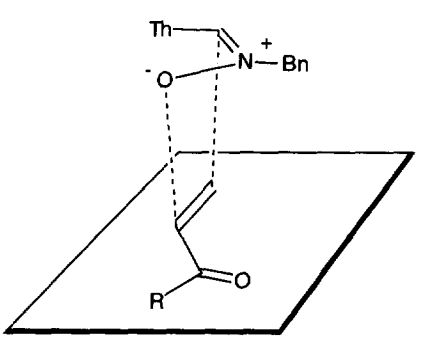
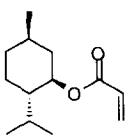


Figure 4: Z-Endo approach of nitrone **1a** to acrylates.

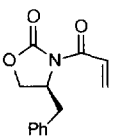
Obviously, an *E*-exo approach would lead to the same trans-substituted cycloadduct. In favour of the former hypothesis is the *Z* configuration of the nitrone **1a** as shown by NOE difference spectroscopy and the preservation of this geometry under prolonged heating (72 h at 110 °C). Unfortunately, attempts to prepare the *E*-isomer of **1a** by literature methods[9] were unsuccessful and therefore we could not verify the stereochemical outcome of a possible *E*-exo approach.

We next turned out the attention to the asymmetric version of the cycloaddition of nitrones **1** to acrylates and considered either the use of chiral catalysts or chiral dipolarophiles. Substantial increase of rate and levels of regio and diastereoselectivity[10] have been recently reported by the presence of a Lewis acid catalyst in 1,3-dipolar cycloadditions of nitrones to allylic alcohols,[10a-e] crotonamides[10f] or α-β-unsaturated ketones.[10g] Moreover asymmetric synthesis of isoxazolidines has been achieved by the use of chiral Lewis acids.[11] By contrast in our case stoichiometric amounts of various Lewis acids (ZnI_2, $TiCl_4$, $Ti(O^iPr)_3Cl$, $Ti(O^iPr)_2Cl_2$, TMSTf) proved to be detrimental as their presence inhibited the reaction completely. Very likely the preferential coordination of the metal to the nitrone produced an inactive complex or increased the transition state energy of the process.[12]

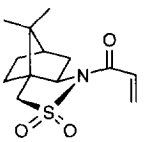
Chiral acrylate esters and amides have been successfully employed in asymmetric cycloadditions, mainly Diels-Alder reactions and 1,3-dipolar cycloadditions to nitrile oxides.[13] Hence, (-)-menthyl acrylate **10** and the amides **11** and **12** derived from (4*S*)-4-(phenylmethyl)-2-oxazolidinone and the Oppolzer's camphor sultam respectively were chosen in the present study.



10

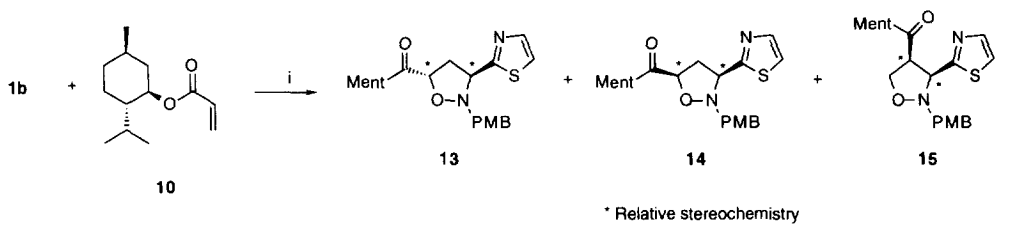


11



12

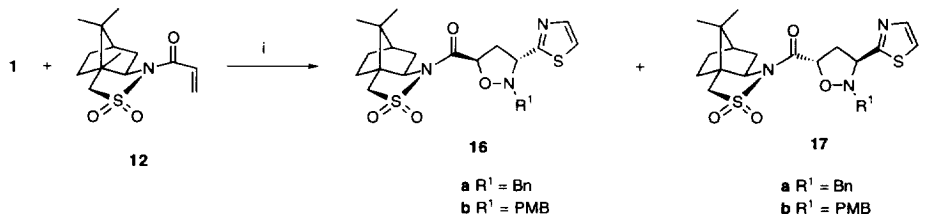
The cycloaddition of **1b** with (-)-menthyl acrylate **10**[13a] produced a mixture of isoxazolidines **13**, **14**, and **15** in 80:10:10 ratio (Scheme 3). Each compound was isolated as a pair of diastereoisomers in 1:1 ratio, thus indicating the absence of asymmetric induction in the cycloaddition reaction. The *N*-acryloyl oxazolidinone **11**[13b] proved to be unreactive with both nitrones **1a** and **1b** as unaltered starting materials were recovered after heating in toluene or CH_2Cl_2 for three days. In both cases, the presence of Lewis acid did not produce any observable reaction product.



Scheme 3: i) Toluene or CH_2Cl_2, reflux.

By contrast, the cycloaddition of the *N*-acryloyl camphor sultam **12**[14] to nitrones **1a** and **1b** (Scheme 4) proceeded with complete control of the regio and diastereoselectivity to give exclusively the trans 3,5-disubstituted isoxazolidines **16** and **17** in good overall yield (Table 2). In both cases a satisfactory level of

asymmetric induction (78:22) was obtained in refluxing CH_2Cl_2. From these reactions, the individual cycloadducts **16** and **17** were isolated by column chromatography.



Scheme 4: i) Toluene or CH_2Cl_2, reflux

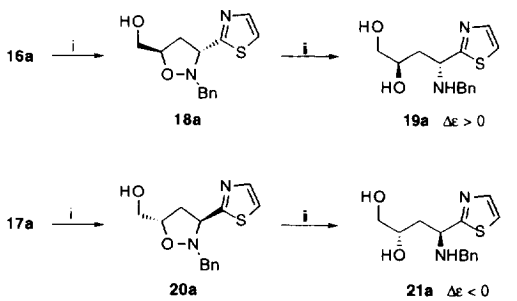
Table 2: Cycloaddition of nitrones **1** to the *N*-acryloyl sultam **12**.

Nitrone	Solvent	T (°C)	t (hour)	Yield (%)[a]	**16, 17** %[b] (ratio)
1a	Toluene	110	72	79	100 (63:37)
1a	CH_2Cl_2	40	120	74	100 (78:22)
1b	Toluene	110	72	74	100 (65:35)
1b	CH_2Cl_2	40	120	72	100 (78:22)

a) Isolated overall yield.

b) Normalised ratio deriving from the ^1H NMR analysis of the crude reaction mixture

The absolute configuration at the isoxazolidine ring in compounds **16a** and **17a** was assigned by the circular dichroism method applied to the α-amino-2-alkylthiazoles **19a** and **21a** obtained by removal of the chiral auxiliary and reductive isoxazolidine ring opening (Scheme 5). Compound **19a** showed a positive CE at 223 nm with $\Delta\varepsilon = +2.98$ and, obviously, **21a** presented a negative CE value at the same wavelength. (Figure 6). In accordance with our previous studies on the circular dichroism of α-amino-2-alkylthiazoles,[15] compound **19a** was assigned the *R* configuration at C_α whereas **21a** was the *S* stereoisomer. The same *R* and *S* configuration should be present at C-3 in the isoxazolidine precursors **16a** and **17a** respectively. The same absolute configurations were assumed for isoxazolidines **16b** and **17b.**



Scheme 5: i) $LiAlH_4$, Et_2O, 0 °C, 15 min; ii) Zn dust, AcOH, THF, H_2O, 60 °C, 5 h.

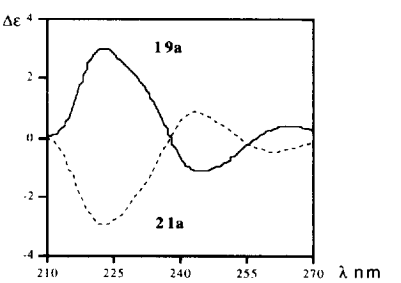


Figure 6: CD spectra of compounds **19a** and **21a**

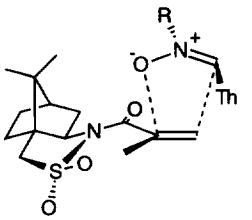
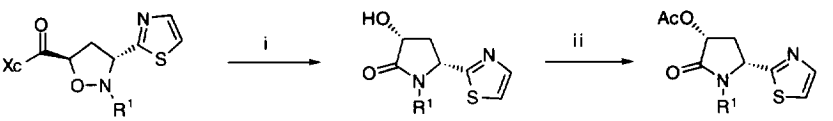


Figure 7: Proposed most-favoured approach of nitrones **1** to **12**.

The observed stereoselectivity is in line with the model of Kim and Curran[13c] for asymmetric thermal reactions of *N*-acryloyl derivatives of the Oppolzer's camphor sultam. Accordingly the *Z*-endo attack of the nitrones **1** to **12** should take place on the "top face" of the most favoured anti, s-cis rotamer (Figure 7), thus leading to (*3R,5R*)-isoxazolidines as major products.

The reduction of the main cycloadducts **16a** and **16b** with Zn/AcOH proceeded in a similar way of **4a-c** to give the chiral 5-(2-thiazolyl)-3-hydroxy-2-pyrrolidinones **22** (Scheme 6). From this reaction, the chiral inductor (2*R*)-10-2-bornanesultam was recovered almost quantitatively.



16a,b **22a,b** **23a,b**

Scheme 6: i) Zn, AcOH, H_2O, THF, 60 °C, 5h. ii) Ac_2O, TEA, CH_2Cl_2, 12h (**16a, 22a, 23a**, R^1 = Bn; **16b, 22b, 23b**, R^1 = PMB)

3-Acetoxy pyrrolidinones **23** showed physical and spectroscopic properties, except for the rotatory power, identical to those of the racemic derivatives **9**. The X-ray diffraction analysis of compound **23b** (Figure 8) confirmed the *cis* relationship between the thiazole ring and the acetoxy group deduced from NOE data but could not confirm the absolute configuration assigned by CD.

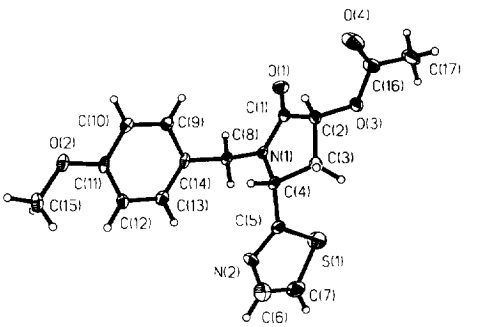
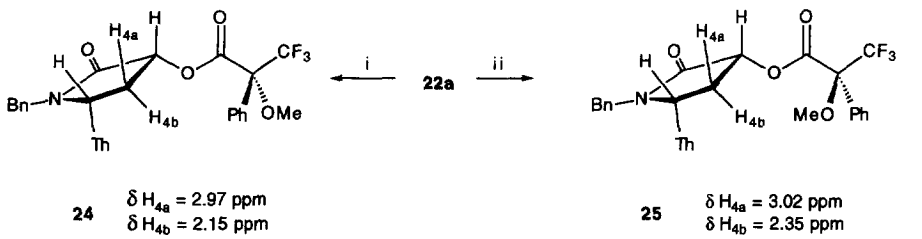


Figure 8: ORTEP representation of compound **23b** showing ellipsoids at 30% probability level

Various derivatives of 3-hydroxypyrrolidinone **22a** were prepared with the aim to establish the absolute configuration by different methods. Interestingly the ^{1}H NMR spectra of (+) and (-)-α-methoxy-α-(trifluoromethyl)-phenyl-acetic acid (MTPA) esters **24** and **25** respectively, showed differences between their chemical shifts in good agreement with a 3*R* configuration according to the Kakisawa's rule.[16] Consequently the 5*R* configuration should be present in **22a** and in the precursor isoxazolidine **16a** as well (Scheme 7). Fortunately enough, the crystalline (1*S*)-camphanyl ester **26** was suitable for an X-ray diffraction analysis with

a good refinement (R = 0.043) for the assignment of the absolute stereochemistry (Figure 9). This result confirms our circular dichroism thiazole rule.[15]



Scheme 7: i) (+)-MTPA, DCC, DMAP, CH_2Cl_2, 12h. ii) (-)-MTPA, DCC, DMAP, CH_2Cl_2, 12h.

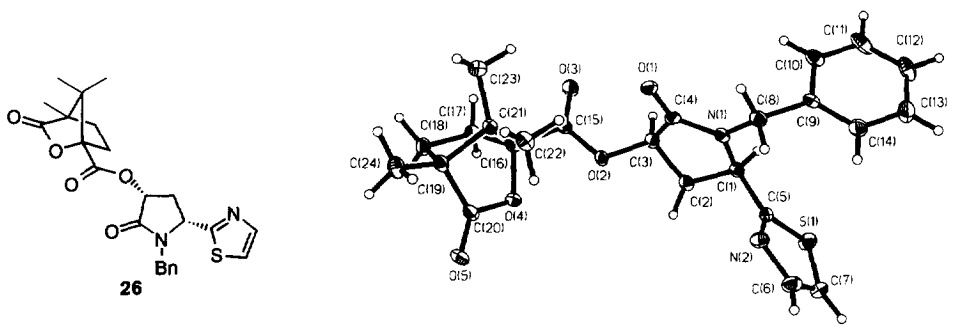
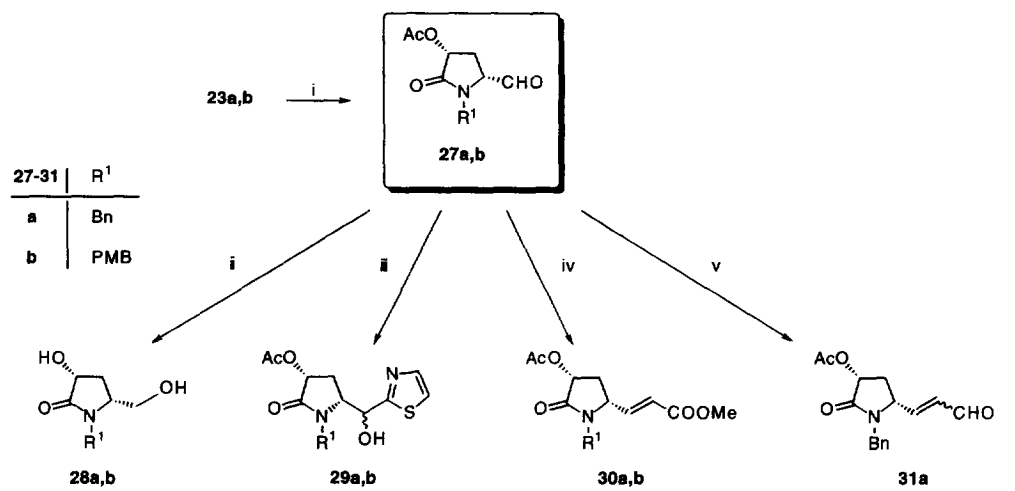


Figure 9: ORTEP representation of compound **26** showing ellipsoids at 30% probability level.

By taking advantage of the thiazolyl-to-formyl synthetic equivalence,[17] thiazolyl pyrrolidinones proved to be useful intermediates to functionalized chiral pyrrolidines (Scheme 8).



Scheme 8: i) MeOTf, MeCN; $NaBH_4$, MeOH; CuO, $CuCl_2$, H_2O, MeCN. ii) $NaBH_4$, MeOH. iii) 2-(Trimethyl silyl)thiazole, THF. iv) Ph_3P=CHCOOMe, $CHCl_3$. v) Ph_3P=CHCHO

The unmasking of the formyl group of **23a,b** by a well established protocol gave the corresponding aldehydes **27a,b** that in turn were simply reduced to the alcohols **28** or subjected to the one-carbon or two-carbon chain elongation by reaction with 2-(trimethylsilyl)thiazole (formation of **29**) or phosphoranes (formation of **30** and **31**) respectively. These model reactions to highly functionalized chiral pyrrolidines may become of interest in natural product synthesis.[18]

Acknowledgements: *Financial support from DGICYT (PB94-0598, Madrid, Spain) and MURST (Rome, Italy) is gratefully acknowledged. One of us (I.R.) is also grateful to CAPV (Spain) for a fellowship.*

Experimental

Column chromatography was performed on SiO_2 (60-240 mesh). Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were obtained on a Perkin-Elmer 241-C polarimeter with a thermally-jacketed 10 cm cell at 25 °C (concentrations c given as g/100 mL) and CD spectra on a Jasco J-710 spectrometer. IR spectra were recorded in nujol and measured in cm^{-1}, using a Perkin-Elmer 1600 FTIR infrared spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Varian Unity 300 or a Bruker AMX 300 spectrometer (300 MHz ^1H, 75.5 MHz ^{13}C and 282.1 MHz ^{19}F). Chemical shifts are quoted in ppm relative to TMS or $CFCl_3$ (^{19}F), and coupling constants were measured in Hertz. Mass spectra were recorded on a VG AutoSpec mass spectrometer. Elemental analyses were performed on a Perkin Elmer 240B microanalyser. Nitrone **1a** was prepared as described,[19] and chiral acryloyl derivatives **10**, **11** and **12** were prepared according to the literature procedures.[20]

N-(4-methoxybenzyl)-C-(2-thiazolyl)nitrone 1b . To a solution of thiazole-2-carbaldehyde[21] (2.26 g, 20 mmol) in CH_2Cl_2 (150 mL) N-(4-methoxybenzyl)-hydroxylamine (3.06 g, 20 mmol) and $MgSO_4$ (2.41 g, 20 mmol) were added and the mixture stirred for 6 hours. Then, the solution was filtered and the solvent was removed under reduced pressure. The residue was chromatographed using Et_2O/EtOAc (1:5) as eluent to yield 3.52 g (71 %) of **1b**. M.p.: 124-126 °C. IR (Nujol, cm^{-1}): 1514, 1456, 1252. ^1H NMR ($CDCl_3$): 3.80 (s, 3H), 5.06 (s, 2H), 6.90-6.94 (m, 2H), 7.35-7.40 (m, 2H), 7.43 (dd, 1H, J = 3.2, 0.7 Hz), 7.98 (d, 1H, J = 3.2 Hz), 8.06 (d, 1H, J = 0.7 Hz). ^{13}C NMR ($CDCl_3$): 55.3, 68.8, 114.6, 120.6, 123.6, 130.2, 131.4, 143.9, 156.5, 160.4. EM (EI$^+$, m/z (%)): 249 [$(M+1)^{+\cdot}$, 28], 121 (100). Anal. calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 57.89; H, 4.80; N, 11.23.

General procedure for the cycloaddition reactions.
The solution of nitrone (2.0 mmol) and dipolarophile (10.0 mmol) in the selected solvent (25 mL) was refluxed (Table 1 and 2). After the reaction went to completion (TLC), the solvent was removed in vacuo, and the residue was examined by ^1H NMR and then chromatographed.

CYCLOADDITION OF **1a** WITH METHYL ACRYLATE **2**.
Column chromatography using hexane/Et_2O (1:1) afforded pure **4a** and **6a** and a mixture of **5a** and **7a** from which the ^1H NMR data were collected.

Methyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-t-5-carboxylate 4a.
Obtained 426 mg, 70 %, in toluene (419 mg, 69 %, in CH_2Cl_2). R_f: 0.30. M.p.: 70-72 °C. IR: 1748. ^1H NMR: 2.98 (dt, 1H, J = 12.7, 7.3 Hz), 3.07 (ddd, 1H, J = 12.7, 7.3, 4.4 Hz), 3.77 (s, 3H), 4.01 (d, 1H, J = 13.2 Hz), 4.30 (d, 1H, J = 13.2 Hz), 4.59 (t, 1H, J =7.3 Hz), 4.61 (dd, 1H, J = 7.3, 4.4 Hz), 7.20-7.35 (m,

4H), 7.40-7.44 (m, 2H), 7.68 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 27.1, 39.3, 52.5, 61.6, 66.0, 120.1, 127.6, 128.4, 128.9, 136.6, 142.6, 171.0, 172.1. EM (FAB$^+$, m/z): 305 $(M+1)^+$, 245. Anal. calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.34; H, 5.14; N, 9.16.

Methyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-c-4-carboxylate 6a.

Obtained 61 mg, 10 %, in toluene (44 mg, 7 %, in CH_2Cl_2). R_f: 0.38. M.p.: 70-72 °C. IR: 1734. ^1H NMR: 3.80 (s, 3H), 3.95 (ddd, 1H, J = 8.8, 5.8, 3.9 Hz), 4.10 (d, 1H, J = 12.9 Hz), 4.17 (d, 1H, J = 12.9 Hz), 4.28 (t, 1H, J = 8.8 Hz), 4.39 (dd, 1H, J = 8.8, 5.8 Hz), 4.82 (d, 1H, J = 3.9 Hz), 7.20-7.36 (m, 4H), 7.42 (m, 2H), 7.70 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 52.7, 54.9, 59.9, 68.7, 69.1, 120.8, 127.7, 128.4, 129.1, 136.3, 143.0, 172.6, 175.7. EM (FAB$^+$, m/z): 305 $(M+1)^+$. Anal. calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.20; H, 5.35; N, 9.13.

Mixture of **5a** and **7a**, obtained 73 mg, 12 %, in toluene (85 mg, 14 %, in CH_2Cl_2). R_f: 0.25. Selected ^1H NMR signals:

Methyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-c-5-carboxylate 5a.

^1H NMR: 2.81 (ddd, 1H, J = 12.9, 8.3. 4.4 Hz), 3.09 (ddd, 1H, J = 12.9, 9.5, 5.4 Hz), 3.67 (s, 3H), 4.09 (s, 2H), 4.42 (dd, 1H, J = 8.3, 5.4 Hz), 4.76 (dd, 1H, J = 9.5, 4.4 Hz), 7.20-7.41 (m, 6H), 7.70 (d, 1H, J = 3.2 Hz).

Methyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-t-4-carboxylate 7a.

^1H NMR: 3.45 (s, 3H), 3.92 (ddd, 1H, J = 10.0, 8.8, 4.2 Hz), 4.02 (s, 2H), 4.20 (dd, 1H, J = 6.1, 4.2 Hz), 4.36 (dd, 1H, J = 8.8, 6.1 Hz), 4.78 (d, 1H, J = 10.0 Hz), 7.20-7.41 (m, 6H), 7.70 (d, 1H, J = 3.2 Hz).

CYCLOADDITION OF **1a** WITH ETHYL ACRYLATE **3**.

Column chromatography using hexane/Et_2O (1:1) afforded pure **4b**, **5b** and **6b**.

Ethyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-t-5-carboxylate 4b.

Obtained 477 mg, 75 %. R_f: 0.32. M.p.: 75-77 °C. IR: 1747. ^1H NMR: 1.28 (t, 3H, J = 7.1 Hz), 2.98 (dt, 1H, J = 12.7, 7.3 Hz), 3.08 (ddd, 1H, J = 12.7, 7.3, 4.4 Hz), 4.01 (d, 1H, J = 13.4 Hz), 4.23-4.29 (m, 2H), 4.31 (d, 1H, J = 13.4 Hz), 4.57 (t, 1H, J = 7.3 Hz), 4.62 (dd, 1H, J = 7.3, 4.4 Hz), 7.20-7.35 (m, 4H), 7.40-7.43 (m, 2H), 7.69 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 14.1, 39.4, 61.5, 66.1, 76.7, 77.3, 120.0, 127.6, 128.4, 129.0, 136.7, 142.6, 170.9, 171.6. EM (FAB$^+$, m/z): 319 $(M+1)^+$, 245. Anal. calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.49; H, 5.64; N, 8.64.

Ethyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-c-5-carboxylate 5b.

Obtained 44 mg, 7 %. R_f: 0.27. Oil. IR: 1749. ^1H NMR: 1.30 (t, 3H, J = 7.3 Hz), 2.97 (dt, 1H, J = 12.1, 5.2 Hz), 3.18 (ddd, 1H, J = 12.1, 9.0, 5.2 Hz), 4.10 (s, 2H), 4.18 (c, 2H, J = 7.3 Hz), 4.42 (t, 1H, J = 5.2 Hz), 4.78 (dd, 1H, J = 9.0, 5.2 Hz), 7.20-7.44 (m, 6H), 7.69 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 14.9, 39.2, 60.3, 66.3, 75.9, 77.6, 118.9, 127.7, 128.4, 129.1, 135.7, 142.9, 171.9, 173.1. EM (FAB$^+$, m/z): 319 $(M+1)^+$. Anal. calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.30; H, 5.55; N, 8.88.

Ethyl 2-benzyl-r-3-(2-thiazolyl)isoxazolidine-c-4-carboxylate 6b.

Obtained 64 mg, 10 %. R_f: 0.38. M.p.: 74-77 °C. IR: 1747. ^1H NMR: 1.30 (t, 3H, J = 7.3 Hz), 3.95 (ddd, 1H, J = 8.8, 5.8, 3.6 Hz), 4.10 (d, 1H, J = 13.0 Hz), 4.18 (d, 1H, J = 13.0 Hz), 4.26 (c, 2H, J = 7.3 Hz), 4.28 (t, 1H, J = 8.8, 8.8 Hz), 4.38 (dd, 1H, J = 8.8, 5.8 Hz), 4.83 (d, 1H, J = 3.6 Hz), 7.20-7.35 (m, 4H), 7.40-7.44 (m, 2H), 7.70 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 14.2, 55.0, 59.9, 61.7, 68.1, 69.1, 120.0, 127.7, 128.4, 129.1, 136.3, 142.9, 172.1, 173.0. EM (FAB$^+$, m/z): 319 $(M+1)^+$. Anal. calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.38; H, 5.80; N, 8.86.

CYCLOADDITION OF **1b** WITH ETHYL ACRYLATE **3**.

Column chromatography using hexane/Et_2O (1:1) afforded pure **4c**, **5c** and **6c**.

Ethyl 2-(4-methoxybenzyl)-r-3-(2-thiazolyl)isoxazolidine-t-5-carboxylate 4c.

Obtained 522 mg, 75 %. R_f: 0.28. M.p.: 78-81 °C. IR: 1730. ^1H NMR: 1.35 (t, 3H, J = 7.1 Hz), 2.95 (ddd, 1H, J = 12.8, 7.2, 7.2 Hz), 3.08 (ddd, 1H, J = 12.8, 8.5, 4.3 Hz), 3.76 (s, 3H), 3.95 (d, 1H, J = 13.0 Hz), 4.23 (m, 2H), 4.25 (d, 1H, J = 13.0 Hz), 4.58 (dd, 1H, J = 8.5, 7.2 Hz), 4.60 (dd, 1H, J = 7.2, 4.3 Hz), 6.80-6.84 (m, 2H), 7.27 (d, 1H, J = 3.2 Hz), 7.32-7.38 (m, 2 H), 7.68 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 14.0, 39.7, 55.2, 59.7, 61.2, 65.8, 75.5, 113.7, 120.0, 128.2, 129.9, 142.5, 159.0, 171.1, 171.4. EM (FAB$^+$, m/z): 349 $(M+1)^+$. Anal. calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.74; H, 5.84; N, 7.96.

Ethyl 2-(4-methoxybenzyl)-r-3-(2-thiazolyl)isoxazolidine-c-5-carboxylate 5c.

Obtained 42 mg, 6 %, as an oil. R_f: 0.22. IR: 1730. ^1H NMR: 1.16 (t, 3H, J = 7.3 Hz), 2.87 (dt, 1H, J = 12.3, 5.7 Hz), 3.12 (dt, 1H, J = 12.3, 8.8 Hz), 3.75 (s, 3H), 4.03 (d, 1H, J = 14.7 Hz), 4.06 (d, 1H, J = 14.7 Hz), 4.10 (c, 1H, J = 7.3 Hz), 4.46 (dd, 1H, J = 8.8, 5.7 Hz), 4.75 (dd, 1H, J = 8.8, 5.7 Hz), 6.72-6.78 (m, 2H), 7.25 (d, 1H, J = 3.2 Hz), 7.31-7.34 (m, 2H), 7.70 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 14.0, 39.5, 55.9, 60.3, 61.2, 65.3 75.7, 114.8, 121.2, 128.2, 129.9, 142.6, 159.1, 171.3, 171.6. EM (FAB$^+$, m/z): 349 $(M+1)^+$. Anal. calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.56; H, 5.89; N, 7.97.

Ethyl 2-(4-methoxybenzyl)-r-3-(2-thiazolyl)isoxazolidine-c-4-carboxylate 6c.

Obtained 63 mg, 9 %. R_f: 0.32. M.p.: 82-84 °C. IR: 1730. ^1H NMR: 1.29 (t, 3H, J = 7.0 Hz), 3.76 (s, 3H), 3.95 (ddd, 1H, J = 9.1, 6.0, 4.3 Hz), 4.03 (d, 1H, J = 12.3 Hz), 4.10 (d, 1H, J = 12.3 Hz), 4.25 (c, 2H, J = 7.0 Hz), 4.28 (t, 1H, J = 6.0 Hz), 4.36 (dd, 1H, J = 9.1, 6.0 Hz), 4.83 (d, 1H, J = 4.3 Hz), 6.84 (m, 2H), 7.23 (d, 1H, J = 3.2. Hz), 7.35 (m, 2H), 7.69 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 14.2, 38.7, 55.0, 55.2, 59.2, 61.7, 68.2, 69.1, 113.8, 120.0, 128.3, 130.4, 142.9, 159.1, 172.1. EM (FAB$^+$, m/z): 349 $(M+1)^+$. Anal. calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.57; H, 5.91; N, 8.00.

CYCLOADDITION OF **1a** WITH N-ACRYLOYL-(2R)-BORNANE-10,2-SULTAM **12**.

Column chromatography using hexane/Et_2O (3:2) afforded pure **16a** and **17a**.

(2R)-N-[[(3R,5R)-2-Benzyl-3-(2-thiazolyl)-isoxazolidin-5-yl]carbonyl]-bornane-10,2-sultam 16a.

Obtained 565 mg, 58 %, in CH_2Cl_2 (485 mg, 50 %, in toluene). R_f: 0.18. M.p.: 78-80 °C. $[\alpha]_D^{20}$: -42.3 (0.6, $CHCl_3$). IR: 1694. ^1H NMR: 0.92 (s, 3H), 1.08 (s, 3H), 1.20-1.28 (m, 2H), 1.65-2.20 (m, 5H), 3.18-3.23 (m, 2H), 3.40 (d, 1H, J = 13.7 Hz), 3.42 (d, 1H, J = 13.7 Hz), 3.88 (t, 1H, J = 7.5 Hz), 4.08 (d, 1H, J = 13.4 Hz), 4.29 (d, 1H, J = 13.4 Hz), 4.68 (t, 1H, J = 5.4 Hz), 5.05 (t, 1H, J = 7.4 Hz), 7.19-7.35 (m, 4H), 7.40-7.45 (m, 2H), 7.69 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 19.8, 20.8, 26.3, 32.9, 38.3, 38.9, 44.7, 47.8, 48.9, 52.9, 61.6, 65.3, 66.6, 77.2, 119.9, 127.5, 128.4, 128.9, 136.9, 142.7, 170.4, 171.4. EM (FAB$^+$, m/z): 488 (M+1). Anal. calcd for $C_{24}H_{29}N_3O_4S_2$: C, 59.11; H, 5.99; N, 8.62. Found: C, 59.12; H, 6.04; N, 8.51.

(2R)-N-[[(3S,5S)-2-Benzyl-3-(2-thiazolyl)-isoxazolidin-5-yl]carbonyl]-bornane-10,2-sultam 17a.

Obtained 285 mg, 29 %, in toluene (159 mg, 16 %, in CH_2Cl_2). R_f: 0.20. M.p.: 76-78 °C. $[\alpha]_D^{20}$: -45.4 (0.21, $CHCl_3$). IR: 1694. ^1H NMR: 0.85 (s, 3H), 1.05 (s, 3H), 1.20-1.38 (m, 2H), 1.65-2.20 (m, 5H), 2.85 (ddd, 1H, J = 12.7, 7.8, 5.7 Hz), 3.15 (ddd, 1H, J = 12.7, 7.8, 5.7 Hz). 3.40 (d, 1H, J = 13.7 Hz), 3.42 (d, 1H, J = 13.7 Hz), 3.88 (t, 1H, J = 7.5 Hz), 4.08 (d, 1H, J = 13.7 Hz), 4.29 (d, 1H, J = 13.7 Hz), 4.58 (t, 1H, J = 5.7 Hz), 5.18 (t, 1H, J = 7.8 Hz), 7.18-7.35 (m, 4 H), 7.40-7.45 (m, 2H), 7.66 (d, 1H, J = 3.2 Hz).

^{13}C NMR: 19.7, 20.7, 26.3, 32.7, 35.3, 38.9, 44.5, 47.6, 49.7, 52.7, 61.5, 64.9, 67.1, 76.8, 119.9, 127.3, 128.2, 128.8, 136.9, 142.5, 169.1, 170.3. EM (FAB^+, m/z): 488 (M+1). Anal. calcd for $C_{24}H_{29}N_3O_4S_2$: C, 59.11; H, 5.99; N, 8.62. Found: C, 58.97; H, 6.01; N, 8.55.

CYCLOADDITION OF **1b** WITH N-ACRYLOYL-(2R)-BORNANE-10,2-SULTAM **12**.

Column chromatography using hexane/Et_2O (1:1) afforded pure **16b** and **17b**.

(2R)-N-[[(3R,5R)-2-(4-methoxybenzyl)-3-(2-thiazolyl)-isoxazolidin-5-yl]carbonyl]-bornane-10,2-sultam 16b.

Obtained 579 mg, 56 %, in CH_2Cl_2 (498 mg, 48 %, in toluene). R_f: 0.20. M.p.: 80-82 °C. $[\alpha]_D^{20}$: -54.3 (0.4, $CHCl_3$). IR: 1697. ^1H NMR: 0.95 (s, 3H), 1.11 (s, 3H), 1.24-1.40 (m, 2H), 1.65-2.00 (m, 3H), 2.07-2.21 (m, 2H), 3.18 (dd, 2H, J = 7.5, 5.8 Hz), 3.42 (d, 1H, J = 13.6 Hz), 3.46 (d, 1H, J = 13.6 Hz), 3.78 (s, 3H), 3.88 (dd, 1H, J = 7.3, 5.4 Hz), 4.01 (d, 1H, J = 12.9 Hz), 4.22 (d, 1H, J = 12.9 Hz), 4.68 (t, 1H, J = 5.8 Hz), 5.07 (t, 1H, J = 7.5 Hz), 6.82-6.88 (m, 2H), 7.22 (d, 1H, J = 3.2 Hz), 7.33-7.38 (m, 2H), 7.70 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 19.8, 20.8, 26.3, 32.9, 38.3, 38.8, 44.7, 47.7, 48.9, 52.8, 55.2, 61.0, 65.4, 66.6, 77.2, 113.8, 119.9, 128.9, 130.2, 142.7, 159.0, 170.5, 171.4. EM (FAB^+, m/z): 518 $(M+1)^+$. Anal. calcd for $C_{25}H_{31}N_3O_5S_2$: C, 58.01; H, 6.04; N, 8.12. Found: C, 57.94; H, 6.19; N, 7.95.

(2R)-N-[[(3S,5S)-2-(4-methoxybenzyl)-3-(2-thiazolyl)-isoxazolidin-5-yl]carbonyl]-bornane-10,2-sultam 17b.

Obtained 268 mg, 26 %, in toluene (165 mg, 16 %, in CH_2Cl_2). R_f: 0.23. M.p.: 77-79 °C. $[\alpha]_D^{20}$: -59.4 (0.2, $CHCl_3$). IR: 1700. ^1H NMR: 0.96 (s, 3H), 1.12 (s, 3H), 1.24-1.45 (m, 2H), 1.85-2.00 (m, 3H), 2.12-2.21 (m, 2H), 2.85 (dt, 1H, J = 13.2, 6.6 Hz), 3.18 (ddd, 1H, J = 13.2, 7.8, 6.6 Hz), 3.40 (d, 1H, J = 13.6 Hz), 3.49 (d, 1H, J = 13.6 Hz), 3.77 (s, 3H), 3.91 (t, 1H, J = 4.6 Hz), 4.01 (d, 1H, J = 13.2 Hz), 4.32 (d, 1H, J = 13.2 Hz), 4.60 (t, 1H, J = 6.6 Hz), 5.19 (dd, 1H, J = 7.8, 6.6 Hz), 6.82-6.88 (m, 2 H), 7.28 (d, 1H, J = 3.2 Hz), 7.33-7.38 (m, 2H), 7.69 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 19.8, 20.8, 26.4, 32.7, 38.2, 41.3, 44.5, 47.8, 48.9, 52.8, 55.2, 61.1, 65.1, 66.0, 77.2, 113.8, 120.0, 129.1, 130.4, 142.6, 159.0, 170.4, 170.7. EM (FAB^+, m/z): 518 $(M+1)^+$. Anal. calcd for $C_{25}H_{31}N_3O_5S_2$: C, 58.01; H, 6.04; N, 8.12. Found: C, 57.93; H, 5.93; N, 8.23.

Ring opening of the isoxazolidines 4a,c and 16a,b.

To a solution of the corresponding isoxazolidine (1.0 mmol) in AcOH:THF:H_2O (2:1:1, 40 mL) at 60 °C Zn dust (0.4 g, 6.1 mmol) was added. The reaction mixture was stirred for 5h, the remaining Zn was filtered off and the filtrate was neutralized with saturated Na_2SO_4 (aqueous). The mixture was extracted with $CHCl_3$ (3x15 mL), the combined organic phases dried and the solvent removed under reduced pressure. The residue was purified by column chromatography using EtOAc/MeOH (1:9) as eluent to give the pure pyrrolidinones.

Racemic 1-Benzyl-r-3-hydroxy-c-5-(2-thiazolyl)-2-pyrrolidinone 8a.

From isoxazolidine **4a** (304 mg). Compound **8a** was obtained 260 mg, 95 %. M.p.: 118-120 °C. IR (Nujol, cm^{-1}): 3172, 1694. ^1H NMR: 2.17 (ddd, 1H, J = 13.7, 9.6, 4.8 Hz), 2.74 (dt, 1H, J = 13.7, 7.7 Hz), 3.72 (d, 1H, J = 14.8 Hz), 4.41-4.46 (m, 1H), 4.72 (br s, 1H), 4.76 (dd, 1H, J = 7.7, 4.8 Hz), 4.95 (d, 1H, J = 14.8 Hz), 7.12-7.31 (m, 5H), 7.33 (d, 1H, J = 3.2 Hz), 7.77 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 35.8, 44.9, 55.7, 69.4, 120.3, 127.8, 128.5, 128.7, 135.4, 143.0, 169.2, 174.4. EM (FAB^+, m/z): 275 $(M+1)^+$. EM (EI^+, m/z (%)): 169 (50), 112 (100). Anal. calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.28; H, 5.29; N, 10.15.

(3R,5R)-1-Benzyl-3-hydroxy-5-(2-thiazolyl)-2-pyrrolidinone 22a.
From isoxazolidine **16a** (487 mg). Compound **22a** was obtained 263 mg, 96 %. M.p.: 118-120 °C. $[\alpha]_D^{20}$: -62.2 (0.2, $CHCl_3$). Anal. calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.15; H, 5.12; N, 10.37.

Racemic 1-(4-Methoxybenzyl)-r-3-hydroxy-c-5-(2-thiazolyl)-2-pyrrolidinone 8b.
From isoxazolidine **4c** (348 mg). Compound **8b** was obtained 283 mg, 93 %. M.p.: 118-121 °C. IR (Nujol, cm^{-1}): 3297, 1664. ^1H NMR: 2.15 (dt, 1H, J = 13.6, 6.6 Hz), 2.75 (dt, 1H, J = 13.6, 7.7 Hz), 3.65 (d, 1H, J = 14.8 Hz), 3.75 (s, 3H), 4.38 (dd, 1H, J = 7.7, 6.6 Hz), 4.57 (br s, 1H, ex. D_2O) 4.76 (dd, 1H, J = 7.7, 6.6 Hz), 4.85 (d, 1H, J = 14.8 Hz), 6.78-6.82 (m, 2H), 7.02-7.05 (m, 2H), 7.35 (d, 1H, J = 3.2 Hz), 7.78 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 35.8, 44.3, 55.3, 55.6, 69.7, 114.8, 120.3, 127.6, 129.9, 143.1, 159.3, 169.3, 174.0. EM (EI^+, m/z (%)): 304 ($M^{+\cdot}$, 50), 136 (47), 112 (100). Anal. calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.13; H, 5.24; N, 9.33.

(3R,5R)-3-Hydroxy-1-(4-methoxybenzyl)-5-(2-thiazolyl)-2-pyrrolidinone 22b.
From isoxazolidine **16b** (517 mg). Compound **22b** was obtained 280 mg, 92 %. M.p.: 120-122 °C. $[\alpha]_D^{20}$: -63.1 (0.2, $CHCl_3$). Anal. calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.15; H, 5.35; N, 9.03.

Synthesis of 3-acetoxy-5-(2-thiazolyl)-2-pyrrolidinones 9 and 23.
To a solution of the 3-hydroxypyrrolidinone (1.0 mmol) in CH_2Cl_2 (3 mL) acetic anhydride (0.5 mL) and TEA (0.5 mL) were added. The mixture was stirred overnight and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography using hexane/Et_2O (1:4) as eluent.

Racemic r-3-Acetoxy-1-benzyl-c-5-(2-thiazolyl)-2-pyrrolidinone 9a.
From **8a** (274 mg), compound **9a** was obtained (300 mg, 95 %) as a white solid. M.p.: 134-136 °C. IR: 1742, 1698. ^1H NMR: 2.15 (s, 3H), 2.16 (ddd, 1H, J = 13.6, 8.5, 7.5 Hz), 2.99 (dt, 1H, J = 13.6, 7.5 Hz), 3.62 (d, 1H, J = 14.5 Hz), 4.85 (t, 1H, J = 7.5 Hz), 5.00 (d, 1H, J = 14.5 Hz), 5.37 (dd, 1H, J = 8.5, 7.5 Hz), 7.08-7.15 (m, 2H), 7.20-7.31 (m, 3H), 7.38 (d, 1H, J = 3.2 Hz), 7.77 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 20.8, 34.6, 45.3, 55.8, 70.0, 120.6, 127.9, 128.6, 128.7, 135.3, 142.9, 169.3, 170.0, 170.2. EM (FAB^+, m/z): 317 $(M+1)^+$. Anal. calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.66; H, 5.06; N, 9.01.

(3R,5R)-3-Acetoxy-1-benzyl-5-(2-thiazolyl)-2-pyrrolidinone 23a.
From **22a** (274 mg), compound **23a** was obtained (310 mg, 98 %) as a white solid. M.p.: 135-137 °C. $[\alpha]_D^{20}$: -81.0 (0.2, $CHCl_3$). Anal. calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.89; H, 5.20; N, 8.73.

Racemic r-3-Acetoxy-1-(4-methoxybenzyl)-c-5-(2-thiazolyl)-2-pyrrolidinone 9b.
From **8b** (304 mg), compound **9b** was obtained (315 mg, 91 %) as a white solid. M.p.: 139-141 °C. IR: 1741, 1693. ^1H NMR: 2.12 (ddd, 1H, J = 13.6, 9.0, 7.1 Hz), 2.15 (s, 3H), 2.97 (ddd, 1H, J = 13.6, 8.4, 7.1 Hz), 3.75 (d, 1H, J = 14.0 Hz), 3.76 (s, 3H), 4.83 (t, 1H, J = 7.1 Hz), 4.96 (d, 1H, J = 14.0 Hz), 5.35 (dd, 1H, J = 9.0, 8.4 Hz), 6.78-6.80 (m, 2H), 7.03-7.07 (m, 2H), 7.40 (d, 1H, J = 3.2 Hz), 7.78 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 20.7, 34.6, 44.7, 55.2, 55.7, 70.1, 114.1, 120.6, 127.3, 130.1, 142.9, 159.3, 169.5, 169.9, 170.2. EM (EI^+, m/z (%)): 121 (100), 136 (46). Anal. calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found: C, 59.01; H, 5.12; N, 8.07.

(3R,5R)-3-Acetoxy-1-(4-methoxybenzyl)-5-(2-thiazolyl)-2-pyrrolidinone 23b.
From **22b** (304 mg), compound **23b** was obtained (339 mg, 98 %) as a white solid. M.p.: 139-141 °C. $[\alpha]_D^{20}$: -62.0 (1.0, $CHCl_3$). Crystallised from hexane/Et_2O (4:1). Anal. calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found: C, 58.93; H, 5.13; N, 8.02.

X-Ray crystallographic data of compound **23b**: $C_{17}H_{18}N_2O_4S$, monoclinic, space group $P2_1$, a = 4.931(2), b = 17.795(17), c = 19.583(13) Å, β = 92.75° (from 41 orientation reflections, 9.68° < θ < 24.63°), V = 1716.4(20) $Å^3$, Z = 4, D_{calcd} = 1.341 g/cm^3, F(000) = 728 (MoKα radiation, λ =0.71069 A). Intensity data were recorded on a Siemens P4 diffractometer (θ-2θ scans, θ_{max} = 26.0°). The intensities of the three standard reflections remeasured every 97 reflections during data collection to monitor crystal stability, indicated a decay of 5.01 %. From a total of 6708 measurements those 4080 reflections with $I > 2\sigma(I)$ were retained for the analysis. The crystal structure was solved by direct methods (SHELXS-86, Sheldrick, 1990). All non-hydrogen atoms were refined anisotropically and the hydrogen atoms at calculated positions. The final cycle of full-matrix least-squares refinement was based on 4080 observed reflections and 436 variable parameters with 1 restraint, and converged with agreement factors of: R = 0.0698, wR_2 = 0.1518, S = 1.120. Crystallographic calculations were performed on a Micro-Vax Alpha using SHELXL-93 software (Sheldrick, 1993). In the least-square iterations, $w = 1/[\sigma^2(Fo^2)+(0.0904P)^2]$, $P = (Fo^2-2Fc^2)/3$ was minimized.

Synthesis of 5-(hydroxymethyl)-3-(2-thiazolyl)isoxazolidines 18a and 20a.

To an ice-cooled solution of isoxazolidine (390 mg, 0.8 mmol) in Et_2O (5 mL) under argon, $LiAlH_4$ (38 mg, 1.0 mmol) was added. The mixture was stirred for 15 min and then treated with H_2O (10 mL). The organic layer was extracted with Et_2O (3x10 mL), the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed in silica using Et_2O as eluent to give homochiral isoxazolidines **17** and recovering the chiral inductor (2R)-bornane-10,2-sultam (ca 70 % yield).

(3R,5R)-2-Benzyl-5-(hydroxymethyl)-3-(2-thiazolyl)isoxazolidine 18a.

From **16a** (390 mg), compound **18a** was obtained (205 mg, 93 %) as an oil. $[\alpha]_D^{20}$: +47.0 (0.5, $CHCl_3$). IR: 3405. ^1H NMR: 1.82 (br s, 1H), 2.55 (ddd, 1H, J = 13.1, 7.3, 5.0 Hz), 2.72 (dt, 1H, J = 13.1, 8.2 Hz), 3.62 (dd, 1H, J = 13.3, 5.5 Hz), 3.83 (dd, 1H, J = 13.3, 3.8 Hz), 4.02, (d, 1H, J = 14.0 Hz), 4.08 (d, 1H, J = 14.0 Hz), 4.25-4.30 (m, 1H), 4.45 (dd, 1H, J = 8.2, 7.3 Hz), 7.21-7.38 (m, 6H), 7.67 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 29.5, 37.7, 62.9, 66.5, 78.1, 119.7, 127.03, 128.2, 128.6, 136.0, 142.4, 170.1. Anal. calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.82; H, 5.67; N, 10.08.

(3S,5S)-2-Benzyl-5-(hydroxymethyl)-3-(2-thiazolyl)isoxazolidine 20a.

From **17a** (390 mg), compound **20a** was obtained (203 mg, 92 %) as an oil. $[\alpha]_D^{20}$: -46.0 (0.7, $CHCl_3$). Anal. calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.94; H, 5.78; N, 10.22.

Synthesis of 2-(1-(benzylamino)-3,4-dihydroxybutyl)thiazoles 19a and 21a.

The same procedure described for the ring opening of isoxazolidines **4** was used. In this case, the residue was purified by column chromatography using EtOAc/MeOH (99:1) as eluent to give the pure compounds.

2-[(1R,3R)-1-(Benzylamino)-3,4-dihydroxybutyl]thiazole 19a.

From **18a** (138 mg), compound **19a** was obtained (124 mg, 89 %) as an oil. $[\alpha]_D^{20}$: +5.9 (0.4, $CHCl_3$). Δε (λ nm): +2.98 (223). IR: 3354. ^1H NMR: 2.02-2.12 (m, 2H), 2.6 (br s 2H), 3.47 (dd, 1H, J = 11.1, 6.3 Hz), 3.60 (dd, 1H, J = 11.1, 6.3 Hz), 3.76 (d, 1H, J = 12.9 Hz), 3.85 (d, 1H, J = 12.9 Hz), 3.92-3.95 (m, 1H), 4.21 (br s, 1H), 4.32 (t, 1H, J = 6.1 Hz), 7.30-7.45 (m, 6H), 7.72 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 38.4, 51.4, 57.3, 66.5, 69.9, 119.1, 127.5, 128.4, 128.6, 138.7, 142.3, 174.5. EM (FAB^+, m/z): 203, 173, 155, 91. Anal. calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.35; H, 6.36; N, 10.07.

2-[(1S,3S)-1-(Benzylamino)-3,4-dihydroxybutyl]thiazole 21a.

From **20a** (138 mg), compound **21a** was obtained (125 mg, 90 %) as an oil. $[\alpha]_D^{20}$: +5.7 (0.7, $CHCl_3$). Δε (λ nm): -2.98 (223). Anal. calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.34; H, 6.59; N, 10.19.

Synthesis of α-methoxy-α-(trifluoromethyl)phenylacetates 24 and 25.

To a solution of the 3-hydroxy-2-pyrrolidinone **22a** (137 mg, 0.5 mmol) in CH_2Cl_2 (15 mL) the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) (145 mg, 0.62 mmol), DCC (154 mg, 0.75 mmol) and DMAP (6 mg, 0.05 mmol) were added. The mixture was stirred overnight and then the solvent was removed in vacuo and the product isolated by column chromatography using hexane/Et_2O (7:3).

(+)-MTPA ester of (3R,5R)-1-benzyl-3-hydroxy-5-(2-thiazolyl)-2-pyrrolidinone 24.

Obtained 238 mg, 97 %. $[\alpha]_D^{20}$: -18.2 (0.4, $CHCl_3$). IR: 1759, 1714. ^1H NMR: 2.15 (dt, 1H, J = 14.5, 7.0 Hz), 2.97 (dt, 1H, J = 14.5, 7.0 Hz), 3.64 (s, 3H), 3.80 (d, 1H, J = 14.0 Hz), 4.90 (t, 1H, J = 7.0 Hz), 5.02 (d, 1H, J = 14.0 Hz), 5.77 (t, 1H, J = 7.0 Hz), 7.11-7.19 (m, 2H),7.22-7.35 (m, 4H), 7.37-7.41 (m, 3H), 7.57-7.65 (m, 2H), 7.77 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 33.7, 43.3, 55.7, 55.8, 71.0, 85.0 (c), 120.8, 122.0 (c), 127.2, 128.1, 128.4, 128.7, 128.8, 129.6, 131.8, 135.0, 142.8, 165.9, 168.7, 168.8. ^{19}F NMR: -72.15. EM (FAB$^+$, m/z): 491 $(M+1)^+$. Anal. calcd for $C_{24}H_{21}F_3N_2O_4S$: C, 58.77; H, 4.32; N, 5.71. Found: C, 58.63; H, 4.23; N, 5.74.

(-)-MTPA ester of (3R,5R)-1-benzyl-3-hydroxy-5-(2-thiazolyl)-2-pyrrolidinone 25.

Obtained 228 mg, 93 %. $[\alpha]_D^{20}$: -38.6 (0.6, $CHCl_3$). IR: 1725, 1715. ^1H NMR: 2.35 (dt, 1H, J = 13.7, 8.0 Hz), 3.02 (dt, 1H, J = 13.7, 8.0 Hz), 3.76 (s, 3H), 3.80 (d, 1H, J = 14.6 Hz), 4.90 (t, 1H, J = 8.0 Hz), 5.02 (d, 1H, J = 14.6 Hz), 5.65 (t, 1H, J = 8.0 Hz), 7.11-7.19 (m, 2H), 7.22-7.37 (m, 4H), 7.39-7.41 (m, 3H), 7.57-7.65 (m, 2H), 7.80 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 33.8, 45.4, 55.5, 55.7, 71.4, 85.0 (c), 120.8, 122.0 (c), 127.7, 128.1, 128.5, 128.7, 128.8, 129.8, 131.4, 135.1, 143.0, 165.9, 168.7, 168.9. ^{19}F NMR: -72.62. EM (FAB$^+$, m/z): 491 $(M+1)^+$. Anal. calcd for $C_{24}H_{21}F_3N_2O_4S$: C, 58.77; H, 4.32; N, 5.71. Found: C, 58.77; H, 4.20; N, 5.77.

Synthesis of (1S)-camphanic ester 26.

To a solution of **22a** (137 mg, 0.5 mmol), TEA (50 mg, 0.5 mmol) and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C (1S)-(-)-camphanic chloride (217 mg, 1.0 mmol) was added. The resulting mixture was stirred for 5 h and then washed with dilute HCl (1N, 3x20 mL), saturated $NaHCO_3$ (3x20 mL) and brine (3x20 mL). The organic layer was dried ($NaSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography using hexane/Et2O (2:3) as eluent to yield 222 mg (98%) of the ester **26** as a colourless oil. This product could be crystallised from hexane/Et_2O (4:1). M.p.: 135-138 °C. $[\alpha]_D^{20}$: -48.7 (0.2, $CHCl_3$). IR: 1795, 1736, 1700. ^1H NMR: 1.04 (s, 3H), 1.06 (s, 3H), 1.10 (s, 3H), 1.68 (ddd, 1H, J = 13.2, 9.0, 4.9 Hz), 1.82-2.08 (m, 2H), 2.29 (dt, 1H, J = 13.6, 7.5 Hz), 2.48 (ddd, 1H, J = 13.2, 10.4, 4.2 Hz), 2.96 (ddd, 1H, J = 13.6, 8.5, 7.5 Hz), 3.79 (d, 1H, J = 14.6 Hz), 4.85 (t, 1H, J = 7.5 Hz), 5.00 (d, 1H, J = 14.6 Hz), 5.61 (dd, 1H, J = 8.5, 7.5 Hz), 7.06-7.11 (m, 2H), 7.21-7.27 (m, 3H), 7.40 (d, 1H, J = 3.2 Hz), 7.77 (d, 1H, J = 3.2 Hz). ^{13}C NMR: 16.5, 16.6, 28.7, 30.5, 34.0, 45.2, 54.6, 54.8, 55.5, 70.4, 90.7, 120.8, 127.9, 128.6, 128.7, 135.1, 142.9, 166.7, 168.6, 169.1, 177.7. Anal. calcd for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.54; H, 5.74; N, 6.02.

X-Ray crystallographic data of compound **26**: $C_{24}H_{26}N_2O_5S$, monoclinic, space group $P2_1$, a = 9.625(5), b = 10.688(5), c = 11.619(5) Å, β = 110.318(5)° (from 38 orientation reflections, 2.85° < θ < 10.70°), V = 1120.9(9) Å^3, Z = 2, D_{calcd} = 1.347 g/cm^3, F(000) = 480, μ = 0.183 (MoKα radiation, λ = 0.71069 A). Intensity data were recorded on a Siemens P4 diffractometer (θ-2θ scans, θ_{max} = 26.0°). The intensities of the three standard reflections remeasured every 97 reflections during data collection to monitor crystal stability, indicated a decay of 7.29%. From a total of 2554 measurements those 2206 reflections with $I > 2\sigma(I)$ were retained for the analysis. The crystal structure was solved by direct methods (SIR-92, Giacovazzo). All non-hydrogen atoms were refined anisotropically and the hydrogen atoms at calculated positions. The final cycle of

full-matrix least-squares refinement was based on 2206 observed reflections and 292 variable parameters with 1 restraint, and converged with agreement factors of: R = 0.043, wR_2 = 0.104, S = 1.049. Crystallographic calculations were performed on a Micro-Vax Alpha using SHELXL-93 software (Sheldrick, 1993). In the least-square iterations, $w = 1/[\sigma^2(Fo^2)+(0.0745P)^2]$, $P = (Fo^2-2Fc^2)/3$ was minimized.

Synthesis of 5-formyl-2-pyrrolidinones 27.

A mixture of the corresponding thiazolylpyrrolidinone **23** (1 mmol), activated 4 Å molecular sieves (2.0 g) and acetonitrile (20 mL) was stirred at room temperature for 10 min. Methyl triflate (120 µL, 1.1 mmol) was added and the suspension was stirred for 20 min. The solvent was removed under reduced pressure. The residue was diluted with MeOH (20 mL), cooled to 0 °C and treated with $NaBH_4$ (84 mg, 2.2 mmol). The mixture was stirred at room temperature for 15 min, diluted with acetone (2 mL), filtered through celite and concentrated in vacuo. The residue was dissolved in a 10:1 CH_3CN-H_2O mixture (20 mL) and then treated with CuO (237 mg, 3 mmol) and $CuCl_2$-$2H_2O$ (186 mg, 1.1 mmol). The suspension was stirred at room temperature for 10 min, then filtered through celite and concentrated in vacuo below 30 °C. The residue was partitioned between brine (30 mL) and Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted twice with Et_2O (30 mL). The combined organic extracts were dried (Na_2SO_4) and passed through a plug of Florisil washing with Et_2O. The solvent was then evaporated under reduced pressure to give the essentially pure aldehydes.

(3R,5R)-3-Acetoxy-1-benzyl-5-formyl-2-pyrrolidinone 27a.

From **23a** (316 mg), compound **27a** was obtained (201 mg, 77 %) as an oil. $[\alpha]_D^{20}$: -44.6 (0.1, MeOH). ^1H NMR: 1.90 (dt, 1H, J = 14.2, 5.0 Hz), 2.10 (s, 3H), 2.65 (dt, 1H, J = 14.2, 8.1 Hz), 3.87 (ddd, 1H, J = 8.1, 5.0, 3.0 Hz), 4.32 (d, 1H, J = 14.8 Hz), 4.85 (d, 1H, J = 14.8 Hz), 5.25 (dd, 1H, J = 8.1, 5.0 Hz), 7.15-7.35 (m, 5H), 9.32 (d, 1H, J = 3 Hz). ^{13}C NMR: 20.7, 27.0, 46.4, 61.9, 69.7, 128.3, 128.6, 129.0, 134.6, 170.0, 170.4, 197.4.

(3R,5R)-3-Acetoxy-5-formyl-1-(4-methoxybenzyl)-2-pyrrolidinone 27b.

From **23b** (346 mg), compound **27b** was obtained (210 mg, 72 %) as an oil. $[\alpha]_D^{20}$: -7.7 (1.0, MeOH). ^1H NMR: 1.93 (dt, 1H, J = 14.2, 5.7 Hz), 2.11 (s, 3H), 2.66 (dt, 1H, J = 14.2, 8.5 Hz), 3.77 (s, 3H), 3.85 (ddd, 1H, J = 8.5, 5.7, 3.0 Hz), 4.32 (d, 1H, J = 14.7 Hz), 4.78 (d, 1H, J = 14.7 Hz), 5.26 (dd, 1H, J = 8.5, 5.7 Hz), 6.78-6.82 (m, 2H), 7.15-7.20 (m, 2H), 9.30 (d, 1H, J = 3.0 Hz). ^{13}C NMR: 20.8, 27.1, 46.0, 55.3, 62.0, 69.8, 114, 4, 126.7, 130.2, 159.6, 170.0, 170.4, 197.6.

Reduction of 5-formyl-2-pyrrolidinones 27.

An ice-cooled solution of the corresponding aldehyde **27** (0.25 mmol) in MeOH (5 mL) was treated with $NaBH_4$ (23 mg, 0.6 mmol) and stirred for 1 h. Then, solvent was removed in vacuo, saturated $NaHCO_3$ (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography using EtOAc as eluent.

(3R,5R)-1-Benzyl-3-hydroxy-5-(hydroxymethyl)-2-pyrrolidinone 28a.

From **27a** (65 mg), compound **28a** was obtained (46 mg, 83 %) as an oil. $[\alpha]_D^{20}$: -44.8 (1.3, $CHCl_3$). IR: 3328, 1674. ^1H NMR: 1.87 (dt, 1H, J = 13.1, 5.0 Hz), 2.31 (dt, 1H, J = 13.1, 8.2 Hz), 3.41-3.48 (m, 2H), 3.75 (d, 1H, J = 10.0 Hz), 4.07 (d, 1H, J = 15.1 Hz), 4.30 (br s, 1H), 4.55 (br s, 1H), 4.98 (d, 1H, J = 15.1 Hz), 5.28 (br s, 1H), 7.12-7.38 (m, 5H). ^{13}C NMR: 30.7, 44.2, 55.9, 59.9, 69.4, 127.6, 127.9, 128.7, 135.8, 175.4. EM (FAB^+, m/z): 222 $(M+1)^+$. Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.14; H, 6.99; N, 6.29.

(3R,5R)-3-Hydroxy-5-(hydroxymethyl)-1-(4-methoxybenzyl)-2-pyrrolidinone 28b.
From **27b** (73 mg), compound **28b** was obtained (50 mg, 80 %) as an oil. $[\alpha]_D^{20}$: -7.5 (0.2, MeOH). IR: 3386, 1673. ^{1}H NMR: δ 1.86 (dt, 1H, J = 13.6, 4.4 Hz), 2.38 (dt, 1H, J = 13.6, 8.3 Hz), 3.44-3.52 (m, 3H), 3.78 (s, 3H), 3.84 (dd, 1H, J = 11.7, 2.4 Hz), 3.98 (d, 1H, J = 14.8 Hz), 4.29 (dd, 1H, J = 8.3, 4.4 Hz), 4.67 (br s, 1H), 4.87 (d, 1H, J = 14.8 Hz), 6.78 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 8.5 Hz). ^{13}C NMR: 29.6, 43.8, 55.2, 56.0, 60.0, 69.5, 114.1, 127.7, 129.3, 159.1, 177.9. EM (FAB$^+$, m/z): 252 $(M+1)^+$. Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.14; H, 6.96; N, 5.64.

Addition of 2-(trimethylsilyl)thiazole to 5-formyl-2-pyrrolidinones 27.
To a solution of corresponding aldehyde **27** (0.3 mmol) in THF (5 mL) at -30 °C freshly distilled 2-(trimethylsilyl)thiazole[22] (1.0 mmol, 157 mg) in THF (5 mL) was added dropwise. The reaction mixture was stirred for two days and then the solvent was removed under reduced pressure. The residue was treated with Bu_4NF (1.5 mL, 1M in THF) and then with CH_2Cl_2 (15 mL). The solution was washed with H_2O (2x10 mL) dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was purified by column chromatography using Et_2O as eluent to yield the homologated pyrrolidinone as mixture of diastereomers. The ^{1}H NMR data were collected from the spectra of the diastereomeric mixtures.
(3R,5R)-3-Acetoxy-1-benzyl-5-[1-hydroxy-1-(2-thiazolyl)methyl]-2-pyrrolidinone 29a.
From **27a** (78 mg), compound **29a** was obtained (64 mg, 62 %) as a 70:30 mixture of diastereomers.
Major isomer: ^{1}H NMR: 1.87 (dt, 1H, J = 14.7, 7.3 Hz), 2.12 (s, 3H), 2.18 (dt, 1H, J = 14.7, 7.3 Hz), 2.65 (d, 1H, J = 4.2 Hz), 4.19 (dt, 1H, J = 7.3, 2.5 Hz), 4.61 (d, 1H, J = 15.1 Hz), 4.72 (d, 1H, J = 15.1 Hz), 5.18-5.35 (m, 2H), 7.25-7.40 (m, 6H), 7.71 (d, 1H, J = 3.2 Hz).
Minor isomer: ^{1}H NMR: 1.82 (dt, 1H, J = 15.1, 7.2 Hz), 2.07 (s, 3H), 2.44 (ddd, 1H, J = 15.1, 6.3, 5.4 Hz), 3.23 (d, 1H, J = 4.8 Hz), 4.03 (dt, 1H, J = 7.2, 5.4 Hz), 4.32 (d, 1H, J = 14.2 Hz), 4.96 (d, 1H, J = 14.2 Hz), 5.08 (dd, 1H, J = 7.2, 6.3 Hz), 5.18-5.35 (m, 1H), 7.25-7.40 (m, 6H), 7.74 (d, 1H, J = 3.2 Hz).
(3R,5R)-3-Acetoxy-5-[1-hydroxy-1-(2-thiazolyl)methyl]-1-(4-methoxybenzyl)-2-pyrrolidinone 29b.
From **27b** (87 mg), compound **29b** was obtained (68 mg, 60 %) as a 60:40 mixture of diastereomers.
Major isomer: ^{1}H NMR: δ 1.86 (ddd, 1H, J = 13.4, 6.7, 6.0 Hz), 2.18 (s, 3H), 2.20 (ddd, 1H, J = 13.4, 6.9, 6.0 Hz), 2.68 (d, 1H, J = 4.4 Hz), 3.80 (s, 3H), 4.18 (dt, 1H, J = 6.0, 1.9 Hz), 4.55 (d, 1H, J = 15.1 Hz), 4.64 (d, 1H, J = 15.1 Hz), 5.20 (dd, 1H, J = 4.4, 1.9 Hz), 5.28-5.32 (m, 1H), 6.87-6.92 (m, 2H), 7.25-7.29 (m, 2H), 7.31 (d, 1H, J = 3.2 Hz), 7.72 (d, 1H, J = 3.2 Hz).
Minor isomer: ^{1}H NMR: δ 1.82 (dt, 1H, J = 14.5, 5.4 Hz), 2.04 (s, 3H), 2.42 (dt, 1H, J = 14.5, 5.4 Hz), 2.85 (d, 1H, J = 4.5 Hz), 3.78 (s, 3H), 4.05 (dt, 1H, J = 6.0, 5.4 Hz), 4.25 (d, 1H, J = 14.9 Hz), 4.91 (d, 1H, J = 14.9 Hz), 5.09 (t, 1H, J = 5.4 Hz), 5.20 (dd, 1H, J = 6.0, 4.5 Hz), 6.80-6.84 (m, 2H), 7.08-7.11 (m, 2H), 7.37 (d, 1H, J = 3.2 Hz), 7.78 (d, 1H, J = 3.2 Hz).

Wittig reactions of 5-formyl-2-pyrrolidinones 27.
A solution of the aldehyde **27** (0.1 mmol) and the corresponding phosphorane (0.15 mmol) in $CHCl_3$ (5 mL) protected from the sunlight was stirred for two days. The solvent was removed in vacuo and the crude product purified by column chromatography.
Methyl (E)-3-[(2R,4R)-4-acetyl-1-benzyl-5-oxo-pyrrolidin-2-yl]propenoate 30a.
From **27a** (27 mg) and methyl triphenylphosphoranylidenacetate (50 mg). Purified using CH_2Cl_2/EtOAc (74:26) as eluent. Obtained 25 mg (79 %) as a yellow oil. $[\alpha]_D^{20}$: -21.0 (0.2, $CHCl_3$). IR: 1734, 1705, 1689, 1489. ^{1}H NMR: 1.71 (dt, 1H, J = 13.5, 7.1 Hz), 2.21 (s, 3H), 2.52 (dt, 1H, J = 13.5, 7.1 Hz), 3.72 (s, 3H), 3.90 (d, 1H, J = 14.7 Hz), 3.91 (dt, 1H, J = 7.9, 7.1 Hz), 4.32 (t, 1H, J = 7.1 Hz), 5.0 (d, 1H, J = 14.7

Hz), 5.78 (d, 1H, J = 15.4 Hz), 6.68 (dd, 1H, J = 15.4, 7.9 Hz), 7.12-7.40 (m, 5H). ^{13}C NMR: 20.9, 30.1, 32.2, 44.6, 53.1, 70.1, 124.6, 125.7, 127.9, 128.2, 128.7, 135.3, 147.4, 166.8, 171.3. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.23; H, 6.18; N, 4.30.

Methyl (E)-3-[(2R,4R)-4-acetyl-1-(4-methoxybenzyl)-5-oxo-pyrrolidin-2-yl]propenoate 30b.

From **27b** (29 mg) and methyl triphenylphosphoranylidenacetate (50 mg). Purified using hexane/Et_2O (2:3) as eluent. Obtained 29 mg (83 %) as a yellow oil. $[\alpha]_D^{20}$: -25.7 (1.3, $CHCl_3$). IR: 1730, 1696, 1687, 1501. ^1H NMR: δ 1.74 (dt, 1H, J = 13.7, 6.9 Hz), 2.13 (s, 3H), 2.66 (dt, 1H, J = 13.7, 6.9 Hz), 3.75 (s, 3H), 3.77 (s, 3H), 3.84 (d, 1H, J = 14.5 Hz), 3.94 (dt, 1H, J = 8.8, 6.9 Hz), 4.95 (d, 1H, J = 14.5 Hz), 5.29 (t, 1H, J = 6.9 Hz), 5.90 (d, 1H, J = 15.4 Hz), 6.68 (dd, 1H, J = 15.4, 8.8 Hz), 6.81-6.83 (m, 2H), 7.08-7.12 (m, 2H). ^{13}C NMR: 20.7, 29.7, 32.4, 44.6, 51.9, 55.2, 70.1, 114.3, 124.5, 125.5, 127.5, 129.8, 145.6, 159.4, 165.6, 170.0. Anal. calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.27; H, 5.93; N, 3.87.

3-[(2R,4R)-4-acetyl-1-benzyl-5-oxo-pyrrolidin-2-yl]propenal 31a.

From **27a** (27 mg) and triphenylphosphoranylidenacetaldehyde (46 mg). Purified using hexane/Et_2O (2:3). Obtained 24 mg (83 %) as a 60:40 mixture of diastereomers. The ^1H NMR data were collected from the spectrum of the mixture.

Major isomer; E: ^1H NMR: 1.81 (dt, 1H, J = 13.6, 6.8 Hz), 2.01 (s, 3H), 2.62 (dt, 1H, J = 13.5, 6.8 Hz), 3.98 (d, 1H, J = 14.7 Hz), 4.02 (t, 1H, J = 6.8 Hz), 4.36 (dt, 1H, J = 8.9, 6.8 Hz), 4.85 (d, 1H, J = 14.7 Hz), 6.13 (dd, 1H, J = 15.7, 7.7 Hz), 6.50 (dd, 1H, J = 15.7, 8.9 Hz), 7.15-7.60 (m, 5H), 9.41 (d, 1H, J = 7.7 Hz). Minor isomer; Z: ^1H NMR: 1.78 (dt, 1H, J = 13.6, 7.2 Hz), 2.03 (s, 3H), 2.58 (dt, 1H, J = 13.6, 7.2 Hz), 3.21 (d, 1H, J = 14.7 Hz), 3.96 (t, 1H, J = 7.2 Hz), 4.88 (d, 1H, J = 14.7 Hz), 5.92 (dd, 1H, J = 12.3, 7.8 Hz), 6.14 (dt, 1H, J = 7.9, 7.2 Hz), 6.31 (dd, 1H, J = 12.3, 7.9 Hz), 7.15-7.60 (m, 5H), 9.58 (d, 1H, J = 7.8 Hz).

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