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4-Alkenyl-2-aminothiazoles: Smart Dienes for Polar [4+2] Cycloadditions

Mateo Alajarin,*[a] Jose Cabrera,[a] Pilar Sanchez-Andrada,[a,b] Raul-Angel Orenes,[c] and Aurelia Pastor*[a]

Dedicated to Professor Waldemar Adam on the occasion of his 75th birthday

Keywords: Cycloaddition / Cyclization / Nitrogen heterocycles / Zwitterions / Reaction mechanisms

An exhaustive investigation into the [4+2] cycloadditions of 4-alkenyl-2-aminothiazoles with a wide range of dienophiles has been carried out. 4-Alkenyl-2-aminothiazoles act as good in-out dienes, reacting with dienophiles bearing electron-withdrawing groups. The heteroannulations, typically conducted under mild conditions, were *endo*-selective when cyclic dienophiles were used, and regioselective when the reactions are conducted with unsymmetrical dienophiles. The *endo*-selective processes presumably take place by concerted but highly asynchronous mechanisms. In contrast, the low levels of *endo* selectivity and the lack of stereospecificity in the reactions with certain acyclic dienophiles indicate a stepwise mechanism with a zwitterion as the most plausible intermediate. The course of the reaction changes when the highly reactive PTAD and TCNE are used as dienophiles, since in these cases, only addition products were obtained. Calculations of the HOMO and LUMO energy values of representative 4-alkenyl-2-aminothiazoles, and the results of π-facial diastereoselective processes by using chiral substrates are also disclosed.

Introduction

The Diels–Alder reaction, a [4π + 2π] cycloaddition, results in six-membered-ring products through carbon–carbon bond formation.[1] This process has been extensively investigated since its discovery, and a large number of variants are known.[2] Nowadays, the Diels–Alder reaction continues to play a central role in the total syntheses of many natural products, and also in the construction of a large number of compounds of biological importance.[3]

The use of heteroaromatic compounds as either the diene or dienophile component is an area of great interest in Diels–Alder chemistry.[4] Aromatic vinyl heterocycles may undergo Diels–Alder reaction as dienes by involving either the aromatic nucleus (intra-annular addition) or the diene moiety including the side-chain double bond (extra-annular addition). In general, the latter mode of reaction is preferred, and this allows substituted condensed heterocyclic systems to be prepared.[5] Diverse polycyclic structures have been synthesized in this way from vinylfurans,[6] vinylindoles,[7] vinylpyrroles,[8] and vinylimidazoles.[9]

In recent years, there has been considerable interest in substituted and bicyclic derivatives of thiazoles, as the 1,3-thiazole ring appears in a diverse range of natural products and other biologically active compounds.[10] For instance, thiazolo[5,4-*b*]pyridin-5(4*H*)-one derivatives are efficient HIV integrase strand-transfer inhibitors,[11] 2-aminothiazole derivatives are inhibitors of cdk5/p25, and thus are potentially useful for the treatment of Alzheimer's disease and other neurodegenerative disorders,[12] and 5-arylidene-2-imino-4-thiazolidinones show significant levels of anti-inflammatory activity.[13] Unfortunately, functionalization of the thiazole ring is usually a difficult task, since, due to its electron-deficient aromatic character, this heterocycle is very reluctant to undergo electrophilic substitution or addition, or indeed cycloaddition across the formal C=C and C=N double bonds.[14] The loss of the aromaticity results in reactions that are less exothermic than classical Diels–Alder processes.[15] In fact, only reactions with highly reactive dienophiles have been described to date. These processes lead to intermediate bicyclic products that subsequently undergo chelotropic extrusion of sulfur[16] or elimination of a nitrile molecule.[17]

Recently, we have demonstrated that 4-alkenyl-2-methyl- and 4-alkenyl-2-phenylthiazoles react with classical dienophiles such as maleimides,[18] maleic anhydride,[18] or 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD),[19] which opens a

[a] Department of Organic Chemistry, Faculty of Chemistry, University of Murcia, Regional Campus of International Excellence "Campus Mare Nostrum", 30100 Murcia, Spain
Fax: +34-868884149
E-mail: alajarin@um.es
aureliap@um.es
[b] University Centre of Defence, at the Spanish Air Force Academy, Base Aerea de San Javier, c/ Coronel Lopez Peña s/n, 30720 Santiago de la Ribera, Murcia, Spain
[c] SAI, University of Murcia, Campus de Espinardo, 30100 Murcia, Spain

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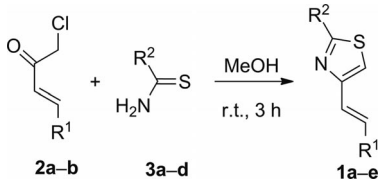
new route to polyheterocyclic derivatives. Given the scarcity of reports of the participation of thiazoles in Diels–Alder processes, and the significance of the thiazolyl moiety in medicinal chemistry, it seemed to be desirable to develop this area of synthetic chemistry. To expand the scope of the [4 + 2] cycloaddition reactions of 4-alkenylthiazoles, we decided to investigate the reactions of these substrates bearing an amino group at 2-position, in the hope that this substitution pattern would activate the thiazole ring.[14a,20] It is well known that for normal-electron-demand Diels–Alder reactions, an increase in the electron-rich character of the diene and an increase in the electron-poor character of the dienophile result in an enhancement of the charge transfer and a decrease in the activation barrier.[21] Taking these ideas into account, 4-alkenyl-2-aminothiazoles should be much more reactive than their previously investigated 2-alkyl- and 2-aryl-substituted conterparts, and thus they would potentially be able to participate as highly reactive dienes in a more varied collection of Diels–Alder reactions.

In this paper, we disclose our findings regarding the synthesis of 4-alkenyl-2-aminothiazoles and their reactivity as dienes in [4 + 2] cycloaddition reactions with a wide range of dienophiles. Issues pertaining to stereocontrol and regiochemistry are also discussed. Finally, we have investigated some striking aspects of the mechanism, namely the operation of a concerted vs. a stepwise process.

Results and Discussion

Synthesis of 4-Alkenyl-2-aminothiazoles 1

The 4-alkenyl-2-aminothiazoles (i.e., **1a**–**e**) were prepared by a Hantzsch synthesis,[22] by reacting previously reported α-chloro ketones **2a**–**b** with thioureas **3a**–**d** at room temperature (Scheme 1). Thiazoles **1a**–**e** were isolated in yields of 82–90% (Table 1). Thioureas **3**, except for *N*,*N*-dimethylthiourea (**3d**), are commercially available. Thiourea **3d** was prepared following a previously reported method.[16b]



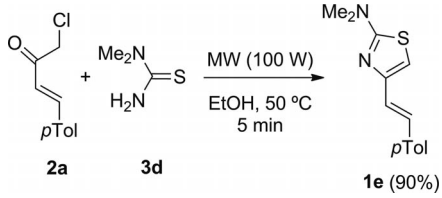
Scheme 1. Synthesis of 4-alkenyl-2-aminothiazoles **1a**–**e** (**2a**: R^1 = 4-MeC_6H_4, **2b**: R^1 = 4-$MeOC_6H_4$, **3a**: R^2 = NH_2, **3b**: R^2 = NHPh, **3c**: R^2 = NHMe, **3d**: R^2 = NMe_2).

Table 1. Synthesis of 4-alkenyl-2-aminothiazoles **1a**–**e**.

Entry	R^1	R^2	Product	Yield [%]
1	4-MeC_6H_4	NH_2	**1a**	82[a]
2	4-MeC_6H_4	NHPh	**1b**	83[a]
3	4-MeC_6H_4	NHMe	**1c**	90
4	4-$MeOC_6H_4$	NHMe	**1d**	86
5	4-MeC_6H_4	NMe_2	**1e**	88[a]

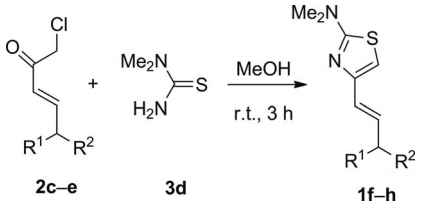
[a] Previously described in ref.[16b]

4-Alkenyl-2-(dimethylamino)thiazole **1e** was also synthesized using microwave irradiation (Scheme 2). Thiazole **1e** was thus isolated in a yield comparable to that obtained in the thermal reaction, but in a shorter reaction time.



Scheme 2. Synthesis of 4-alkenyl-2-aminothiazole **1e** by MW irradiation.

Racemic 2-(dimethylamino)thiazoles **1f**–**h** were easily prepared from the corresponding α-chloro ketones (i.e., **2c**–**e**) and thiourea **3d** (Scheme 3, Table 2). α-Chloro ketones **2c** and **2e** have been reported previously.[19] The synthesis of α-chloro ketone **2d** is described in the Supporting Information.



Scheme 3. Synthesis of chiral 4-alkenyl-2-aminothiazoles **1f**–**h** (**2c**: R^1 = Ph, R^2 = Me, **2d**: R^1 = Et, R^2 = Me, **2e**: R^1,R^2 = $CH_2OCH_2CH_2$).

Table 2. Synthesis of chiral 4-alkenyl-2-aminothiazoles **1f**–**h**.

Entry	R^1	R^2	Product	Yield [%]
1	Ph	Me	**1f**	87
2	Et	Me	**1g**	60
3	–$CH_2OCH_2CH_2$–		**1h**	62

HOMO Energies of Thiazoles 1

The HOMO energies of the 4-alkenyl-2-amino-, 4-vinyl-2-hydroxy-, and 4-vinyl-2-mercaptothiazoles (i.e., **1i**–**m**; Figure 1) were obtained through single-point Hartree–Fock (HF) calculations with the 6-31G basis set using B3LYP/6-31G geometries, as this procedure has been shown to provide more accurate orbital energies than the B3LYP level.[23] The computed B3LYP/6-31G structures of thiazoles **1i**–**m** in their reactive *s-cis* conformations are shown in Figure 2. In Table 3 we summarize the HOMO energies and the $2p_z$ eigenvectors of the HOMOs of dienes **1i**–**m**.

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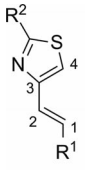


1i R^1 = Ph, R^2 = NH_2
1j R^1 = H, R^2 = NH_2
1k R^1 = H, R^2 = NHMe
1l R^1 = H, R^2 = OH
1m R^1 = H, R^2 = SH

Figure 1. Structures of 4-alkenyl-2-amino-, 2-hydroxy-4-vinyl-, and 2-mercapto-4-vinylthiazoles **1i**–**m**.

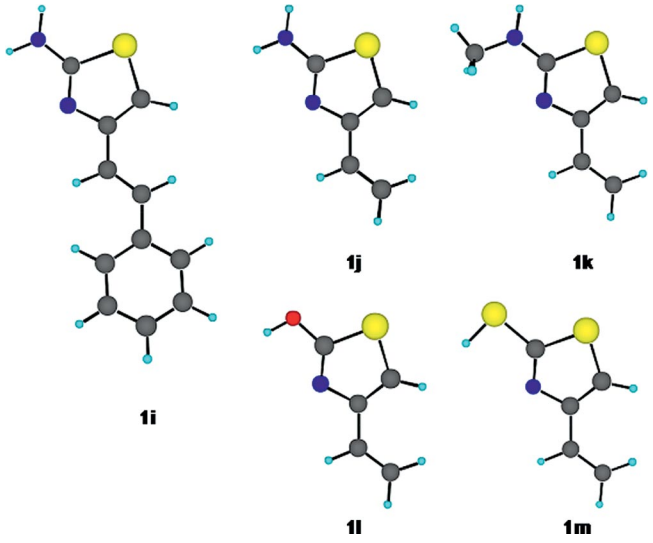


Figure 2. Computed B3LYP/6-31G geometries of 4-alkenyl-2-amino-, 2-hydroxy-4-vinyl-, and 2-mercapto-4-vinylthiazoles **1i**–**m** in their respective *s-cis* conformations.

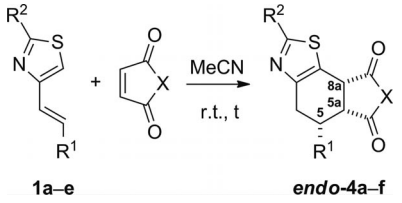
Table 3. HOMO values for 4-alkenyl-2-amino-, 2-hydroxy-4-vinyl-, and 2-mercapto-4-vinylthiazoles **1i**–**m** in their respective *s-cis* conformations (for the numbering of the diene carbon atoms, see Figure 1).

Entry	Diene	Eigenvalue [eV]	$2p_z$ coefficients			
			C-1	C-2	C-3	C-4
1	*s-cis*-**1i**	–7.40	–0.21	–0.22	0.17	0.27
2	*s-cis*-**1j**	–7.98	–0.21	–0.14	0.23	0.33
3	*s-cis*-**1k**	–7.84	–0.20	–0.13	0.23	0.33
4	*s-cis*-**1l**	–8.57	–0.25	–0.18	0.25	0.32
5	*s-cis*-**1m**	–8.56	–0.24	–0.17	0.24	0.30

According to the FMO theory, dienes with substituents capable of donating electron density into the conjugated π-system show higher reactivity in normal-electron-demand Diels–Alder reactions.[21,24] Thus, we used the computed HOMO values of thiazoles **1i**–**m** to predict their relative reactivities. Contrary to our expectations, the presence of an amino group induces only a slight increase in the HOMO energies of 2-aminothiazoles **1i**–**k** compared to those of their 2-methyl- and 2-phenyl-substituted counterparts.[18] Thus, the HOMO value of 2-amino-4-vinylthiazole **1j** is –7.98 eV (Table 3, entry 2), whereas the previously reported values for 2-phenyl- and 2-methyl-4-vinylthiazoles are –8.01 eV and –8.41 eV, respectively.[18] The data shown in Table 3 show that the HOMO energy is slightly enhanced by the presence of a phenyl group at C-1 (Figure 1 and Table 3, entry 1), as was also found for the analogous 2-phenyl-substituted thiazole.[18] Finally, the introduction of a hydroxy or thiol group at the 2-position did not result in any significant increase of the HOMO energy (Table 3, entries 4–5). Hence, we should expect that 4-alkenyl-2-aminothiazoles behave as activated dienes in normal-electron-demand [4 + 2] cycloaddition reactions, but their reactivities are predicted to be only slightly higher than those of the 2-methyl and 2-phenyl derivatives.

[4 + 2] Cycloadditions of 4-Alkenyl-2-aminothiazoles 1a–e

The reactions of thiazoles **1a**–**e** with *N*-phenylmaleimide (NPM) or maleic anhydride (MA) were conducted in acetonitrile at room temperature (Scheme 4). Under these conditions, tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-diones *endo*-**4a**–**e** and tetrahydrofuro[3,4-*g*]benzothiazole-6,8-dione *endo*-**4f** were obtained in excellent yields (Table 4). Compounds *endo*-**4a**–**f** are the result of a [4 + 2] cycloaddition and a further 1,3-hydrogen migration. The possible presence of the primary cycloadducts or those resulting from a further ene reaction with a second equivalent of dienophile was ruled out by analysis of the ^{1}H NMR spectra of the crude products.[18] As far as it could be determined, only the stereoisomer deriving from an *endo* transition state is formed in each case, as shown by the X-ray crystal structure of **4e** (see below).



Scheme 4. Reactions of 4-alkenyl-2-aminothiazoles **1a**–**e** with NPM and MA (R^1 and R^2 defined in Table 4).

Table 4. Reactions of 4-alkenylthiazoles **1a**–**e** with NPM and MA.

Entry	R^1	R^2	X	*t* [h]	Product	Yield [%]
1	4-MeC_6H_4	NH_2	NPh	48	*endo*-**4a**	90
2	4-MeC_6H_4	NHPh	NPh	48	*endo*-**4b**	90
3	4-MeC_6H_4	NHMe	NPh	48	*endo*-**4c**	91
4	4-$MeOC_6H_4$	NHMe	NPh	48	*endo*-**4d**	90
5	4-MeC_6H_4	NMe_2	NPh	48	*endo*-**4e**	91
6	4-MeC_6H_4	NMe_2	O	24	*endo*-**4f**	72

Notably, the reactions shown in Scheme 4 take place under exceedingly mild reaction conditions considering that the cycloaddition step involves the dearomatization of the thiazole ring. For the sake of comparison, previously described reactions of 4-alkenyl-2-methyl- and 4-alkenyl-2-

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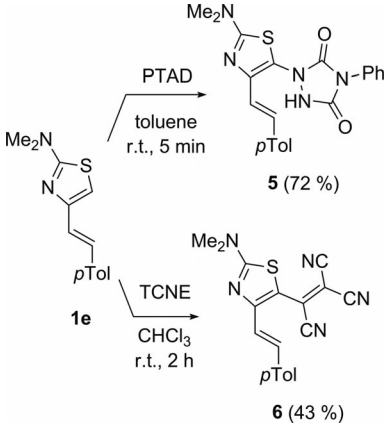
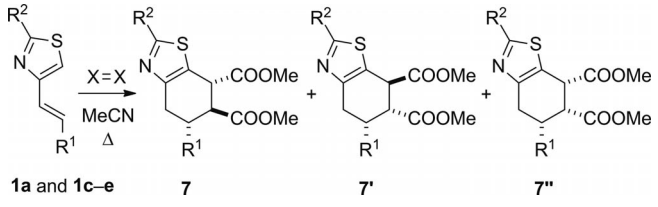
phenylthiazoles with the same dienophiles had to be conducted at 120 °C in the same solvent.[18] This fact indicates that 4-alkenyl-2-aminothiazoles **1** are considerably more reactive, despite the predictions done on the basis of their HOMO levels.

Next, we investigated the reactions of 4-alkenyl-2-aminothiazole **1e** with the highly reactive dienophiles PTAD and tetracyanoethylene (TCNE). Much to our surprise, the expected [4 + 2] cycloadducts were not isolated in either case. Instead, thiazoles **5** and **6**, resulting from an initial electrophilic addition of PTAD or TCNE to the C-5 atom of the thiazole ring, were obtained (Scheme 5).



Scheme 5. Reaction of 4-alkenyl-2-(dimethylamino)thiazole **1e** with PTAD and TCNE.

Next, the reactions of 4-alkenylthiazoles **1a**–**e** with dimethyl maleate (DMMa) and dimethyl fumarate (DMFu) were explored. These reactions were conducted in acetonitrile under reflux for 48 h (Scheme 6, Table 5). That higher reaction temperatures and a large excess of dienophile (15 equiv.) were required is consistent with the lower reactivity of DMMa or DMFu arising from their acyclic structures. The reaction products, dimethyl 4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylates **7**, **7′**, and **7′′**, are the result of a Diels–Alder cycloaddition followed by a 1,3-hydrogen migration. Notably, no reaction was observed when 4-alkenyl-2-(phenylamino)thiazole **1b** was used as starting material (result not shown). The cycloadditions of thiazoles **1a** and **1c**–**e** with DMMa were not stereospecific. Thus, cycloadducts **7** and/or **7′**, in which the two carboxymethyl substituents have a *trans* arrangement, were isolated along



Scheme 6. Reactions of 4-alkenyl-2-aminothiazoles **1a** and **1c**–**e** with dimethyl maleate (DMMa) and dimethyl fumarate (DMFu) (R^1, R^2 and X=X defined in Table 5).

with the expected cycloadduct (i.e., **7′′**) when DMMa was used (Table 5, entries 1–4). The reactions with DMFu were also not diastereoselective (Table 5, entries 5 and 6), and no discrimination between the *endo* (**7**) and the *exo* (**7′**) approaches was seen.

Table 5. Reactions of 4-alkenyl-2-aminothiazoles **1a** and **1c**–**e** with dimethyl maleate (DMMa) and dimethyl fumarate (DMFu).

Entry	R^1	R^2	X=X	Yield [%]	**7**/**7′**/**7′′**[a]	
1	4-MeC_6H_4	NH_2	DMMa	35	43:00[b]:57	**a**
2	4-MeC_6H_4	NHMe	DMMa	64	36:10[c]:54	**b**
3	4-$MeOC_6H_4$	NHMe	DMMa	72	42:00[b]:58	**c**
4	4-MeC_6H_4	NMe_2	DMMa	93	23:28:49	**d**
5	4-MeC_6H_4	NHMe	DMFu	81	41:59:00[b]	**b**
6	4-MeC_6H_4	NMe_2	DMFu	96	47:53:00[b]	**d**

[a] Determined by analysis of characteristics signals in the ^{1}H NMR spectrum of the crude product (error ± 5% of the stated value). [b] Not detected in the ^{1}H NMR spectrum of the reaction mixture. [c] Not isolated, but detected in the ^{1}H NMR spectrum of the reaction mixture.

Regioselectivity in the [4 + 2] Cycloadditions of 4-Alkenyl-2-aminothiazoles with Unsymmetrical Dienophiles

The regioselectivity of this kind of Diels–Alder reactions can be investigated by using unsymmetrical dienophiles. According to FMO theory, the regiochemistry of the Diels–Alder reaction is controlled by the complementarity of the frontier orbitals of the diene and the dienophile. Thus, more effective overlap takes place between the ends of the two components with the highest coefficients.[1a] For 4-alkenyl-2-aminothiazoles **1**, the atom with the coefficient with the highest absolute value is C-5 of the thiazole ring (labelled as C-4 in Figure 1 and Table 3). Regarding the LUMO of the dienophile, when an electron-withdrawing substituent is present at the α-position, the atom with the highest coefficient is at the adjacent β-position.[25]

Methyl acrylate, α-chloroacrylonitrile, ethyl 2,3-butadienoate, and ethyl propiolate were chosen as model dienophiles to probe the regioselectivity of the cycloaddition reactions of **1**. The reaction of **1c** with a large excess of methyl acrylate in acetonitrile under reflux led to cycloadducts **8a** and **8b**, both as *endo*/*exo* mixtures, in a moderate overall yield (Scheme 7). This process was highly regioselective, although negligible *endo*/*exo* selectivities were observed for both **8a** and **8b**. To avoid the undesired addition of the dienophile to the amino group (cycloadducts *endo*-**8b** and *exo*-**8b**), the reaction of dimethylamino derivative **1e** with methyl acrylate was conducted under analogous conditions, giving a mixture of *endo*-**8c** and *exo*-**8c** exclusively (Scheme 8).

The reaction of **1e** with α-chloroacrylonitrile was carried out in acetonitrile at reflux temperature (Scheme 9). Cycloadduct **9** was isolated in good yield as a single regioisomer. The formation of **9** was highly diastereoselective,

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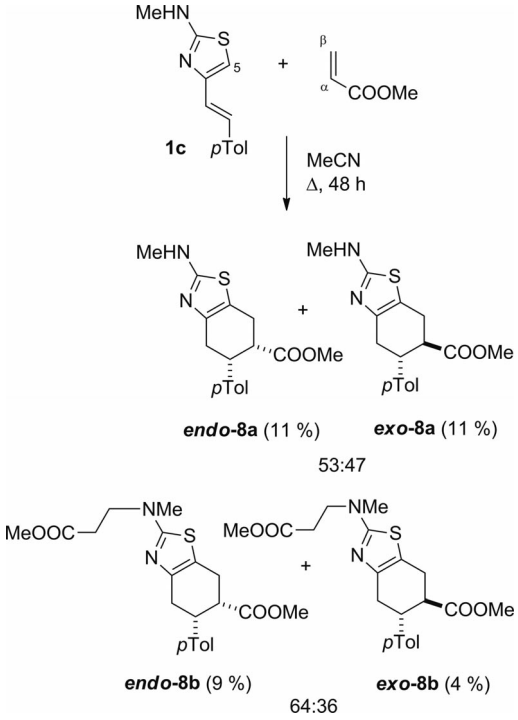
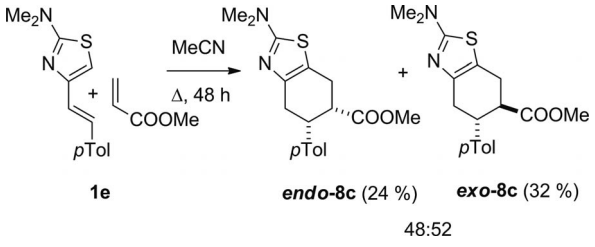


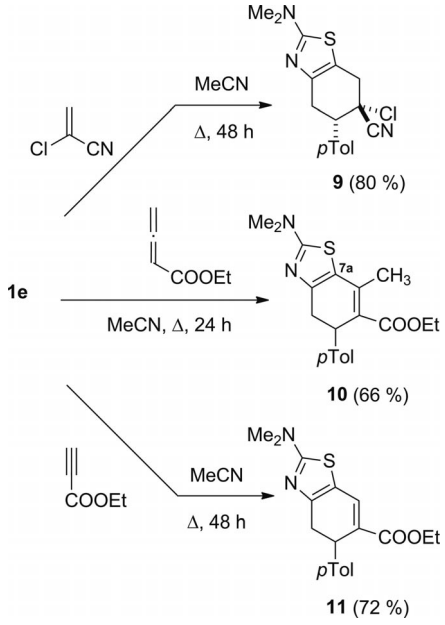
Scheme 7. Reaction of 4-alkenyl-2-(methylamino)thiazole **1c** with methyl acrylate. Diastereomeric ratio determined by analysis of characteristic signals in the ^{1}H NMR spectrum of the crude product (error ± 5% of the stated value).



Scheme 8. Reaction of 4-alkenyl-2-(dimethylamino)thiazole **1e** with methyl acrylate. Diastereomeric ratio determined by analysis of characteristic signals in the ^{1}H NMR spectrum of the crude product (error ± 5% of the stated value).

and a single diastereoisomer was formed exclusively. Thiazole **1e** also reacted with allenyl and alkynyl dienophiles such as ethyl 2,3-butadienoate and ethyl propiolate to give ethyl 4,5-dihydrobenzothiazole-6-carboxylate derivatives **10** and **11** in good yields (Scheme 9).

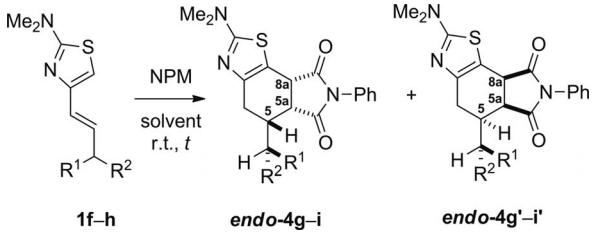
This study thus corroborates that the reactions of 4-alkenyl-2-aminothiazoles **1** with unsymmetrical dienophiles are regioselective. It must be also stressed that substrates **1** react with NPM, MA, dimethyl fumarate, dimethyl maleate, methyl acrylate, and other typical dienophiles with the exclusive participation of the side-chain double bond (extra-annular addition). Therefore, these reactions may be also described as site-selective.



Scheme 9. Reaction of 4-alkenyl-2-(dimethylamino)thiazole **1e** with α-chloroacrylonitrile, ethyl 2,3-butadienoate, and ethyl propiolate. The unequivocal assignment of **10** was established on the basis of a cross-peak between C-7a and the protons of the methyl group attached to the benzothiazole ring, observed in its 2D HMBC spectrum (see next section).

[4 + 2] Cycloadditions of Chiral 4-Alkenyl-2-aminothiazoles

The reactions of **1f**–**h**, which contain a chiral carbon atom in the 4-alkenyl side chain, with NPM were initially carried out in acetonitrile at room temperature (Scheme 10 and Table 6, entries 1–3). Under these conditions, tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-diones *endo*-**4g**–**i** and *endo*-**4g′**–**i′** were obtained as 50:50 mixtures of diastereomers. We were unable to separate these mixtures, except for *endo*-**4g** and *endo*-**4g′**, whose separation could be achieved by chromatographic techniques. The use of a less polar reaction solvent, such as toluene, resulted in a slight diastereomeric excess (Table 6, entry 4). The relative configuration of the chiral centres of the major diastereomer was not assigned, due to the low levels of diastereoselectivity (see below).



Scheme 10. Reactions of chiral 4-alkenyl-2-aminothiazoles **1f**–**h** with NPM (R^1 and R^2 defined in Table 6).

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Table 6. Reactions of chiral 4-alkenyl-2-aminothiazoles **1f**–**h** with NPM.

Entry	R^1	R^2	Solvent	*t* [h]	*endo*-**4**/*endo*-**4′**[a]		Yield [%]
1	Ph	Me	MeCN	72	50:50	**g**	80[b]
2	Et	Me	MeCN	16	50:50	**h**	80[c]
3	$CH_2OCH_2CH_2$	MeCN	48	50:50	**i**	99[c]	
4	Ph	Me	toluene	72	60:40[d]	**g**	–

[a] Determined by analysis of characteristic signals in the ^{1}H NMR spectrum of the crude product (error ± 5% of the stated value). [b] The diastereomeric mixture was separated and the two diastereomers were isolated in 42 and 38% yield. [c] Inseparable diastereomeric mixture. [d] The relative configurations of the major and minor diastereomers are unassigned.

Structural and Configurational Assignment

The relative configuration of *endo*-**4e** was unequivocally established by single-crystal X-ray analysis (see Supporting Information). The configurational assignment of compounds *endo*-**4a**–**d** and *endo*-**4f** was done by comparison of their ^{1}H NMR spectroscopic data with that of *endo*-**4e**. The coupling constants between protons 5-H/5a-H and 5a-H/8a-H were especially informative, being in the ranges 4.2–5.6 and 7.6–8.0 Hz, respectively. The overlapping of the resonances of protons 5-H, 5a-H, and 8a-H in the ^{1}H NMR spectra of *endo*-**4g**–**i** and *endo*-**4g′**–**i′** hampered an unambiguous assignment. Nevertheless, bearing in mind that reactions of achiral **1a**–**e** with NPM were completely *endo*-selective, the mixtures of diastereomers obtained in the reactions of **1f**–**h** with NPM, namely *endo*-**4g**–**i** and *endo*-**4g′**–**i′**, were assigned to result from an *endo* approach of the dienophile to the two diastereotopic faces of the diene.

The relative stereochemistry of **7**, **7′**, and **7′′** was established on the basis of the values of the coupling constants between the protons of the six-membered ring, and of significant cross-peaks in their respective ^{1}H,^{1}H-NOESY spectra (Figure 3). We worked on the basis that cycloadducts **7**, **7′**, and **7′′** would, in solution, have the half-chair conformation shown in Figure 3.[7d] The most significant coupling constants for these assignments are those between protons 6-H/5-H and 6-H/7-H. For stereoisomers **7**, the coupling constants between these pairs of protons have values in the ranges 11.3–11.4 and 9.3–9.9 Hz, respectively, indicating that 5-H, 6-H, and 7-H adopt 1,2-transdiaxial arrangements.[7d] For cycloadducts **7′**, the coupling constants between 6-H/7-H are between 8.8 and 8.9 Hz, which is consistent with a relative *trans* arrangement, and the *J* values for the pairs of protons 5-H/6-H, 4-H/5-H, and 4'-H/5-H indicate a *cis* arrangement for 5-H and 6-H (Figure 3).[7d] Finally, all of the *J* values for the 5-H, 6-H, and 7-H protons in stereoisomers **7′′** are lower than 7 Hz, which indicates that they have relative 1,2-*cis* arrangements.[7d]

The most representative contacts shown in the ^{1}H,^{1}H-NOESY spectra of **7b**, **7d′**, and **7b′′** (Supporting Information) are also shown in Figure 3. The cross-peaks observed between the 5-H/7-H and 4′-H/6-H pairs of protons in the spectrum of **7b** are consistent with the assignment based on the coupling constants. Regarding **7d′**, the most relevant contacts are those shown between protons H_{ortho}/7-H and 4′-H/6-H, which suggest that 4′-H and 6-H adopt a 1,3-*cis* arrangement. Finally, the lack of a cross-peak between H_{ortho} and 7-H in the spectrum of **7b′′** is consistent with the relative configuration assigned with the aid of the coupling constants.

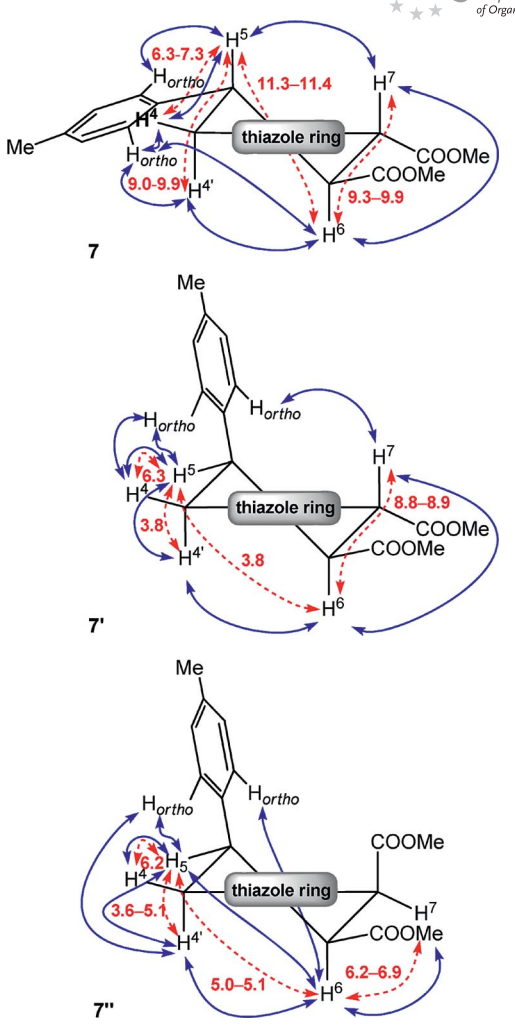

Figure 3. Significant coupling constants (red colour, dashed arrows [Hz]) and NOE effects (blue colour, solid arrows) for the assignment of the relative configuration of cycloadducts **7**, **7′**, and **7′′**.

Some of the resonances for the protons of the six-membered rings in the ^{1}H NMR spectra of the *endo*/*exo* structures of **8a**–**c** were partially overlapping, which hampered the unequivocal configurational assignment of these structures. Unfortunately, the NOESY spectrum of *endo*-**8a** did not reveal conclusive information. Nevertheless, their structures were tentatively attributed by comparison of selected coupling constants with those of **7**, **7′** and **7′′** (see Exp. Sect.).

The structures of regioisomers **9**, **10**, and **11** were unequivocally identified according to the pattern of coupling of the protons in the six-membered rings. It was not possible to determine the relative configuration of the two chiral centres in **9**. Nevertheless, on the basis of previous reports,[26] the relative configuration of **9** was tentatively assigned by considering a "chloro-*endo*" approach of the di-

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enophile. This assumption is supported by the fact that the resonances of the aromatic protons of the *p*-tolyl substituent at the 5-position of the benzothiazole ring are shifted by more than 0.2 ppm to higher frequencies in compound **9** compared to tetrahydrobenzothiazoles *endo*-**8**. This paramagnetic shift could be induced by the anisotropic effect of the nitrile functionality in the adjacent pseudoequatorial position (Figure 4).

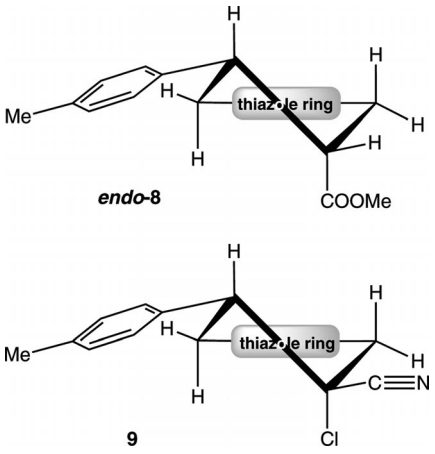


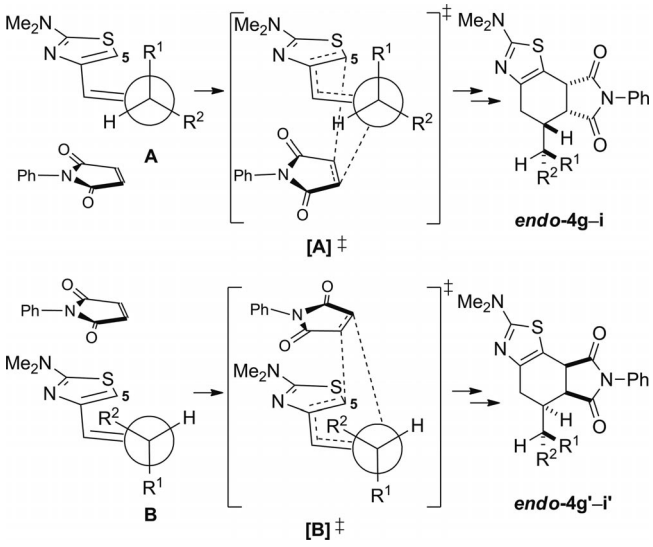
Figure 4. Proposed preferred conformations for compounds *endo*-**8** and **9** on the basis of their ^{1}H NMR spectroscopic data.

Finally, the structural determination of cycloadduct **10** was done taking into account the information contained in the 2D HMQC, 2D HMBC and ^{1}H,^{1}H-NOESY spectra. The appearance of a cross-peak relating the protons of the methyl group attached to the benzothiazole ring with C-7a in the 2D HMBC experiment was the key evidence in its unambiguous assignment (Scheme 9).

Proposed Mechanism for the [4 + 2] Cycloadditions of 4-Alkenyl-2-aminothiazoles 1a–h with Dienophiles

In a previous paper, we proposed that [4 + 2] cycloadditions of 4-alkenyl-2-methyl- and 4-alkenyl-2-phenylthiazoles with dienophiles is a concerted $HOMO_{diene}$–$LUMO_{dienophile}$-controlled process.[18] According to FMO theory, the presence of the amino group at C-2 of the thiazole ring in 4-alkenylthiazoles **1** should result in an increase in reactivity in normal-electron-demand Diels–Alder reactions.[24] In fact, computed HOMO values of representative 4-alkenyl-2-aminothiazoles **1i**–**m** are slightly higher than those of reported 4-alkenyl-2-methyl- and 4-alkenyl-2-phenylthiazoles. However, this slight increase does not reflect the dramatic enhancement of reactivity shown by dienes **1a**–**e** (Scheme 4). This experimental evidence reveals that factors other than the HOMO values, such as polar effects, may come into play.[27] As Domingo and co-workers stated, the feasibility of a Diels–Alder reaction is mainly related to the polar character of the process, described by the charge transfer at the corresponding TS.[21]

On the basis of the stereospecificity and high *endo* selectivity observed, we propose a concerted mechanism for the reactions of the 4-alkenyl-2-aminothiazoles **1a**–**e** with NPM and MA. Nevertheless, the transition states for these processes may be highly asynchronous, due to the unsymmetrical nature of the dienes.[21,28] Based on the electron-donating character of the amino group of the diene, formation of the C-5(thiazole ring)–C(NPM) bond should be more advanced in the putative transition state. This fact would explain the lack of π-facial diastereoselectivity observed in the reactions of thiazoles **1f**–**h** with NPM. In order to rationalize the observed results, we propose an *endo* approach of NPM to conformers **A** and **B** of **1f**–**h** (Scheme 11). In structures **A** and **B**, the largest group (R^1) would be located antiperiplanar to the approaching trajectory of the dienophile.[29] In principle, the transition state resulting from the approach of NPM to conformer **A** would be favoured, as the hydrogen atom is placed at the inside position, thus avoiding 1,3-allylic strain.[30] The lack of diastereoselectivity may be explained by considering the highly asynchronous nature of the transition states shown in Scheme 11. In these transition states, the bond forming adjacent to the stereogenic centre is longer, and so the influence of the chiral substituent would be minimal, thus it would be unable to induce facial differentiation.



Scheme 11. Suggested mechanism for the formation of cycloadducts *endo*-**4g**–**i** and *endo*-**4g′**–**i′** (R^1 and R^2 defined in Tables 2 and 6).

Several experimental observations indicate a change from a concerted cycloaddition process to a stepwise mechanism in the reactions of 4-alkenyl-2-aminothiazoles **1** with the acyclic dienophiles tested. That appropriate substitutents on the diene and the dienophile can favour the stabilization of charges of opposite signs and change the mechanism from concerted to stepwise is supported by previous work.[21,27–28,31] We propose the mechanism shown in Scheme 12 to explain the reactions of thiazoles **1** with acyclic dienophiles of generic structure X=Y. As we stated above, C-5 of the thiazole ring is activated by the presence of the amino group. The increase in electron density at this position is substantiated by the fact that the resonances of

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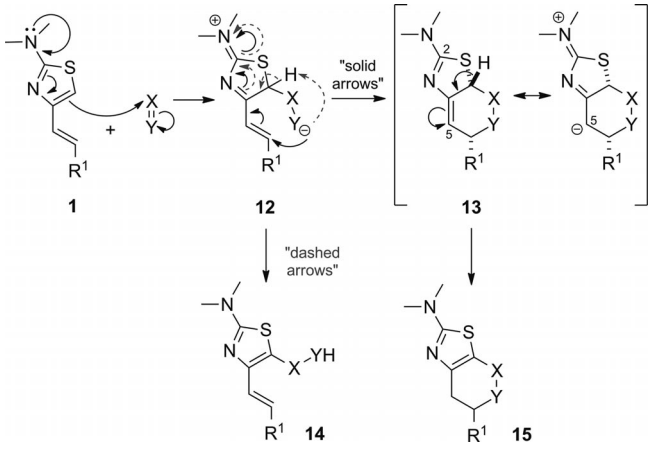
the C-5 protons are shifted to lower frequencies than those of unsubstituted thiazoles in their respective NMR spectra.[16b] The nucleophilic attack of C-5 of the thiazole, at the most electron-deficient position of the dienophile would give zwitterionic intermediate **12**. This process would be assisted by the lone pair of the amino group at C-2. The low reactivity shown by thiazole **1b** in its reactions with DMMa and DMFu (see above) supports the important role of this electron pair, which in compound **1b** is partially delocalized over the phenyl group attached to the amino functionality.

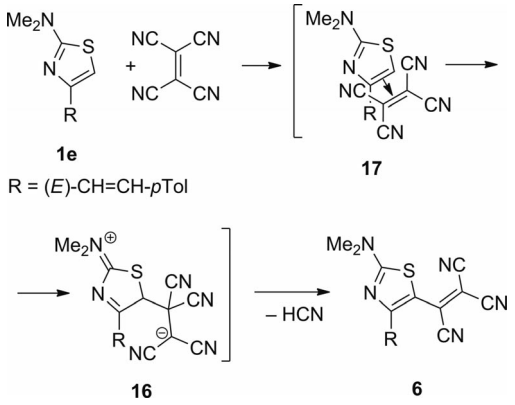


Scheme 12. General mechanism for the reactions of 4-alkenyl-2-aminothiazoles **1** with acyclic dienophiles.

The zwitterionic intermediate (i.e., **12**) may react further by either of two alternative routes depending on the nature of the dienophile (Scheme 12). The cyclization of **12** would lead to the formal [4 + 2] cycloadduct (i.e., **13**). A consecutive 1,3-hydrogen migration, favoured by the rearomatization of the thiazole ring, would give the final cyclic product (i.e., **15**). The 1,3-hydrogen shift may be intermolecular, since a concerted reaction is expected to have a very high activation barrier.[32] This migration step,[33] which may have a polar character, would also be favoured by the presence of the amino functionality at C-2. We propose that the hydrogen atom migrates with a positive charge density. The negative charge generated at the carbon atom to which it was initially bonded would be stabilized by the adjacent sulfur atom.[34] Moreover, the lone pair of the exocyclic nitrogen would be delocalized over the unsaturated fragment of the bicyclic structure in **13**, so increasing the basic character of C-5 (see structure **13** in Scheme 12) and facilitating the migration of the hydrogen atom as a proton. Alternatively, **12** would experience a 1,3-hydrogen migration leading to the corresponding addition product (i.e., **14**). The following findings support the proposal of a stepwise [4 + 2] cycloaddition for this group of reactions.

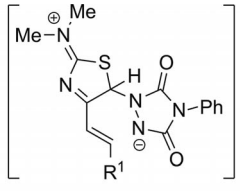
1) Chemoselectivity

In the tricyanovinylation reaction of **1e**, the formation of zwitterionic intermediate **16** would presumably be preceded by a charge-transfer π complex **17** (Scheme 13).[14a] Intermediate **16** would gain extra stabilization arising from the two electron-withdrawing nitrile groups. Following the 1,3-hydrogen migration, intermediate **16** would eliminate a molecule of hydrogen cyanide. Previous reports have shown that other 2-aminothiazoles react easily with TCNE to give analogous products.[14a] In a more general sense, dienes with substituents that are able to stabilize zwitterionic intermediates usually react with TCNE to give the corresponding addition products, followed by β-elimination of hydrogen cyanide.[35]



Scheme 13. Proposed mechanism for the formation of compound **6**.

In contrast to the other cyclic dienophiles tested, PTAD reacted with **1e** to give the corresponding addition product (i.e., **5**). This change in the course of the reaction may be explained by taking into account the stabilization of zwitterionic intermediate **18** by delocalization of the negative charge into the urea fragment. This extra stabilization would increase the lifetime of **18**, favouring the 1,3-hydrogen migration to the nitrogen atom.[14a]



2) Stereospecificity and endolexo Stereoselectivity

It is commonly accepted that in most Diels–Alder reactions, the two new σ-bonds are formed in a concerted, although not necessarily synchronous, manner. This requires the diene to adopt an *s-cis* conformation. Consistent with this mode of addition, Diels–Alder reactions are generally stereospecific, i.e. the configurations of both diene and dienophile components are "retained" in the adduct.[1]

The most revealing facts about stereochemical aspects of the [4 + 2] cycloaddition processes of thiazoles **1**, in terms of elucidation of the mechanism, come from their reactions with DMMa (Scheme 6 and Table 5). In a concerted process, the reactions of thiazoles **1** with DMMa should be stereospecific and lead to tetrahydrobenzothiazoles **7′′** (*endo* attack) and/or **7′′′** (*exo* attack) shown in Figure 5. However, besides diastereoisomer **7′′**, which retains the *cis*

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arrangement of the two carboxylate groups, diastereoisomers **7** and **7′** were isolated, in which these two substituents have a *trans* arrangement (Table 5). The lack of stereospecificity in the reactions with DMMa shows that the cycloaddition must be a stepwise process, with the configurational stability of the chiral carbanion in the corresponding intermediate (i.e., **12**) (Scheme 12) being diminished under the harsh reaction conditions.

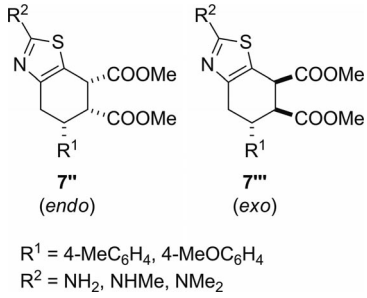
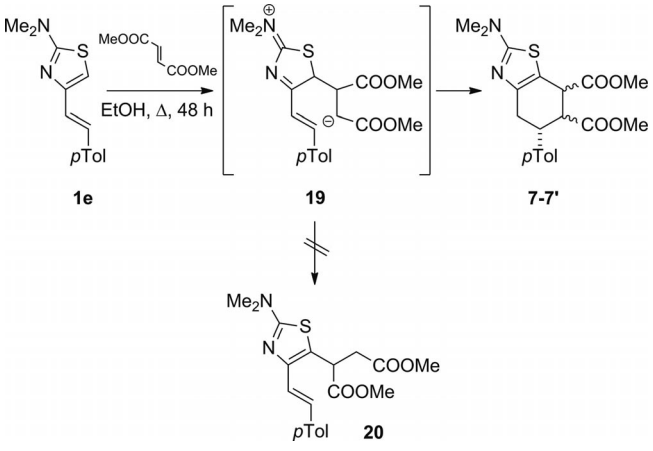


Figure 5. Expected cycloadducts (**7′′** and **7′′′**) for a concerted [4+2] cycloaddition of 4-alkenyl-2-aminothiazoles **1** with DMMa.

The possibility of the isomerization of DMMa to give DMFu under the reaction conditions can be discounted, bearing in mind the different results obtained in the reactions of **1b** and **1d** with DMMa and DMFu. The reactions of **1b** and **1d** with DMMa led to mixtures of **7**, **7′**, and **7′′**, whereas those with DMFu gave mixtures of **7** and **7′** only (compare entries 2 and 4 with entries 5 and 6 in Table 5). As expectedly the ^{1}H NMR spectrum of a sample of DMMa heated in refluxing acetonitrile for 48 h showed the total absence of DMFu.

The reaction of **1e** with DMFu was also carried out in a protic solvent in an attempt to trap putative zwitterionic intermediate **19** (Scheme 14).[36] However, we observed the exclusive formation of cycloadducts **7** and **7′**, suggesting that the lifetime of zwitterionic intermediate **19** is rather short, and that the intramolecular cyclization takes place before the intermolecular 1,3-hydrogen migration occurs.



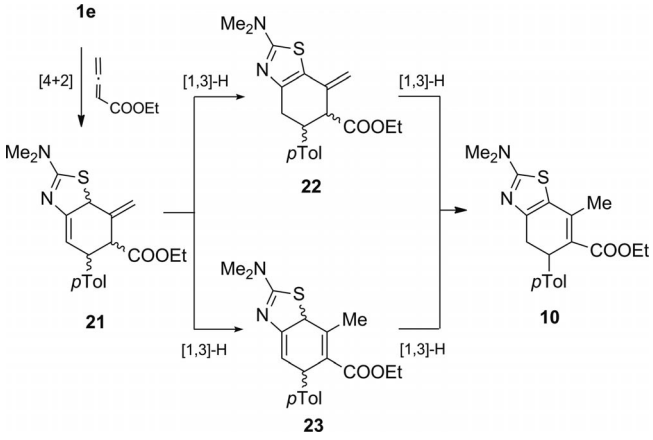
Scheme 14. Reaction of **1e** with dimethyl fumarate in ethanol as solvent, and structure of putative zwitterionic intermediate **19**.

The isolation of diastereomeric mixtures of compounds **8a**–**c**, which were assigned as *endo*-**8a**–**c** and *exo*-**8a**–**c**, is also consistent with the involvement of zwitterionic species of general structure **12** (Scheme 12). Surprisingly, the formation of cycloadduct **9** from α-chloroacrylonitrile was completely diastereoselective. Probably, steric hindrance in the ionic intermediate makes rotation about single bonds slower than ring closure, and the initial relative configuration is preserved.[1b]

3) Regioselectivity

The proposed stepwise mechanism is also consistent with the regioselectivity observed in the reactions of thiazole **1e** with methyl acrylate, α-chloroacrylonitrile, ethyl 2,3-butadienoate, and ethyl propiolate. The structures of the resulting cycloadducts (i.e., **8**–**11**) would be the result of the nucleophilic attack of C-5 of thiazole **1e** at the most electron-deficient position of the dienophile. Therefore, the regioselectivity is fully controlled by the resonance effect of the amino group at C-2.

The formation of ethyl 4,5-dihydrobenzothiazole-6-carboxylate **10** may be explained by the reaction of **1e** with the more electron-deficient double bond of the allene, i.e. the C-2=C-3 bond, to give [4+2] cycloaddition product **21**, followed by two consecutive 1,3-hydrogen migrations via intermediates **22** or **23** (Scheme 15). The isomerization of an exocyclic double bond to an endocyclic one (transformations **21**→**23** and **22**→**10**) has previously been observed in cycloadducts resulting from the Diels–Alder reactions of 2,3-butadienoates with other dienes.[37]



Scheme 15. Alternative sequence of steps for the formation of **10** via intermediates **21**–**23**.

Conclusions

We have demonstrated that 4-alkenyl-2-aminothiazoles **1** can be prepared in an efficient manner, and they behave as effective dienes in [4+2] cycloadditions. The reactions of **1** with classical electron-poor dienophiles, except for PTAD and TCNE, are site-selective, since only the diene moiety that comprises the formal ring C=C and the side-chain double bond is involved (extra-annular addition). The iso-

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lated compounds are the result of a [4+2] cycloaddition followed by a 1,3-hydrogen migration. The reactions with PTAD and TCNE lead to addition products instead of the corresponding [4+2] cycloadducts. The reactions with cyclic dienes such as NPM or MA are stereoselective, providing a single diastereoisomer derived from an *endo* transition state. In this case, a concerted but highly asynchronous mechanism is proposed.

Acyclic dienophiles such as DMMa and DMFu also react, but require considerably more forcing reaction conditions. These processes are not stereospecific. The reactions with unsymmetrical dienophiles such as methyl acrylate, α-chloroacrylonitrile, ethyl 2,3-butadienoate, and ethyl propiolate are highly regioselective, the exclusive regioisomer being the result of the nucleophilic addition of C-5 of the thiazole to the most electron-deficient position of the dienophile. All the data compiled for the reactions with acyclic dienophiles suggest a stepwise mechanism for the [4+2] cycloaddition step, with zwitterionic species as the most plausible intermediates. Presumably, the resonance effect of the amino group at C-2 of the thiazole ring is a key controlling element for the reactivity and regioselectivity of this type of cycloaddition.

The reactions of 4-alkenyl-2-aminothiazoles **1** with dienophiles described here open up a new route to complex polycyclic thiazole derivatives that are not easily accessible by other methods.

Experimental Section

General Remarks: IR spectra were recorded neat or as nujol emulsions. ^{1}H NMR spectra were recorded at 300, 401, or 600 MHz. ^{13}C NMR spectra were recorded at 50, 75, or 101 MHz. Chemical shifts are expressed in ppm, using TMS at δ = 0.00 ppm as an internal reference for ^{1}H spectra, and $CDCl_3$ at δ = 77.1 ppm for ^{13}C spectra. Mass spectra were recorded using EI (70 eV) or FAB$^+$ (using 3-nitrobenzyl alcohol as matrix) ionization modes.

Synthesis of 4-Alkenyl-2-aminothiazoles 1a–h: Thiazoles **1a**–**b**[16b] and **1e**[16b] are known compounds, and they were prepared following methods previously described in the literature. The general procedure for the synthesis of thiazoles **1c**–**d** and **1f**–**h** and their structural characterization have been included in the Supporting Information.

Synthesis of α-Chloro Ketones 2a–e: α-Chloro ketones **2a**–**b**,[18] **2c**,[19] and **2e**[19] are known compounds, and they were prepared following methods previously described in the literature. The general procedure for the synthesis of the α-chloro ketone **2d** and its structural characterization have been included in the Supporting Information.

Synthesis of Thioureas 3: Thioureas **3a**–**c** are commercially available. *N*,*N*-Dimethylthiourea **3d** was prepared following a previously reported method.[16b]

General Procedure for the Synthesis of *endo*-4: A solution of the corresponding 4-alkenyl-2-aminothiazole (**1**; 0.75 mmol) and *N*-phenylmaleimide (0.39 g, 2.25 mmol) in acetonitrile (10 mL) was stirred at room temperature for 48 h. The isolation and purification is described in each case.

(5*R,5a*R**,8a*S**)-2-Amino-5-(4-methylphenyl)-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4a):** The product precipitated from the reaction mixture, and it was filtered and dried under vacuum. The mother liquors were evaporated under vacuum and further product was precipitated by addition of Et_2O. R_f = 0.17 (2:1 EtOAc/*n*-hexane), yield 90% (0.263 g), m.p. 249–251 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3450, 3270, 1778, 1712, 1630, 1589, 1519, 1313, 1286, 1216, 1191, 1157, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.30 (s, 3 H, C_6H_4*Me*), 3.08 (dd, *J* = 5.8, *J* = 1.6 Hz, 2 H, 4-H, 4′-H), 3.70 (q, *J* = 5.6 Hz, 1 H, 5-H), 3.79 (dd, *J* = 8.0, *J* = 5.4 Hz, 1 H, 5a-H), 4.21 (dt, *J* = 8.0, *J* = 1.6 Hz, 1 H, 8a-H), 5.02 (br. s, 2 H, NH_2), 6.73–6.75 (m, 2 H), 7.07 (d, *J* = 8.2 Hz, 2 H), 7.12 (d, *J* = 8.2 Hz, 2 H), 7.27–7.32 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 20.9 (q, C_6H_4*Me*), 29.7 (t, C-4), 39.4 (d, C-5), 41.3 (d, C-8a), 46.0 (d, C-5a), 110.9 (s, C-8b), 126.3 (2 d), 128.3 (2 d), 128.5 (d), 128.9 (2 d), 129.2 (2 d), 131.2 (s), 136.9 (s), 137.1 (s), 147.6 (s, C-3a), 167.9 (s, C-2), 174.4 (s, CO), 175.4 (s, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 390 (25) [M + 1]$^+$, 389 (100) [M]$^+$, 284 (33), 242 (72), 241 (42), 209 (22), 183 (25), 151 (31), 137 (40), 119 (26), 91 (37). $C_{22}H_{19}N_3O_2S$ (389.47): calcd. C 67.84, H 4.92, N 10.79, S 8.23; found C 67.77, H 5.02, N 10.93, S 8.19.

(5*R,5a*R**,8a*S**)-5-(4-Methylphenyl)-7-phenyl-2-(phenylamino)-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4b):** The solvent was evaporated to dryness and the residue was purified by silica gel chromatography eluting with 1:2 EtOAc/*n*-hexane (R_f = 0.29), yield 90% (0.314 g), m.p. 240–241 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3360, 1782, 1698, 1603, 1544, 1526, 1496, 1196, 1181, 744 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.29 (s, 3 H, C_6H_4*Me*), 3.14 (dd, *J* = 5.8, *J* = 1.6 Hz, 2 H, 4-H + 4′-H), 3.71 (q, *J* = 5.6 Hz, 1 H, 5-H), 3.79 (dd, *J* = 8.0, *J* = 5.4 Hz, 1 H, 5a-H), 4.23 (dt, *J* = 8.0, *J* = 1.6 Hz, 1 H, 8a-H), 6.75–6.78 (m, 2 H), 7.05–7-12 (m, 5 H), 7.25–7.37 (m, 7 H), 7.47 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 20.9 (q, C_6H_4*Me*), 30.0 (t, C-4), 39.7 (d, C-5), 41.4 (d, C-8a), 46.1 (d, C-5a), 110.1 (s, C-8b), 118.8 (2 d), 123.5 (d), 126.3 (2 d), 128.4 (2 d), 128.5 (d), 128.8 (2 d), 129.3 (2 d), 129.6 (2 d), 131.5 (s), 137.0 (s), 137.1 (s), 140.1 (s), 147.9 (s, C-3a), 165.6 (s, C-2), 174.3 (s, CO), 175.3 (s, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 466 (32) [M + 1]$^+$, 465 (100) [M]$^+$, 318 (39), 317 (29), 315 (20), 213 (37), 119 (25), 91 (36), 77 (43). $C_{28}H_{23}N_3O_2S$ (465.57): calcd. C 72.23, H 4.98, N 9.03, S 6.89; found C 72.01, H 5.13, N 8.94, S 6.90.

(5*R,5a*R**,8a*S**)-2-(Methylamino)-5-(4-methylphenyl)-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4c):** The product precipitated from the reaction mixture, and it was filtered and dried under vacuum. The mother liquors were evaporated, and further product was precipitated by the addition of acetonitrile. R_f = 0.50 (EtOAc), yield 91% (0.275 g), m.p. 223–225 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3209, 3113, 1716, 1597, 1499, 1413, 1156, 1130, 757, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300.10 MHz): δ = 2.30 (s, 3 H, C_6H_4*Me*), 3.00 (s, 3 H, NH*Me*), 3.07 (dd, *J* = 6.0, *J* = 1.6 Hz, 2 H, 4-H + 4′-H), 3.68 (q, *J* = 5.7 Hz, 1 H, 5-H), 3.78 (dd, *J* = 8.0, *J* = 5.4 Hz, 1 H, 5a-H), 4.22 (dt, *J* = 8.0, *J* = 1.6 Hz, 1 H, 8a-H), 5.72 (br. s, 1 H, NH), 6.75–6.78 (m, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.26–7.35 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 20.9 (q, C_6H_4*Me*), 29.7 (t, C-4), 32.1 (q, NH*Me*), 39.4 (d, C-5), 41.4 (d, C-8a), 46.1 (d, C-5a), 108.4 (s, C-8b), 126.3 (2 d), 128.3 (2 d), 128.5 (d), 128.8 (2 d), 129.2 (2 d), 131.3 (s), 136.96 (s), 137.03 (s), 147.9 (s, C-3a), 171.3 (s, C-2), 174.6 (s, CO), 175.5 (s, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 404 (20) [M + 1]$^+$, 403 (100) [M]$^+$, 256 (43), 255 (26), 165 (32), 151 (43), 91 (25). $C_{23}H_{21}N_3O_2S$ (403.50): calcd. C 68.46, H 5.25, N 10.41, S 7.95; found C 68.11, H 5.37, N 10.52, S 8.09.

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(5*R,5a*R**,8a*S**)-2-(Methylamino)-5-(4-methoxyphenyl)-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4d):** The solvent was evaporated to dryness, and the residue was crystallized from 1:1 CH_2Cl_2/Et_2O. R_f = 0.10 (2:1 EtOAc/*n*-hexane), yield 90% (0.283 g), m.p. 229–231 °C (colourless needles, $CHCl_3$/Et_2O). IR (nujol): $\tilde{\nu}$ = 3211, 3110, 1711, 1594, 1514, 1256, 1181 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.99 (s, 3 H, NH*Me*), 3.05–3.08 (m, 2 H, 4-H + 4′-H), 3.70 (q, *J* = 5.6 Hz, 1 H, 5-H), 3.74–3.78 (m, 4 H, C_6H_4OMe + 5a-H), 4.22 (dt, *J* = 7.9, *J* = 1.4 Hz, 1 H, 8a-H), 5.81 (br. s, 1 H, NH), 6.77–6.81 (m, 4 H), 7.15 (d, *J* = 8.7 Hz, 2 H), 7.27–7.34 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 30.0 (t, C-4), 32.0 (q, NH*Me*), 39.1 (d, C-5), 41.2 (d, C-8a), 46.1 (d, C-5a), 55.2 (q, C_6H_4OMe), 108.3 (s, C-8b), 113.9 (2 d), 126.3 (2 d), 128.5 (d), 128.9 (2 d), 129.5 (2 d), 131.3 (s), 132.1 (s), 147.9 (s, C-3a), 158.8 (s), 171.4 (s, C-2), 174.6 (s, CO), 175.6 (s, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 420 (28) $[M + 1]^+$, 419 (100) $[M]^+$, 272 (37), 271 (25), 246 (24), 121 (45), 119 (20), 91 (21). $C_{23}H_{21}N_3O_3S$ (419.50): calcd. C 65.85, H 5.05, N 10.02, S 7.64; found C 65.54, H 5.17, N 10.23, S 7.60.

(5*R,5a*R**,8a*S**)-2-Dimethylamino-5-(4-methylphenyl)-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4e):** The product precipitated from the reaction mixture, and it was filtered and dried under vacuum. The mother liquors were evaporated to dryness, and further product was precipitated by the addition of acetonitrile. R_f = 0.10 (1:1 EtOAc/*n*-hexane), yield 91% (0.285 g), m.p. 231–233 °C (colourless needles, $CHCl_3$/Et_2O). IR (nujol): $\tilde{\nu}$ = 1722, 1553, 1499, 1425, 1339, 1178, 822, 751, 690 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.30 (s, 3 H, C_6H_4Me), 3.09–3.17 (m, 8 H, NMe_2 + 4-H + 4′-H), 3.66 (q, *J* = 5.6 Hz, 1 H, 5-H), 3.76 (dd, *J* = 7.9, *J* = 5.2 Hz, 1 H, 5a-H), 4.22 (d, *J* = 7.9 Hz, 1 H, 8a-H), 6.77–6.80 (m, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.25–7.32 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 20.9 (q, C_6H_4Me), 29.7 (t, C-4), 39.4 (d, C-5), 40.1 (2 q, NMe_2), 41.5 (d, C-8a), 46.0 (d, C-5a), 108.3 (s, C-8b), 126.3 (2 d), 128.2 (2 d), 128.4 (d), 128.7 (2 d), 129.1 (2 d), 131.3 (s), 136.8 (s), 137.2 (s), 148.7 (s, C-3a), 171.2 (s, C-2), 174.7 (s, CO), 175.5 (s, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 418 (26) $[M + 1]^+$, 417 (100) $[M]^+$, 270 (38), 269 (29), 179 (21), 165 (36), 119 (20), 91 (29). $C_{24}H_{23}N_3O_2S$ (417.51): calcd. C 69.04, H 5.55, N 10.06, S 7.68; found C 68.87, H 5.59, N 10.34, S 7.58.

(5*R,5a*S**,8a*R**)-2-Dimethylamino-7-phenyl-5-[(1*R**)-1-phenylethyl]-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4 g) or (5*R**,5a*S**,8a*R**)-2-Dimethylamino-7-phenyl-5-[(1*S**)-1-phenylethyl]-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4g′):** The solvent was evaporated to dryness, and the residue was purified by silica gel chromatography eluting with 1:2 EtOAc/*n*-hexane (R_f = 0.20), yield 42% (0.136 g), m.p. 214–216 °C (colourless needles, $CHCl_3$/*n*-hexane). IR (nujol): $\tilde{\nu}$ = 1708, 1553, 1444, 1190, 1133, 757, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 1.49 (d, *J* = 6.9 Hz, 3 H), 2.18–2.34 (m, 2 H), 3.41 (br. dd, *J* = 16.2, *J* = 4.2 Hz, 1 H), 3.01 (s, 6 H), 3.68 (dq, *J* = 10.6, *J* = 6.9 Hz, 1 H), 3.89 (ddd, *J* = 7.7, *J* = 4.2, *J* = 0.8 Hz, 1 H), 4.21 (dm, *J* = 7.7 Hz, 1 H), 7.17–7.30 (m, 7 H), 7.34–7.38 (m, 1 H), 7.41–7.46 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 20.5 (q), 29.0 (t), 40.1 (2 q), 41.4 (d), 41.6 (d), 41.9 (d), 42.9 (d), 109.0 (s), 126.3 (2 d), 126.4 (d), 127.4 (2 d), 128.4 (d), 128.7 (2 d), 129.0 (2 d), 131.6 (s), 146.0 (s), 149.7 (s), 170.8 (s), 175.5 (s), 175.9 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 431 (100) $[M]^+$, 258 (41), 179 (71), 164 (36), 136 (34), 109 (40), 105 (57), 88 (31), 77 (37). $C_{25}H_{25}N_3O_2S$ (431.55): calcd. C 69.58, H 5.84, N 9.74, S 7.43; found C 69.42, H 5.90, N 9.79, S 7.32.

(5*R,5a*S**,8a*R**)-2-Dimethylamino-7-phenyl-5-[(1*R**)-1-phenylethyl]-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4g′) or (5*R**,5a*S**,8a*R**)-2-Dimethylamino-7-phenyl-5-[(1*S**)-1-phenylethyl]-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4g′′):** The solvent was evaporated to dryness, and the residue was purified by silica gel chromatography eluting with 1:2 EtOAc/*n*-hexane (R_f = 0.17), yield 38% (0.123 g), m.p. 183–185 °C (colourless needles, $CHCl_3$/*n*-hexane). IR (nujol): $\tilde{\nu}$ = 1714, 1556, 1494, 1282, 1220, 1190, 1026, 878, 816, 758, 729, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 1.36 (d, *J* = 6.9 Hz, 3 H), 2.18–2.27 (m, 1 H), 2.55 (ddd, *J* = 14.9, *J* = 12.2, *J* = 2.6 Hz, 1 H), 3.05–3.17 (m, 8 H), 3.80 (dq, *J* = 11.3, *J* = 6.9 Hz, 1 H), 3.91 (dm, *J* = 7.6 Hz, 1 H), 7.14–7.17 (m, 2 H), 7.20–7.25 (m, 1 H), 7.29–7.41 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 20.9 (q), 28.0 (t), 40.0 (2 q), 40.3 (d), 42.1 (d), 42.2 (d), 42.7 (d), 109.7 (s), 126.3 (2 d), 126.4 (d), 127.4 (2 d), 128.3 (d), 128.7 (2 d), 128.8 (2 d), 131.5 (s), 146.2 (s), 149.2 (s), 170.9 (s), 175.3 (s), 175.8 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 432 (48) $[M + 1]^+$, 431 (100) $[M]^+$, 258 (42), 257 (41), 205 (25), 179 (97), 164 (32), 136 (35), 109 (37), 105 (67), 88 (30), 77 (31). $C_{25}H_{25}N_3O_2S$ (431.55): calcd. C 69.58, H 5.84, N 9.74, S 7.43; found C 69.47, H 5.96, N 9.64, S 7.72.

(5*R,5a*S**,8a*R**)-5-[(2*S**)-2-Butyl]-2-dimethylamino-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione and (5*R**,5a*S**,8a*R**)-5-[(2*R**)-2-butyl]-2-dimethylamino-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4h and *endo*-4h′):** The solvent was evaporated to dryness, and the residue was purified by silica gel chromatography eluting with 1:2 EtOAc/*n*-hexane (R_f = 0.17) to give a 50:50 mixture of diastereomers, yield 80% (0.230 g), m.p. 154–156 °C (colourless needles, $CHCl_3$/Et_2O). IR (nujol): $\tilde{\nu}$ = 1705, 1545, 1498, 1417, 1196, 1132, 763, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 0.89–0.97 (m, 6 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.12 (d, *J* = 6.7 Hz, 3 H), 1.23–1.38 (m, 2 H), 1.67–1.85 (m, 4 H), 2.34–2.45 (m, 4 H), 2.95–3.02 (m, 2 H), 3.08 (s, 12 H), 3.69–3.75 (m, 2 H), 4.12–4.14 (m, 2 H), 7.20–7.22 (m, 4 H), 7.31–7.36 (m, 2 H), 7.39–7.43 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 10.0 (q), 10.3 (q), 17.1 (q), 17.2 (q), 26.65 (t), 26.70 (t), 28.2 (t), 28.4 (t), 34.3 (d), 34.5 (d), 39.9 (d), 40.0 (d), 40.1 (4 q), 41.7 (d), 42.0 (d), 42.9 (d), 43.0 (d), 109.26 (s), 109.31 (s), 126.3 (2 d), 126.4 (2 d), 128.32 (d), 128.34 (d), 128.88 (2 d), 128.90 (2 d), 131.6 (2 s), 149.7 (s), 149.8 (s), 170.9 (2 s), 175.6 (s), 175.7 (s), 175.91 (s), 175.92 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 384 (56) $[M + 1]^+$, 383 (93) $[M]^+$, 326 (86), 195 (47), 179 (100), 142 (48), 136 (45), 109 (47). $C_{21}H_{25}N_3O_2S$ (383.51): calcd. C 65.77, H 6.57, N 10.96, S 8.36; found C 65.43, H 6.73, N 11.23, S 8.40.

(5*R,5a*S**,8a*R**)-2-Dimethylamino-5-[(3*R**)-3-oxolanyl]-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione and (5*R**,5a*S**,8a*R**)-2-dimethylamino-5-[(3*S**)-3-oxolanyl]-7-phenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-4i and *endo*-4i′):** The solvent was evaporated to dryness, and the residue was purified by silica gel chromatography eluting with 3:1 EtOAc/*n*-hexane (R_f = 0.17) to give a 50:50 mixture of diastereomers, yield 99% (0.295 g), m.p. 224–226 °C (colourless needles, $CHCl_3$/Et_2O). IR (nujol): $\tilde{\nu}$ = 1710, 1549, 1493, 1415, 1195, 1133, 1053, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 1.53–1.73 (m, 2 H), 1.94–2.02 (m, 2 H), 2.17–2.25 (m, 1 H), 2.31–2.38 (m, 1 H), 2.47–2.56 (m, 2 H), 2.69 (br. dd, *J* = 16.4, *J* = 4.5 Hz, 1 H), 2.90 (br. dd, *J* = 16.5, *J* = 4.4 Hz, 1 H), 3.07 (s, 6 H), 3.08 (s, 6 H), 3.18–3.25 (m, 2 H), 3.36–3.42 (m, 2 H), 3.56–3.60 (m, 2 H), 3.79–3.87 (m, 2 H), 3.92–3.99 (m, 2 H), 4.09–4.19 (m, 3 H), 4.23 (t, *J* = 7.7 Hz, 1 H), 7.19 (m, 4 H), 7.32–7.37 (m, 2 H), 7.39–7.45 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 29.4 (t), 29.6 (t), 31.4 (t), 32.3 (t), 39.0 (d), 39.1 (d), 40.05 (2 q), 40.07 (2 q), 41.2 (d), 41.4 (d), 42.38 (d), 42.42 (d), 43.1 (d), 43.2 (d), 68.3 (t), 68.4 (t), 72.0 (t), 73.0 (t), 109.0 (s), 109.1 (s), 126.3 (4 d), 128.5 (2 d),

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129.0 (4 d), 131.5 (2 s), 148.6 (s), 148.8 (s), 170.9 (2 s), 175.1 (s), 175.2 (s), 175.6 (s), 175.7 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 398 (25) [M + 1]$^+$, 397 (87) [M]$^+$, 327 (32), 326 (87), 205 (47), 179 (100). $C_{21}H_{23}N_3O_3S$ (397.50): calcd. C 63.45, H 5.83, N 10.57, S 8.07; found C 63.23, H 6.00, N 10.72, S 7.99.

(5*R,5a*R**,8a*S**)-2-Dimethylamino-5-(4-methylphenyl)-4,5,5a,8a-tetrahydrofuro[3,4-*g*]benzothiazole-6,8-dione (*endo*-4f):** Maleic anhydride (0.04 g, 0.41 mmol) was added to a solution of 4-alkenyl-2-dimethylaminothiazole **1e** (0.10 g, 0.41 mmol) in dry acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated to dryness, and the product was precipitated with dry Et_2O, yield 72% (0.101 g), m.p. 150–152 °C (colourless prisms, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1779, 1716, 1627, 1574, 1227 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300.10 MHz): δ = 2.32 (s, 3 H, C_6H_4*Me*), 3.01–3.08 (m, 8 H, NMe_2 + 4-H + 4′-H), 3.39–3.46 (m, 1 H, 5-H), 3.83 (dd, *J* = 8.1, *J* = 4.2 Hz, 1 H, 5a-H), 4.31 (dt, *J* = 8.1, *J* = 1.8 Hz, 1 H, 8a-H), 7.14 (d, *J* = 8.1 Hz, 2 H), 7.20 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 20.7 (q, C_6H_4*Me*), 28.1 (t), 37.7 (d), 39.9 (2 q), 42.3 (d), 46.7 (d), 106.0 (s, C-8b), 127.4 (2 d), 129.1 (2 d), 135.7 (s), 136.8 (s), 149.4 (s, C-3a), 169.3 (s), 169.5 (s), 171.0 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 341 (28) [M + 1]$^+$, 342 (91) [M]$^+$, 271 (47), 270 (100), 269 (100), 237 (33), 184 (33), 179 (74), 165 (100). $C_{18}H_{18}N_2O_3S$ (342.41): calcd. C 63.14, H 5.30, N 8.18, S 9.36; found C 62.88, H 5.42, N 8.10, S 9.52.

1-{2-Dimethylamino-4-[(*E*)-2-(4-methylphenyl)ethenyl]thiazol-5-yl}-4-phenyl-1,2,4-triazolidin-3,5-dione (5): PTAD (0.07 g, 0.41 mmol) was added to a solution of 4-alkenyl-2-dimethylaminothiazole **1e** (0.10 g, 0.41 mmol) in toluene (5 mL). After 5 min of stirring at room temperature, the solvent was evaporated to dryness, and the product was purified by silica gel chromatography eluting with 1:1 EtOAc/*n*-hexane (R_f = 0.29), yield 72% (0.123 g), m.p. 173–175 °C (colourless prisms, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1762, 1695, 1555, 1142, 800, 721 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.36 (s, 3 H), 3.14 (s, 6 H), 6.80 (d, *J* = 15.8 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.36–7.49 (m, 6 H), 7.53–7.56 (m, 2 H), 8.50 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.3 (q), 39.8 (2 q), 114.0 (s), 116.1 (d), 125.5 (2 d), 127.1 (2 d), 128.4 (d), 129.2 (2 d), 129.4 (2 d), 131.1 (s), 133.8 (s), 134.0 (d), 138.4 (s), 151.1 (s), 151.8 (s), 152.4 (s), 168.7 (s) ppm. MS (FAB$^+$): *m*/*z* (%) = 838 (36) [2M]$^+$, 420 (74) [M + 1]$^+$, 419 (100) [M]$^+$. $C_{22}H_{21}N_5O_2S$ (419.50): calcd. C 62.99, H 5.05, N 16.69, S 7.64; found C 62.72, H 5.17, N 16.72, S 7.88.

2-Dimethylamino-5-(1,2,2-tricyanoethenyl)-4-[(*E*)-2-(4-methylphenyl)ethenyl]thiazole (6): TCNE (0.06 g, 0.50 mmol) was added to a solution of 4-alkenyl-2-dimethylaminothiazole **1e** (0.12 g, 0.50 mmol) in chloroform (5 mL). After 2 h of stirring at room temperature, the solvent was evaporated to dryness, and the product was purified by silica gel chromatography eluting with 1:1 EtOAc/*n*-hexane (R_f = 0.30), yield 43% (0.074 g), m.p. 218–220 °C (red needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 2207, 1594, 1355, 1307, 1263, 808 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300.10 MHz): δ = 2.39 (s, 3 H), 3.26 (br. s, 3 H), 3.47 (br. s, 3 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.88–7.99 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 21.6 (q), 40.0 (q), 40.8 (q), 73.7 (s), 114.2 (s), 114.3 (s), 114.4 (s), 116.8 (d), 117.3 (s), 126.0 (s), 128.5 (2 d), 129.9 (2 d), 132.7 (s), 141.3 (s), 143.9 (d), 166.3 (s), 171.5 (s) ppm. MS (FAB$^+$): *m*/*z* (%) = 346 (65) [M + 1]$^+$, 345 (51) [M]$^+$. $C_{19}H_{15}N_5S$ (345.41): calcd. C 66.07, H 4.38, N 20.27, S 9.28; found C 65.95, H 4.51, N 20.32, S 9.18.

Reactions of 4-Alkenyl-2-aminothiazoles 1a–e with Dimethyl Maleate and Dimethyl Fumarate: Dimethyl maleate or dimethyl fumarate (1.08 g, 7.50 mmol) was added to a solution of 4-alkenyl-2-aminothiazole **1a**–**e** (0.50 mmol) in acetonitrile (5 mL). The reaction mixture was stirred under reflux for 48 h. The solvent was evaporated to dryness and the residue was purified by silica gel chromatography.

Dimethyl (5*R,6*S**,7*S**)-2-Amino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7a):** From dimethyl maleate: 2:1→3:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.25 in 2:1 EtOAc/*n*-hexane), yield 20% (0.036 g) (**7a′′** was also isolated in 15% yield, R_f = 0.18 in 2:1 EtOAc/*n*-hexane), m.p. 223–225 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3425, 3281, 3106, 1725, 1632, 1521, 1292, 1233, 1165, 999, 817 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600.13 MHz): δ = 2.32 (s, 3 H, C_6H_4*Me*), 2.82–2.90 (m, 2 H, 4-H + 4′-H), 3.21 (ddd, *J* = 11.3, *J* = 9.9, *J* = 6.3 Hz, 1 H, 5-H), 3.28 (dd, *J* = 11.3, *J* = 9.9 Hz, 1 H, 6-H), 3.31 (s, 3 H, CO-O*Me*), 3.71 (s, 3 H, COO*Me*), 4.26 (dt, *J* = 9.9, *J* = 2.3 Hz, 1 H, 7-H), 4.90 (br. s, 2 H, NH_2), 7.12 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.1 (q), 33.9 (t), 43.8 (d), 44.8 (d), 50.2 (d), 51.6 (q), 52.5 (q), 113.0 (s), 127.6 (2 d), 129.1 (2 d), 136.8 (s), 138.0 (s), 146.5 (s), 167.2 (s), 171.7 (s), 173.8 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 360 (3) [M]$^+$, 328 (15), 301 (25), 300 (98), 241 (100). $C_{18}H_{20}N_2O_4S$ (360.43): calcd. C 59.98, H 5.59, N 7.77, S 8.90; found C 59.81, H 5.69, N 7.90, S 8.99.

Dimethyl (5*R,6*S**,7*S**)-2-Methylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7b):** From dimethyl maleate: 2:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.24), yield 24% (0.045 g) (**7b′′** was also isolated in 40% yield, R_f = 0.12 in 2:1 EtOAc/*n*-hexane). From dimethyl fumarate: 81% combined yield with **7b′**, m.p. 213–214 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3205, 3102, 1730, 1592, 1407, 1293, 1234, 1165 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600.13 MHz): δ = 2.32 (s, 3 H, C_6H_4*Me*), 2.83–2.90 (m, 2 H, 4-H + 4′-H), 2.96 (s, 3 H, NH*Me*), 3.21 (ddd, *J* = 11.4, *J* = 9.0, *J* = 7.3 Hz, 1 H, 5-H), 3.27 (dd, *J* = 11.4, *J* = 9.9 Hz, 1 H, 6-H), 3.31 (s, 3 H, COO*Me*), 3.72 (s, 3 H, COO*Me*), 4.27 (dt, *J* = 9.9, *J* = 2.3 Hz, 1 H, 7-H), 5.14 (br. s, 1 H, NH), 7.10–7.13 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 21.1 (q), 32.0 (q), 34.0 (t), 43.8 (d), 44.8 (d), 50.3 (d), 51.6 (q), 52.5 (q), 110.6 (s), 127.6 (2 d), 129.1 (2 d), 136.7 (s), 138.1 (s), 146.8 (s), 170.6 (s), 171.9 (s), 173.8 (s) ppm. MS (FAB$^+$): *m*/*z* (%) = 375 (100) [M + 1]$^+$. $C_{19}H_{22}N_2O_4S$ (374.46): calcd. C 60.94, H 5.92, N 7.48, S 8.56; found C 60.77, H 6.01, N 7.81, S 8.49.

Dimethyl (5*R,6*S**,7*S**)-2-Methylamino-5-(4-methoxyphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7c):** From dimethyl maleate: 2:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.30), yield 42% (0.082 g) (**7c′′** was also isolated in 30% yield, R_f = 0.22 in 2:1 EtOAc/*n*-hexane), m.p. 208–210 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3205, 3106, 1729, 1594, 1515, 1407, 1350, 1299, 1247, 1229, 1165, 1027, 833, 730 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.84–2.87 (m, 2 H, 4-H + 4′-H), 2.94 (s, 3 H, NH*Me*), 3.16–3.28 (m, 2 H, 5-H + 6-H), 3.32 (s, 3 H, C_6H_4O*Me*), 3.72 (s, 3 H, COO*Me*), 3.79 (s, 3 H, COO*Me*), 4.27 (dt, *J* = 9.9, *J* = 2.3 Hz, 1 H, 7-H), 5.45 (br. s, 1 H, NH), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.16 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 32.0 (q), 34.1 (t), 43.4 (d), 44.8 (d), 50.4 (d), 51.7 (q), 52.4 (q), 55.2 (q), 110.6 (s), 113.8 (2 d), 128.7 (2 d), 133.2 (s), 146.8 (s), 158.6 (s), 170.6 (s), 171.9 (s), 173.9 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 391 (6) [M + 1]$^+$, 390 (7) [M]$^+$, 358 (15), 331 (30), 330 (100), 271 (89), 121 (55). $C_{19}H_{22}N_2O_5S$ (390.46): calcd. C 58.45, H 5.68, N 7.17, S 8.21; found C 58.27, H 5.79, N 7.37, S 8.26.

Dimethyl (5*R,6*S**,7*S**)-2-Dimethylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7d):** From dimethyl maleate: 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f

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= 0.35 in 1:2 EtOAc/*n*-hexane), yield 21% (0.041 g) (**7d′** and **7d′′** were also isolated in 26 and 46% yields, respectively, R_f = 0.30 and 0.10, respectively, in 2:1 EtOAc/*n*-hexane). From dimethyl fumarate: yield 39% (**7d′** was also isolated in 57% yield), m.p. 165–166 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1737, 1723, 1549, 1224, 1168 cm^{-1}. ^1H NMR ($CDCl_3$, 600.13 MHz): δ = 2.32 (s, 3 H, C_6H_4Me), 2.86–2.93 (m, 2 H, 4-H + 4′-H), 3.07 (s, 6 H, NMe_2), 3.20 (ddd, J = 11.3, J = 9.3, J = 6.9 Hz, 1 H, 5-H), 3.27 (dd, J = 11.3, J = 9.8 Hz, 1 H, 6-H), 3.31 (s, 3 H, COO*Me*), 3.72 (s, 3 H, COO*Me*), 4.27 (dt, J = 9.8, J = 2.3 Hz, 1 H, 7-H), 7.11 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.1 (q), 34.1 (t), 40.1 (2 q), 43.7 (d), 44.8 (d), 50.3 (d), 51.6 (q), 52.4 (q), 110.6 (s), 127.5 (2 d), 129.1 (2 d), 136.6 (s), 138.2 (s), 147.5 (s), 170.6 (s), 172.1 (s), 173.9 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 389 (11) $[M + 1]^+$, 388 (11) $[M]^+$, 356 (13), 329 (34), 328 (100), 269 (77). $C_{20}H_{24}N_2O_4S$ (388.47): calcd. C 61.83, H 6.23, N 7.21, S 8.25; found C 61.69, H 6.29, N 7.37, S 8.17.

Dimethyl (5*R,6*R**,7*R**)-2-Methylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7b′):** From dimethyl fumarate: 1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.20). 81% combined yield (0.151 g) (compound **7b′** was obtained as a diastereomeric mixture with **7b**, and the assignment could be done since **7b** had been obtained in pure form from the reaction with DMMa). ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.28 (s, 3 H, C_6H_4Me), 2.93 (s, 3 H, NH*Me*), 2.98 (ddd, J = 17.1, J = 3.8, J = 1.7 Hz, 1 H, 4-H), 3.11 (ddd, J = 17.1, J = 6.3, J = 2.8 Hz, 1 H, 4′-H), 3.53 (dd, J = 8.9, J = 3.8 Hz, 1 H, 6-H), 3.65 (s, 3 H, COO*Me*), 3.76 (s, 3 H, COO*Me*), 3.78 (dt, J = 6.3, J = 3.8 Hz, 1 H, 5-H), 3.83 (dt, J = 8.9, J = 2.3 Hz, 1 H, 7-H), 5.14 (br. s, 1 H, NH), 6.93 (d, J = 8.0 Hz, 2 H), 7.03 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.0 (q, C_6H_4Me), 31.1 (t, C-4), 32.1 (q, NHMe), 39.2 (d, C-5), 40.3 (d, C-7), 47.4 (d, C-6), 51.8 (q, COO*Me*), 52.4 (q, COO*Me*), 110.8 (s, C-7a), 127.3 (2 d), 129.1 (2 d), 136.7 (s), 137.7 (s), 146.2 (s, C-3a), 171.1 (s, C-2), 172.50 (s, *C*OOMe), 172.51 (s, *C*OOMe) ppm.

Dimethyl (5*R,6*R**,7*R**)-2-Dimethylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7d′):** From dimethyl maleate: 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.30 in 1:2 EtOAc/*n*-hexane), yield 26% (0.051 g) (**7d** and **7d′′** were also isolated in 21 and 46% yields, respectively, R_f = 0.35 and 0.10, respectively, in 2:1 EtOAc/*n*-hexane). From dimethyl fumarate: yield 57% (**7d** was also isolated in 39% yield), m.p. 151–153 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1741, 1731, 1584, 1559, 1343, 1324, 1226, 1170 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.28 (s, 3 H, C_6H_4Me), 3.03 (ddd, J = 17.1, J = 3.8, J = 1.6 Hz, 1 H, 4-H), 3.09 (s, 6 H, NMe_2), 3.15 (ddd, J = 17.1, J = 6.2, J = 2.7 Hz, 1 H, 4′-H), 3.53 (dd, J = 8.8, J = 3.8 Hz, 1 H, 6-H), 3.65 (s, 3 H, COO*Me*), 3.75 (s, 3 H, COO*Me*), 3.78 (dt, J = 6.2, J = 3.8 Hz, 1 H, 5-H), 3.84 (dt, J = 8.8, J = 1.8 Hz, 1 H, 7-H), 6.93 (d, J = 8.1 Hz, 2 H), 7.03 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 21.0 (q, C_6H_4Me), 31.6 (t, C-4), 39.3 (d, C-5), 40.1 (2 q, NMe_2), 40.4 (d, C-7), 47.4 (d, C-6), 51.8 (q, COO*Me*), 52.3 (q, COO*Me*), 111.1 (s, C-7a), 127.3 (2 d), 129.1 (2 d), 136.5 (s), 138.0 (s), 147.4 (s, C-3a), 170.4 (s, C-2), 172.6 (s, *C*OOMe), 172.7 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 389 (14) $[M + 1]^+$, 388 (17) $[M]^+$, 356 (17), 329 (38), 328 (100), 269 (82). $C_{20}H_{24}N_2O_4S$ (388.47): calcd. C 61.83, H 6.23, N 7.21, S 8.25; found C 61.64, H 6.33, N 7.31, S 8.29.

Dimethyl (5*R,6*R**,7*S**)-2-Amino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7a′′):** From dimethyl maleate: 2:1→3:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.18 in 2:1 EtOAc/*n*-hexane), yield 15% (0.027 g) (**7a** was also isolated in 20% yield, R_f = 0.25 in 2:1 EtOAc/*n*-hexane). IR (nujol): $\tilde{\nu}$ = 3425, 3346, 3136, 1738, 1613, 1516, 1203, 1167, 1022, 817 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.31 (s, 3 H, C_6H_4Me), 2.84 (dd, J = 17.7, J = 3.6 Hz, 1 H, 4-H), 2.94 (ddd, J = 17.7, J = 6.2, J = 2.2 Hz, 1 H, 4′-H), 3.48 (dd, J = 6.2, J = 5.1 Hz, 1 H, 6-H), 3.55 (br. s, 1 H, 7-H), 3.61 (s, 3 H, COO*Me*), 3.70 (s, 3 H, COO*Me*), 3.86 (q, J = 5.7 Hz, 1 H, 5-H), 5.22 (br. s, 2 H, NH_2), 7.07–7.14 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.0 (q, C_6H_4Me), 29.7 (t, C-4), 38.7 (d, C-5), 40.0 (d, C-7), 49.3 (d, C-6), 52.2 (q, COO*Me*), 52.4 (q, COO*Me*), 113.3 (s, C-7a), 127.0 (2 d), 129.4 (2 d), 136.6 (s), 139.4 (s), 144.6 (s, C-3a), 167.9 (s, C-2), 171.8 (s, *C*OOMe), 171.9 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 360 (23) $[M]^+$, 301 (35), 300 (52), 241 (100), 184 (30), 149 (23), 105 (27).

Dimethyl (5*R,6*R**,7*S**)-2-Methylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7b′′):** From dimethyl maleate: 2:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.12), yield 40% (0.075 g) (**7b** was also isolated in 24% yield, R_f = 0.24 in 2:1 EtOAc/*n*-hexane), m.p. 146–147 °C (colourless needles, $CHCl_3$/*n*-pentane). IR (nujol): $\tilde{\nu}$ = 3205, 3110, 1732, 1557, 1209, 1167, 1022 cm^{-1}. ^1H NMR ($CDCl_3$, 300.10 MHz): δ = 2.31 (s, 3 H, C_6H_4Me), 2.83 (ddd, J = 17.6, J = 5.1, J = 1.5 Hz, 1 H, 4-H), 2.96 (ddd, J = 17.6, J = 6.3, J = 2.1 Hz, 1 H, 4′-H), 2.97 (s, 3 H, NH*Me*), 3.47 (dd, J = 6.9, J = 5.1 Hz, 1 H, 6-H), 3.59 (s, 3 H, COO*Me*), 3.60–3.62 (m, 1 H, 7-H), 3.70 (s, 3 H, COO*Me*), 3.86 (q, J = 5.7 Hz, 1 H, 5-H), 5.35 (br. s, 1 H, NH), 7.09 (br. s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 21.0 (q, C_6H_4Me), 30.4 (t, C-4), 32.1 (q, NHMe), 38.9 (d, C-5), 40.3 (d, C-7), 49.4 (d, C-6), 52.1 (q, COO*Me*), 52.3 (q, COO*Me*), 111.3 (s, C-7a), 127.0 (2 d), 129.3 (2 d), 136.5 (s), 139.7 (s), 145.9 (s, C-3a), 170.9 (s, C-2), 172.0 (s, *C*OOMe), 172.1 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 374 (44) $[M]^+$, 315 (81), 314 (49), 255 (100), 230 (34), 198 (51), 105 (36). $C_{19}H_{22}N_2O_4S$ (374.46): calcd. C 60.94, H 5.92, N 7.48, S 8.56; found C 60.57, H 5.99, N 7.77, S 8.71.

Dimethyl (5*R,6*R**,7*S**)-2-Methylamino-5-(4-methoxyphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7c′′):** From dimethyl maleate: 2:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.22), yield 30% (0.059 g) (**7c** was also isolated in 42% yield, R_f = 0.30 in 2:1 EtOAc/*n*-hexane), m.p. 84–86 °C. IR (nujol): $\tilde{\nu}$ = 3367, 3206, 1733, 1512, 1259, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.82 (ddd, J = 17.4, J = 4.7, J = 1.2 Hz, 1 H, 4-H), 2.97–2.92 (m, 4 H, 4′-H + NH*Me*), 3.45 (dd, J = 6.6, J = 5.0 Hz, 1 H, 6-H), 3.59 (s, 3 H, C_6H_4OMe), 3.60–3.62 (m, 1 H, 7-H), 3.70 (s, 3 H, COO*Me*), 3.77 (s, 3 H, COO*Me*), 3.85 (m, 1 H, 5-H), 5.40 (br. s, 1 H, NH), 6.82 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 29.3 (t, C-4), 32.0 (q, NHMe), 38.4 (d, C-5), 40.2 (d, C-7), 49.4 (d, C-6), 52.0 (q, COO*Me*), 52.2 (q, COO*Me*), 55.2 (q, C_6H_4OMe), 110.9 (s, C-7a), 114.0 (2 d), 128.2 (2 d), 133.6 (s), 145.8 (s, C-3a), 158.4 (s), 171.2 (s, C-2), 172.0 (s, *C*OOMe), 172.1 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 390 (37) $[M]^+$, 331 (67), 330 (31), 271 (67), 246 (53), 198 (47), 183 (33), 167 (32), 149 (100), 121 (92), 86 (73), 59 (81), 57 (74).

Dimethyl (5*R,6*R**,7*S**)-2-Dimethylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6,7-dicarboxylate (7d′′):** From dimethyl maleate: 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.10 in 1:2 EtOAc/*n*-hexane), yield 46% (0.089 g) (**7d** and **7d′** were also isolated in 21 and 26% yields, respectively, R_f = 0.35 and R_f = 0.30 in 2:1 EtOAc/*n*-hexane), m.p. 96–98 °C (colourless needles, $CHCl_3$/*n*-hexane). IR (nujol): $\tilde{\nu}$ = 1747, 1738, 1556, 1515, 1434, 1345, 1261, 1202, 1166, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.30 (s, 3 H, C_6H_4Me), 2.86 (ddd, J = 17.5, J = 5.1, J = 1.5 Hz, 1 H, 4-H), 2.99 (ddd, J = 17.5, J = 6.2, J = 2.2 Hz, 1 H, 4′-H), 3.09 (s, 6 H, NMe_2), 3.45 (dd, J = 6.7, J = 5.0 Hz, 1 H, 6-H), 3.57

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(s, 3 H, COO*Me*), 3.62–3.65 (m, 1 H, 7-H), 3.69 (s, 3 H, COO*Me*), 3.86 (m, 1 H, 5-H), 7.08 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50.30 MHz): δ = 20.9 (q, C_6H_4*Me*), 30.7 (t, C-4), 38.8 (d, C-5), 40.1 (2 q, NMe_2), 40.3 (d, C-7), 49.3 (d, C-6), 51.9 (q, COO*Me*), 52.1 (q, COO*Me*), 111.0 (s, C-7a), 127.0 (2 d), 129.2 (2 d), 136.2 (s), 139.7 (s), 146.8 (s, C-3a), 170.9 (s, C-2), 172.0 (s, *C*OOMe), 172.2 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 389 (25) [M + 1]$^+$, 388 (81) [M]$^+$, 329 (100), 269 (74), 244 (39), 212 (42), 197 (30). $C_{20}H_{24}N_2O_4S$ (388.47): calcd. C 61.83, H 6.23, N 7.21, S 8.25; found C 61.71, H 6.24, N 7.49, S 8.11.

Reaction of 4-Alkenyl-2-aminothiazoles 1c and 1e with Methyl Acrylate: Methyl acrylate (0.66 g, 7.65 mmol) was added to a solution of the 4-alkenyl-2-aminothiazole **1c** or **1e** (0.50 mmol) in acetonitrile (5 mL). The reaction mixture was stirred under reflux for 48 h. The solvent was removed, and the residue was purified by silica gel chromatography.

Methyl (5*R,6*S**)-2-Methylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6-carboxylate (*endo*-8a):** 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.08 in 1:2 EtOAc/*n*-hexane), yield 11% (0.017 g), m.p. 198–199 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3209, 3117, 1734, 1599, 1410, 1306, 1233, 1167, 1057, 1040, 821 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600.13 MHz): δ = 2.28 (s, 3 H, C_6H_4*Me*), 2.68 (br. dd, *J* = 16.3, *J* = 9.9 Hz, 1 H, 7-H), 2.80 (dd, *J* = 16.3, *J* = 5.0 Hz, 1 H, 7′-H), 2.95 (s, 3 H, N*Me*), 2.98 (br. d, *J* = 17.1 Hz, 1 H, 4-H), 3.09–3.13 (m, 2 H, 6-H + 4′-H), 3.65 (s, 3 H, COO*Me*), 3.72 (td, *J* = 6.5, *J* = 3.3 Hz, 1 H, 5-H), 5.82 (br. s, 1 H, NH), 6.97 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.0 (q, C_6H_4*Me*), 22.2 (t, C-7), 31.7 (t, C-4), 32.0 (q, NMe), 40.1 (d, C-5), 45.1 (d, C-6), 51.5 (q, COO*Me*), 113.9 (s, C-7a), 127.6 (2 d), 129.0 (2 d), 136.4 (s), 138.3 (s), 144.9 (s, C-3a), 169.4 (s, C-2), 173.5 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 316 (33) [M]$^+$, 230 (21), 147 (43), 140 (27), 132 (30), 107 (67), 106 (100), 104 (25), 77 (27). $C_{17}H_{20}N_2O_2S$ (316.42): calcd. C 64.53, H 6.37, N 8.85, S 10.13; found C 64.24, H 6.43, N 8.90, S 9.98.

Methyl (5*R,6*R**)-2-Methylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6-carboxylate (*exo*-8a):** 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.13 in 1:2 EtOAc/*n*-hexane), yield 11% (0.017 g), m.p. 246–248 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 3210, 3111, 1723, 1597, 1407, 1304, 1230, 1168 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.31 (s, 3 H, C_6H_4*Me*), 2.76 (ddm, *J* = 17.6, *J* = 10.9 Hz, 1 H, 4-H), 2.86–3.06 (m, 7 H, 4′-H + N*Me* + 7-H + 7′-H + 5-H), 3.28 (td, *J* = 10.2, *J* = 5.5 Hz, 1 H, 6-H), 3.42 (s, 3 H, COO*Me*), 5.31 (br. s, 1 H, NH), 7.11 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.0 (q), 26.5 (t), 32.1 (q), 33.9 (t), 43.0 (d), 47.4 (d), 51.5 (q), 113.4 (s), 127.3 (2 d), 129.2 (2 d), 136.3 (s), 139.7 (s), 145.2 (s), 169.2 (s), 174.6 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 317 (24) [M + 1]$^+$, 316 (85) [M]$^+$, 230 (91), 140 (100). $C_{17}H_{20}N_2O_2S$ (316.42): calcd. C 64.53, H 6.37, N 8.85, S 10.13; found C 64.29, H 6.39, N 8.97, S 10.21.

Methyl (5*R,6*S**)-2-[(2-Methoxycarbonylethyl)methylamino]-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6-carboxylate (*endo*-8b):** 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.25 in 1:2 EtOAc/*n*-hexane), yield 9% (0.018 g), m.p. 57–59 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1736, 1545, 1306, 1258, 1200, 1167, 1113, 1044, 819, 732 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.29 (s, 3 H, C_6H_4*Me*), 2.65–2.72 (m, 3 H, 7-H + CH_2*CH*$_2$), 2.81 (dd, *J* = 16.2, *J* = 5.3 Hz, 1 H, 7′-H), 3.01 (dm, *J* = 17.1 Hz, 1 H, 4-H), 3.08–3.15 (m, 5 H, N*Me* + 4′-H + 6-H), 3.64 (s, 3 H, COO*Me*), 3.70–3.71 (m, 4 H, 5-H + COO*Me*), 3.77 (m, *J* = 6.9 Hz, 2 H, *CH*$_2$CH$_2$), 6.97 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.0 (q, C_6H_4*Me*), 22.3 (t, C-7), 31.86 (t, C-4), 31.94 (t, CH_2*CH*$_2$), 38.9 (q, NMe), 40.2 (d, C-5), 45.1 (d, C-6), 48.8 (t, *CH*$_2$CH$_2$), 51.5 (q, COO*Me*), 51.8 (q, COO*Me*), 114.2 (s, C-7a), 127.6 (2 d), 129.0 (2 d), 136.3 (s), 138.4 (s), 145.4 (s, C-3a), 168.3 (s, C-2), 172.4 (s, *C*OOMe), 173.5 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 403 (30) [M + 1]$^+$, 402 (100) [M]$^+$, 343 (28), 316 (37), 226 (28), 140 (42), 115 (29), 59 (33), 55 (34). $C_{21}H_{26}N_2O_4S$ (402.51): calcd. C 62.66, H 6.51, N 6.96, S 7.97; found C 62.50, H 6.64, N 6.99, S 8.08.

Methyl (5*R,6*R**)-2-[(2-Methoxycarbonylethyl)methylamino]-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6-carboxylate (*exo*-8b):** 1:2→1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.31 in 1:2 EtOAc/*n*-hexane), yield 4% (0.008 g), m.p. 124–126 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1730, 1547, 1332, 1296, 1206, 1167, 1113, 1045, 811 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.31 (s, 3 H, C_6H_4*Me*), 2.69 (t, *J* = 6.9 Hz, 2 H, CH_2*CH*$_2$), 2.74–3.02 (m, 5 H, 4-H + 4′-H + 7-H + 7′-H + 5-H), 3.06 (s, 3 H, NMe), 3.23–3.28 (m, 1 H, 6-H), 3.42 (s, 3 H, COO*Me*), 3.69 (s, 3 H, COO*Me*), 3.74 (t, *J* = 6.9 Hz, 2 H, *CH*$_2$CH$_2$), 7.10 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.0 (q, C_6H_4*Me*), 26.5 (t), 31.9 (t, CH_2*CH*$_2$), 34.0 (t), 39.0 (q, NMe), 43.1 (d), 47.3 (d), 48.8 (t, *CH*$_2$CH$_2$), 51.5 (q, COO*Me*), 51.8 (q, COO*Me*), 113.5 (s, C-7a), 127.3 (2 d), 129.1 (2 d), 136.2 (s), 139.7 (s), 145.7 (s, C-3a), 168.2 (s, C-2), 172.3 (s, *C*OOMe), 174.6 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 403 (35) [M + 1]$^+$, 402 (100) [M]$^+$, 316 (52), 226 (32), 168 (22), 167 (27), 140 (68), 115 (21). $C_{21}H_{26}N_2O_4S$ (402.51): calcd. C 62.66, H 6.51, N 6.96, S 7.97; found C 62.43, H 6.59, N 7.02, S 8.00.

Methyl (5*R,6*S**)-2-Dimethylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6-carboxylate (*endo*-8c):** 1:2 EtOAc/*n*-hexane was used as eluent (R_f = 0.18), yield 24% (0.040 g), m.p. 120–121 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1731, 1556, 1336, 1249, 1229, 1196, 1167, 1125, 940, 822 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.28 (s, 3 H, C_6H_4*Me*), 2.69 (ddt, *J* = 16.2, *J* = 9.7, *J* = 2.0 Hz, 1 H, 7-H), 2.81 (dd, *J* = 16.2, *J* = 5.1 Hz, 1 H, 7′-H), 2.99–3.06 (m, 1 H, 4-H), 3.08 (s, 6 H, NMe_2), 3.09–3.17 (m, 2 H, 4′-H + 6-H), 3.64 (s, 3 H, COO*Me*), 3.72 (td, *J* = 6.5, *J* = 3.3 Hz, 1 H, 5-H), 6.97 (d, *J* = 8.1 Hz, 2 H), 7.03 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50.30 MHz): δ = 21.0 (q, C_6H_4*Me*), 22.3 (t, C-7), 31.9 (t, C-4), 40.2 (d, C-5), 40.3 (2 q, NMe_2), 45.1 (d, C-6), 51.5 (q, COO*Me*), 114.1 (s, C-7a), 127.6 (2 d), 129.0 (2 d), 136.3 (s), 138.4 (s), 145.6 (s, C-3a), 169.5 (s, C-2), 173.6 (s, *C*OOMe) ppm. MS (EI, 70 eV): *m*/*z* (%) = 331 (33) [M + 1]$^+$, 330 (100) [M]$^+$, 271 (35), 244 (28), 154 (81), 88 (24). $C_{18}H_{22}N_2O_2S$ (330.43): calcd. C 65.42, H 6.71, N 8.48, S 9.70; found C 65.05, H 6.82, N 8.62, S 9.82.

Methyl (5*R,6*R**)-2-Dimethylamino-5-(4-methylphenyl)-4,5,6,7-tetrahydrobenzothiazole-6-carboxylate (*exo*-8c):** 1:2 EtOAc/*n*-hexane was used as eluent (R_f = 0.25), yield 32% (0.053 g), m.p. 169–171 °C (colourless needles, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1728, 1589, 1556, 1515, 1296, 1194, 1166, 1128, 980, 813, 723, 708 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.91 MHz): δ = 2.31 (s, 3 H, C_6H_4*Me*), 2.75–3.04 (m, 5 H, 4-H + 4′-H + 7-H + 7′-H + 5-H), 3.06 (s, 6 H, NMe_2), 3.24–3.31 (m, 1 H, 6-H), 3.64 (s, 3 H, COO*Me*), 7.08–7.12 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50.30 MHz): δ = 21.0 (q), 26.4 (t), 34.0 (t), 40.2 (2 q), 43.1 (d), 47.4 (d), 51.5 (q), 113.4 (s), 127.3 (2 d), 129.1 (2 d), 136.2 (s), 139.8 (s), 145.8 (s), 169.5 (s), 174.6 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 331 (32) [M + 1]$^+$, 330 (92) [M]$^+$, 244 (54), 154 (100), 139 (21), 125 (20). $C_{18}H_{22}N_2O_2S$ (330.43): calcd. C 65.42, H 6.71, N 8.48, S 9.70; found C 65.22, H 6.79, N 8.69, S 9.54.

(5*R,6*R**)-6-Chloro-2-dimethylamino-5-(4-methylphenyl)-7*H*-4,5-dihydrobenzothiazole-6-carbonitrile (9):** α-Chloroacrylonitrile (1.07 g,

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12.27 mmol) was added to a solution of 4-alkenyl-2-aminothiazole **1e** (0.20 g, 0.82 mmol) in acetonitrile (10 mL). The reaction mixture was stirred under reflux for 48 h. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/*n*-hexane (R_f = 0.33), yield 80% (0.218 g), m.p. 203–205 °C (colourless prisms, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1590, 1569, 1135, 1044, 900, 814, 724 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 2.36 (s, 3 H, C_6H_4Me), 3.08 (s, 6 H, NMe_2), 3.15 (br. dd, J = 17.4, J = 6.0 Hz, 1 H, 4-H), 3.23 (br. dd, J = 17.4, J = 8.8 Hz, 1 H, 4′-H), 3.38 (br. d, J = 16.0 Hz, 1 H, 7-H), 3.43 (dd, J = 8.8, J = 6.0 Hz, 1 H, 5-H), 3.52 (br. d, J = 16.0 Hz, 1 H, 7′-H), 7.18 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 21.1 (q, C_6H_4Me), 32.3 (t, C-4), 38.9 (t, C-7), 40.1 (2 q, NMe_2), 50.5 (d, C-5), 59.1 (s, C-6), 109.6 (s, CN), 117.9 (s, C-7a), 128.4 (2 d), 129.3 (2 d), 135.0 (s), 138.2 (s), 145.8 (s, C-3a), 170.2 (s, C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 333 (23) $[M + 2]^+$, 331 (62) $[M]^+$, 154 (100). $C_{17}H_{18}ClN_3S$ (331.85): calcd. C 61.53, H 5.47, N 12.66, S 9.66; found C 61.34, H 5.63, N 12.79, S 9.44.

Ethyl 2-Dimethylamino-7-methyl-5-(4-methylphenyl)-4,5-dihydrobenzothiazole-6-carboxylate (10): Ethyl 2,3-butadienoate (0.28 g, 2.45 mmol) was added to a solution of 4-alkenyl-2-aminothiazole **1e** (0.20 g, 0.82 mmol) in acetonitrile (15 mL). The reaction mixture was stirred under reflux for 24 h. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1:5 EtOAc/*n*-hexane (R_f = 0.15), yield 66% (0.193 g), m.p. 114–115 °C (colourless prisms, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1687, 1558, 1505, 1324, 1245, 1225, 1195, 1128, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 1.18 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 2.25 (s, 3 H, C_6H_4Me), 2.50 (s, 3 H, C-7-Me), 3.00 (dd, J = 17.0, J = 2.2 Hz, 1 H, 4-H), 3.08 (s, 6 H, NMe_2), 3.21 (dd, J = 17.0, J = 9.0 Hz, 1 H, 4′-H), 4.02–4.15 (m, 2 H, $COOCH_2CH_3$), 4.27 (br. d, J = 8.6 Hz, 1 H, 5-H), 6.99 (d, J = 8.0 Hz, 2 H), 7.08 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.81 MHz): δ = 14.2 (q, $COOCH_2CH_3$), 20.8 (q, C-7-*Me*), 20.9 (q, C_6H_4Me), 33.7 (t, C-4), 39.5 (d, C-5), 40.0 (2 q, NMe_2), 59.7 (t, $COOCH_2CH_3$), 117.9 (s, C-7a), 121.2 (s, C-6), 127.0 (2 d), 128.8 (2 d), 135.5 (s), 140.9 (s, C-7), 141.0 (s), 151.4 (s, C-3a), 167.8 (s, *C*OOEt), 171.5 (s, C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 356 (52) $[M]^+$, 284 (20), 283 (100). $C_{20}H_{24}N_2O_2S$ (356.47): calcd. C 67.38, H 6.79, N 7.86, S 9.00; found C 67.03, H 6.92, N 8.04, S 8.89.

Ethyl 2-Dimethylamino-5-(4-methyphenyl)-4,5-dihydrobenzothiazole-6-carboxylate (11): Ethyl propiolate (0.48 g, 4.92 mmol) was added to a solution of 4-alkenyl-2-aminothiazole **1e** (0.20 g, 0.82 mmol) in acetonitrile (15 mL). The reaction mixture was stirred under reflux for 48 h. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/*n*-hexane (R_f = 0.35), yield 72% (0.202 g), m.p. 91–93 °C (colourless prisms, $CHCl_3/Et_2O$). IR (nujol): $\tilde{\nu}$ = 1692, 1564, 1502, 1425, 1309, 1246, 1281, 1216, 1191, 1095, 1034, 817, 721 cm^{-1}. ^1H NMR ($CDCl_3$, 400.91 MHz): δ = 1.22 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 2.25 (s, 3 H, C_6H_4Me), 3.09 (dd, J = 17.2, J = 1.6 Hz, 1 H, 4-H), 3.11 (s, 6 H, NMe_2), 3.28 (dd, J = 17.2, J = 9.6 Hz, 1 H, 4′-H), 4.14 (m, 2 H, $COOCH_2CH_3$), 4.22 (br. d, J = 8.6 Hz, 1 H, 5-H), 7.00 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 8.0 Hz, 2 H), 7.63 (s, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 14.2 (q, $COOCH_2CH_3$), 20.9 (q, C_6H_4Me), 33.7 (t, C-4), 37.7 (d, C-5), 40.1 (2 q, NMe_2), 60.0 (t, $COOCH_2CH_3$), 114.3 (s, C-7a), 122.7 (s, C-6), 126.8 (2 d), 128.9 (2 d), 129.6 (d, C-7), 135.8 (s), 140.3 (s), 152.8 (s, C-3a), 166.7 (s, *C*OOEt), 172.3 (s, C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 344 (20) $[M + 2]^+$, 342 (91) $[M]^+$, 313 (32), 297 (34), 269 (100), 253 (30), 239 (33), 184 (39), 179 (37), 165 (38). $C_{19}H_{22}N_2O_2S$ (342.44): calcd. C 66.64, H 6.48, N 8.18, S 9.36; found C 66.32, H 6.59, N 8.23, S 9.29.

Supporting Information (see footnote on the first page of this article): contains the experimental procedure for the preparation of α-chloro ketone **2d**, a general procedure for the preparation of thiazoles **1c**–**d** and **1f**–**h**, the $^1H,^1H$-NOESY spectra of **7b**, **7d′**, and **7b′′**, the X-ray structure of *endo*-**4e**, the cartesian coordinates, electronic energies, and imaginary frequencies of 4-alkenylthiazoles **1i**–**m** optimized at the B3LYP/6-31+G level, and copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds.

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