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α-Methoxy-α-(*6H*-1,3-thiazin-2-yl)glycinates precursors of *7-methoxycephems* by [3+3] cyclocondensation reaction

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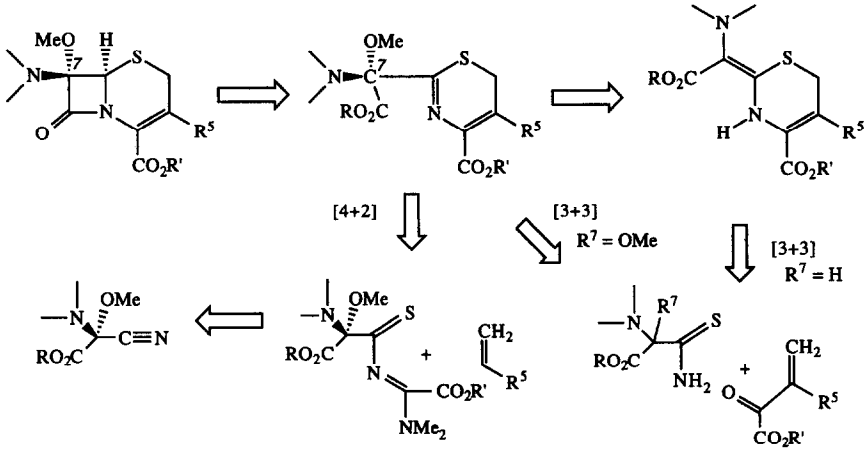
Abstract : We report here a new widely useful and applicable preparation of functionalised *6H*-1,3-thiazinic cycloadducts, versatile key intermediates in the total multistep syntheses of 7-methoxycephems (as analogues of 7-methoxycephalosporins).

In recent years, considerable interest has been focused on varying the different substituents of the cephem nucleus to obtain compounds with enhanced antibacterial activity. The discovery of cephamycins (7-methoxycephalosporins) opened up new possibilities considering their extended pharmacokinetic properties and resistance to pathogens. Development of methodology for the introduction of different substituents on the thiazinic cycle is always of use in the search for biologically active cephems[1].

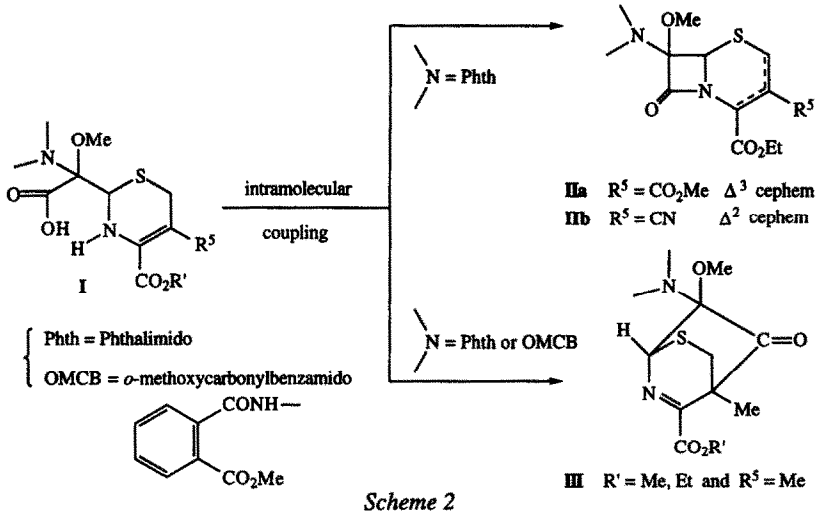
In this context, we have already reported the synthesis of α-methoxy-α-(*6H*-1,3-thiazin-2-yl)glycinates which have been used previously as potential precursors of 7-methoxycephems using either a *[4+2] cycloaddition* reaction[2], or a *[3+3] cyclocondensation* reaction[3]. Different strategies have been carried out to construct a suitable cephamycin framework. Cyanoglycinate derivatives have shown high versatility and were useful synthons for these elaborated compounds, as shown on the following retrosynthetic scheme :



Retrosynthetic scheme

The final step of the synthesis required selective reduction of the endocyclic imine double bond, before cleavage of the protected acid for subsequent lactamisation. The versatile *hetero Diels-Alder reaction* route[2h] from thiazadiene gave the expected 7-methoxycephem isomers[2f], whereas the Michaël-type *[3+3] cyclocondensation* route starting from α-thiocarbamoylglycinate derivatives[3] produced an unexpected bicyclic structure in the final intramolecular coupling[3c].

This last step of intramolecular coupling led to the expected β-lactams **II** when R^5 was an electron-withdrawing group ($R^5 = CO_2Me$, CN) but gave the unexpected and surprising bicyclic structures[3c] **III** when R^5 was an electron-donating group (R^5 = Me). This ring closure was therefore dependent on the electronic effect of the R^5 group linked to the enaminic system of the 1,3-thiazine ring.

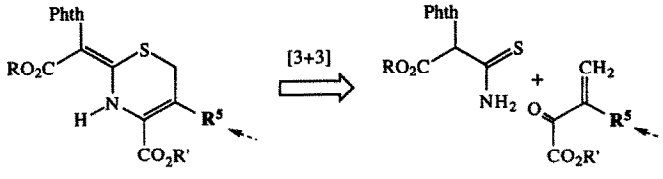


Scheme 2

Our interest was to develop the *[3+3] cycloaddition* route to obtain these highly elaborated compounds. We therefore decided to introduce an electron-withdrawing group at the R^5 position in order to synthesise identical precursors to those obtained from the *[4+2] Diels-Alder cycloaddition* reaction.

We were interested in comparing both strategies introducing a R^5 group which could be similar to that introduced by the dienophile from the *[4+2] cycloaddition* reaction, for example the versatile free or protected formyl group. It is very well known that the biological activity of these 7-methoxycephems correlates with the nature of this substituent at the R^5 position and such a formyl group is sufficiently rich in synthetic possibilities[1b].

In order to proceed along these lines, we had to consider the synthesis of new vinylic ketoesters which could be used as Michaël acceptors for the *[3+3] cyclocondensation* reaction.



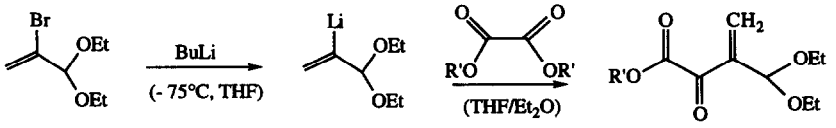
Introduction of the α-methoxy functionality was particularly important. The different possibilities of methoxylation before or after the cycloaddition, as shown on the previous retrosynthetic scheme, will be carried out and discussed, to evaluate a more interesting strategy leading to the target molecule.

Finally, comparison of the advantages and the disadvantages of the *[3+3] cyclocondensation* and the *[4+2] cycloaddition* reactions giving the same functionalised *6H*-thiazinic intermediates, potential precursors of *7-methoxycephems* will be developed.

Results and discussion

Vinylic ketoesters 1 :

Following a previous strategy[4], our choice was to synthesise new vinylic ketoesters bearing a protected formyl group. This synthesis was achieved using acroleïn as starting material. It was treated successively with bromine and ethyl orthoformate to afford the 2,3-dibromo-1,1-diethoxypropane[5], which after dehydrobromination using potassium hydroxide under phase transfer catalysis, gave the 2-bromo-3,3-diethoxypropene[6]. Due to the undesirable β-elimination reaction of the organomagnesium reagent of 2-bromo-3,3-diethoxypropene, we decided to use the 3,3-diethoxy-2-lithiopropene easily obtained using a bromine-lithium exchange[7]. Addition of different dialkyl oxalates afforded the expected new vinylic ketoesters **1** :

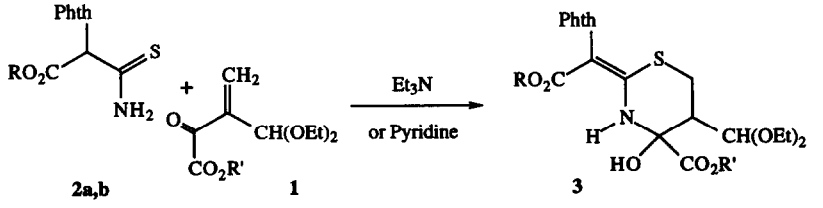


1 R' = Me, Et and t.Bu

Because of easy polymerisation, these unstable structures were used without purification for the *[3+3] cyclocondensation* reaction. This method was carried out with different alkoxy groups OR' and proceeded in 50 to 76% yields allowing a new extension of our planned total syntheses.

Tetrahydro-1,3-thiazines and dihydro-1,3-thiazines by *[3+3] cyclocondensation* :

Considering the easy cleavage of the allylic acetal group under acidic conditions, we performed the *[3+3] cyclocondensation* reaction by treatment of α-thiocarbamoylglycinates **2** with an excess of compounds **1** in the presence of triethylamine (or pyridine). No spontaneous dehydration of the cycloadducts, which were obtained in good yields, was observed as had previously been shown for the condensation in acidic medium[3,4b].



2a,b **1** **3**

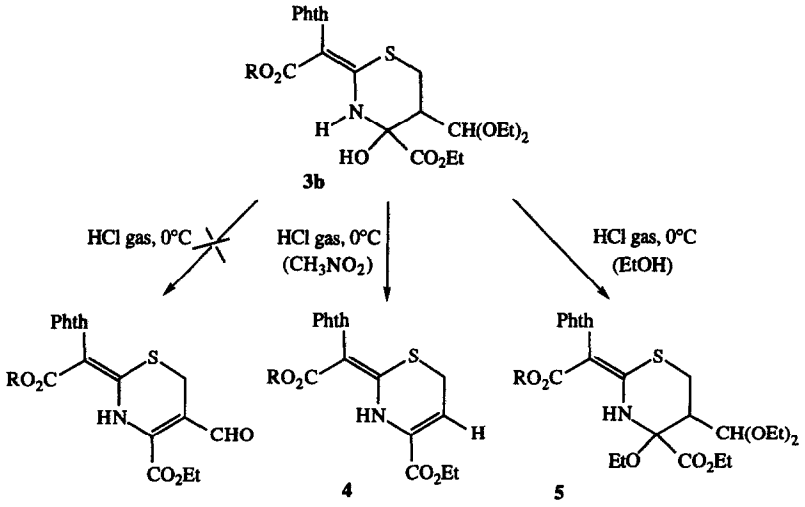
3a	R = R' = Me
3b	R = Me, R' = Et
3c	R = *t*.Bu, R' = Me
3d	R = R' = *t*.Bu

Scheme 3

For R^5 = Me, dehydration of the corresponding tetrahydro-1,3-thiazines had been carried out using gaseous hydrochloric acid[3a,4b]. For $R^5 = CH(OEt)_2$, we hoped to obtain both dehydration and hydrolysis of the acetal function using the same experimental conditions. That would have been certainly an advantage for our further reactions of methoxylation and imine reduction as will be described later.

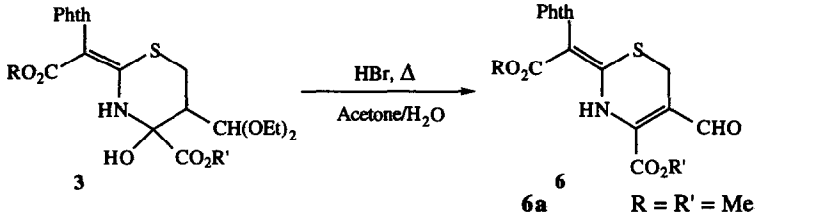
In the presence of nitromethane, dehydration was observed but loss of the carbaldehyde function occurred, by a mechanism involving protonation of the ethoxy group followed by elimination of ethyl formate.

In order to avoid the formation of the compound **4**, we carried out the acidic dehydration reaction using ethanol as solvent. The acetal function was not affected but unexpected addition of ethanol to the thiazine ring was observed.



Scheme 4

After an exhaustive search for a promising reagent, it was finally found that catalytic aqueous hydrobromic acid at reflux of acetone afforded the expected dehydration with removal of acetal protection[8]. The *tert*-butyl ester protection was not cleaved under these acidic conditions[9].



6a R = R' = Me
6b R = Me, R' = Et
6c R = *t*.Bu, R' = Me
6d R = R' = *t*.Bu

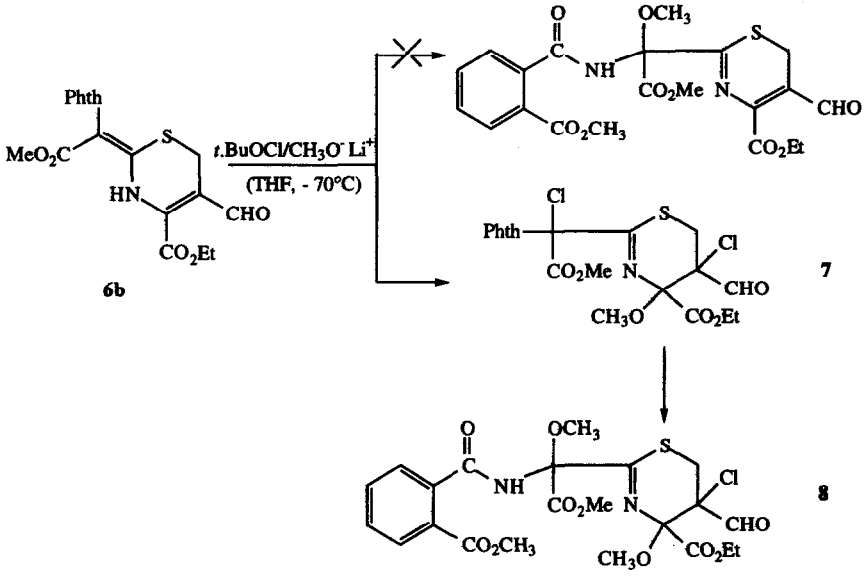
Scheme 5

Because of the difficulties due to introduction of a functional group on position 5, we had to investigate new strategies for the methoxylation of the 2-alkylidene-2*H*-1,3-thiazinic system.

Methoxylation after dehydration of the tetrahydrothiazine :

First we tested the conjugated reaction using *tert*-butyl hypochlorite and lithium methoxide[3a] in THF at - 70°C on the 3,6-dihydro-2*H*-1,3-thiazines **6**. This method was successful in the laboratory on analoguous thiazine derivatives substituted by a methyl group on position 5. In our case, we observed, simultaneous to the required methoxylation, a chloromethoxylation[3a] of the intracyclic C_4-C_5 bond. The structure of compound **8** suggested by ^1H and ^{13}C NMR spectra was confirmed by the characteristic well known *retro Diels-Alder* fragmentation observed in mass spectrometry.

The intermediate in this reaction was the chlorinated structure **7** which could be isolated if an excess of the alkylidenethiazine **6b** was used, compared to lithium methoxide.



Scheme 6

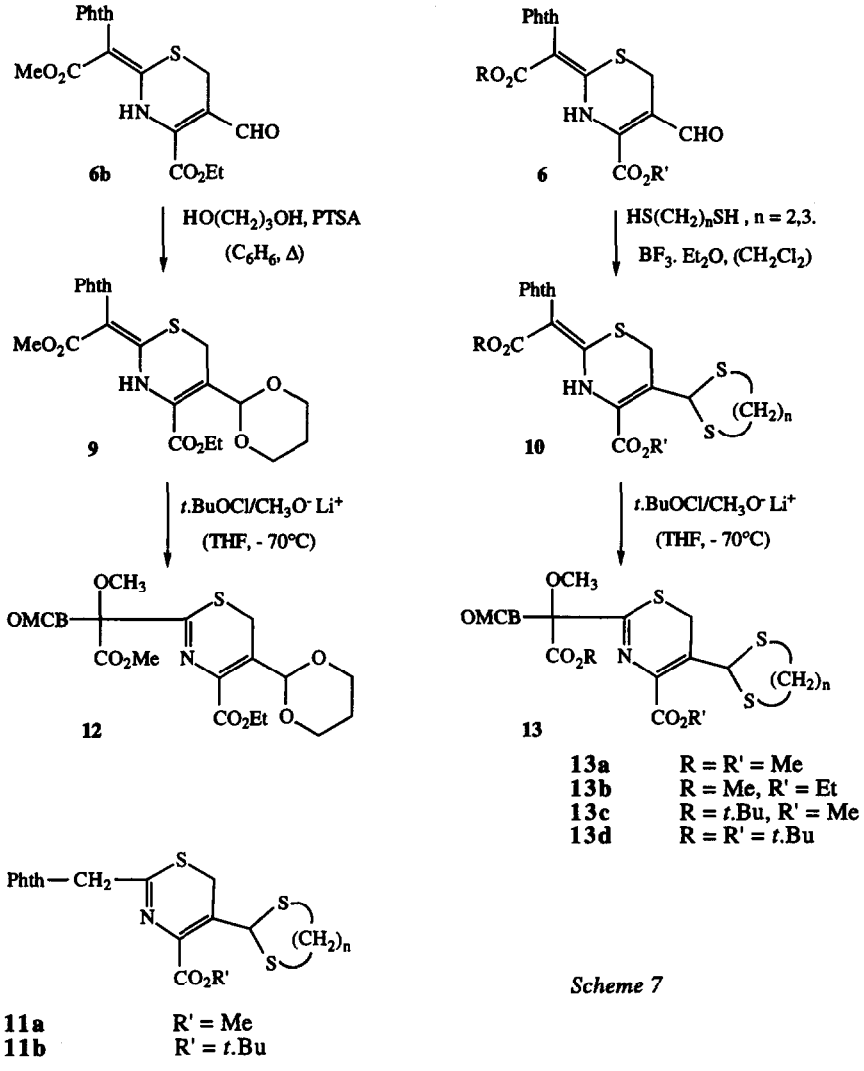
This result suggested that the electron-withdrawing aldehyde in the β position of the enaminic system was activating the endocyclic C_4-C_5 double bond to afford this unexpected addition. To avoid this competitive reaction, we protected the aldehyde group as the acetal and thioacetal in order to decrease the electron-withdrawing effect.

Acetalisation and thioacetalisation of the formyl function at position 5 of the thiazine ring :

We chose propane-1,3-diol instead of ethylene glycol to protect the formyl group. Considering the necessary chemio and regioselective reduction in the next step of the synthesis, we thought that this acetal would be more suitable. The acetalisation reaction carried out in presence of *p*-toluenesulfonic acid[9,10,11d] provided the ylidenic thiazine **9** in good yield.

Thioacetal protection[9b,11] using the corresponding alkyldithiol and boron trifluoride etherate in dichloromethane afforded the thiazines **10** in excellent yields. However we observed some deprotection of the *tert*-butyl ester group followed by decarboxylation for **6c** and **6d**, producing decarboxylated compounds **11a** and **11b**.

Methoxylation of the acetals and thioacetals was effected in good yields without chloromethoxylation of the thiazine ring. Introduction of the methoxy group was always accompanied by methanolysis of the phthaloyl group into the *o*-methoxycarbonylbenzoyl group[3a].

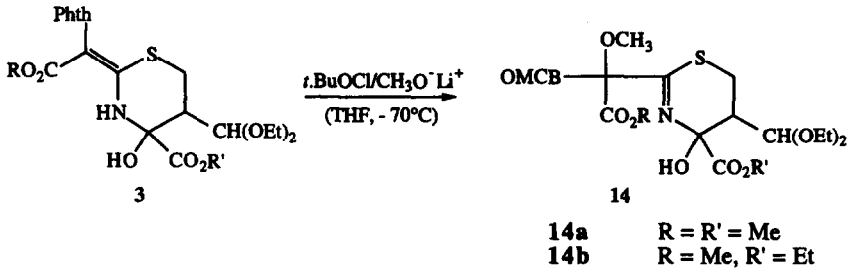


Scheme 7

Methoxylation before dehydration of the tetrahydrothiazines :

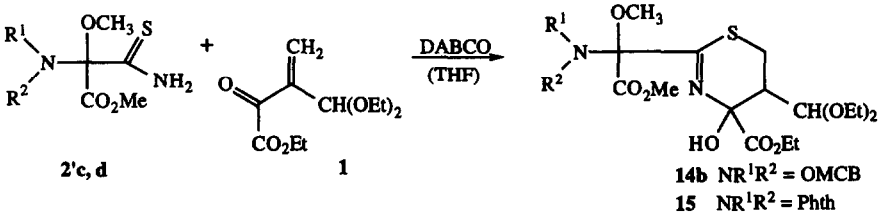
For our synthesis of thiazinic precursors of 7-methoxycephems, we investigated the possibility of methoxylation at different steps in the synthesis from the tetrahydro-1,3-thiazines **3** or the 2-thiocarbamoyl-glycinates **2**. The two routes led finally to the same thiazinic derivatives and this chemical cross-checking established proof of structure for the functionalised thiazines.

The previous methoxylation conditions on *6H*-1,3-thiazines **9** and **10** afforded in excellent yields the non dehydrated tetrahydro-1,3-thiazine homologues **14**.



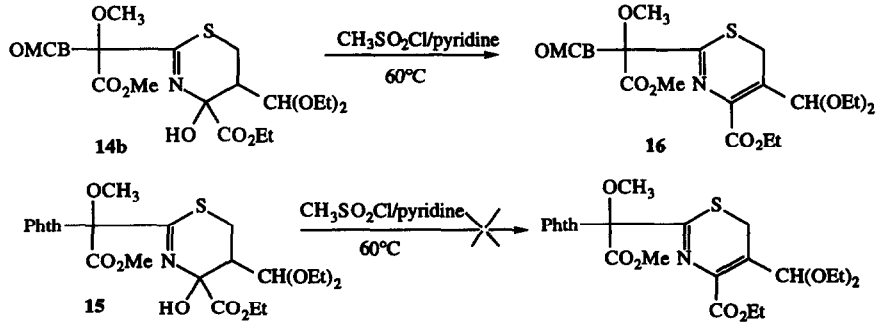
Taking into account potential applications of the synthetic route from 2-methoxy-2-cyanoglycinates[2f], it was important to study construction of the *6H*-1,3-thiazine by *[3+3] condensation* reaction between the corresponding N-protected 2-methoxy-2-thiocarbamoylglycinates and vinylic ketoesters.

After extensive investigations on experimental conditions, it was finally found that this *[3+3] condensation* reaction could be realised using DABCO instead of triethylamine or pyridine, at room temperature in tetrahydrofuran :



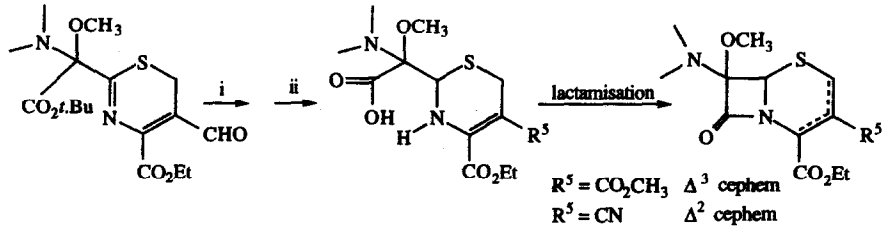
The tetrahydrothiazine **15** with phthalimido protection was particularly interesting because this synthetic scheme did not involve the methanolysis of the amino protecting group, as described for the ylidenic thiazines **3** or **9**. This reaction is also particularly interesting to consider asymmetric synthesis of these tetrahydro-1,3-thiazines because optically pure 2-thiocarbamoylglycinates **2** are available from corresponding α-methoxycyanoglycinates[12,13].

After several experiments, dehydration of the dihydrothiazines was achieved in satisfactory yields using methanesulfonyl chloride in pyridine[14]. Surprisingly, no conversion was observed when the amino protection was phthaloyl rather than *o*-methoxycarbonylbenzoyl.



Further work is still required to successfully carry out this reaction. It should also be possible to use our experience of methanolysis and ring closure of this protective group[13].

Using the *[3+3] cyclocondensation* reaction, we have synthesised the same thiazine precursors of 7-methoxycephems[2f] as had been prepared by the *[4+2] cycloaddition* pathway. This strategy required some functional transformations of the formyl group at position 5 to afford the 7-methoxycephems. It was now necessary to consider these modifications before reduction of the intracyclic imine bond, to avoid the intramolecular transesterification leading to the unexpected lactone[2e,15].



i : functional modifications : CHO ---> CO_2CH_3 and CHO ---> C≡N

ii : reduction of the intracyclic imine bond followed by the *tert*-butyl deprotection.

Conclusion

We have described the different steps leading to racemic precursors of 7-methoxycephems. It is interesting to compare the different strategies used to build this key thiazinic intermediate either by *[4+2] cycloaddition* or *[3+3] cyclocondensation*.

We succeeded in the construction of these *6H*-1,3-thiazines by employing two possible routes in the *[3+3] cyclocondensation* reaction. First, the methoxy group was introduced on ylidenic thiazines obtained from α-thiocarbamoylglycinates not substituted on the α carbon. The same cycloadducts α-methoxy-α-(*6H*-1,3-thiazin-2-yl)glycinates were also afforded by dehydration of the intermediate dihydrothiazines prepared from α-methoxy-α-thiocarbamoyglycinates.

In the case of the *[4+2] cycloaddition/elimination* reactions which gave the same target molecules, this reaction could be realised only from the α-substituted glycinate precursor. The exception is the presence of a labile hydrogen atom on the α position of the thiocarbonyl group (R^7= H) : the condensation between the orthoamide and the thiocarbamoylglycinate is followed by an intramolecular nucleophilic reaction of sulphur to afford an unexpected thiazolinone[16]. So the expected thiazinic enaminoester **6** could not be obtained using the *[4+2] cycloaddition* reaction. Therefore this functionalised ylidenic thiazinyl structure appeared particularly interesting to introduce electrophiles on the β position of the enamine. It is known that the biological activity[1] of cephalosporins depends on the nature of the substituent on this position 7.

Our synthetic strategy to cephems requires protection of the *amine*, *acid* and sometimes *carbaldehyde* functions. Cleavage of these protecting groups has to be considered in catalytic, acidic or basic media, must be selective and must be carried out in high yields at the expected step of the synthesis. For example, the thiazinyl precursors have two alkyl carboxylate functions : the protected carboxylic acid of the glycinate moiety which is the precursor of the β-lactam ring, and the one necessary for biological activity on position 4. This potential carboxylic acid function is introduced differently depending on the cycloaddition pathway.

Using the *[4+2] cycloaddition* route, only the ethoxycarbonyl derivative for the *alkyl carboxylate* CO_2R' group was accessible for the thiazadiene (retrosynthetic scheme). The *alkyl carboxylate* function came from the vinylic ketoester which was considered as the Michaël acceptor for the *[3+3] cyclocondensation*. The expected diversification was then possible using synthesis of these new vinylic ketoesters and in agreement with recent published results[17]. We succeeded in the introduction of an ester function which could be deprotected either in basic medium (R' = Me, Et) or acidic medium (R' = *t*.Bu).

In conclusion, the synthetic strategy using the *[3+3] cyclocondensation* reaction we have developed in this work gave the precursors of *7-methoxycephems* which were functionalised with a protected or deprotected carbaldehyde group in position 5 of the thiazinic ring. Comparison with previous results achieved using the *[4+2] cycloaddition* reaction, showed that this new multistep pathway presents some interesting advantages.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL instrument J.N.M. FX 90-MHz. Chemical shifts are reported as δ values in ppm down field from internal standard (Me_4Si) with notations specifying the number of protons, the multiplicity of the signal : s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet) , t (triplet), q (quartet), m (multiplet) and the coupling constants. IR spectra were measured in KBr with a PERKIN-ELMER 1420 spectrophotometer. Mass spectra were recorded on a HP 5889 A spectrometer at 70 eV. The compounds purity was monitored by thin layer chromatography (TLC) on silica gel plates. Column chromatography was carried out on silica gel (Merck, Kieselgel 60). Elemental microanalyses were performed by the Central Service of Microanalysis of the CNRS (Vernaison, France). Melting points were determined using a microscope with a Kofler hot stage and are uncorrected.

General procedure for the synthesis of acetalised vinylic ketoesters (1)
To a solution of 2-bromo-3,3-diethoxypropene (4 g, 19.2 mmol) and lithium bromide (1 g) in dry THF (60 mL) were added dropwise at -75°C butyllithium (1.4 M in hexane, 15mL, 21 mmol) and the solution was stirred 20 min at -75°C. The organolithium compound was then added at -75°C to a solution of dialkyl oxalate (18 mmol) in a mixture of dry THF (30 mL) and dry ether (30 mL). After stirring for 2 h at -75°C, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was dried ($MgSO_4$) and the residual yellow liquid obtained after concentration was used without purification for the [3+3] cyclocondensation reaction. Crude yield = 50-73%.

Methyl 3-diethoxymethyl-2-oxobut-3-enoate (1a)
^1H NMR δ : 1.17 (t, J = 7Hz, 6H, $2C\underline{H}_3CH_2$); 3.60 (q, J = 7Hz, 4H, $(OC\underline{H}_2CH_3)_2$); 3.85 (s, 3H, CO_2CH_3); 5.40 (s, 1H, $C\underline{H}(OC_2H_5)_2$); 6.38 (s, 2H, H_2C=C). *^{13}C NMR δ :* 15.19 ($(OCH_2\underline{C}H_3)_2$); 52.56 ($CH_3O$); 62.39 ($(O\underline{C}H_2CH_3)_2$); 97.45 ($\underline{C}H(OC_2H_5)_2$); 131,06 ($H_2\underline{C}$=C); 142.60 ($H_2C$=$\underline{C}$-); 163.46 ($\underline{C}O_2CH_3$); 185.77 (C=O). *MS m/e (I%) :* 187(3), 171(28), 157(18), 143(12), 129(28), 115(39), 103(19), 101(31), 83(100). *IR (KBr) cm^{-1} :* 1740 (C=O ester); 1685 (C=O ketone).

Ethyl 3-diethoxymethyl-2-oxobut-3-enoate (1b)
^1H NMR δ : 1.20 (t, J = 7Hz, 6H, $2C\underline{H}_3CH_2O$); 1.37 (t, J = 7Hz, 3H, $CO_2CH_2C\underline{H}_3$); 3.57 (q, J = 7Hz, 4H, $CH(OC\underline{H}_2CH_3)_2$); 4.40 (q, J = 7Hz, 2H, $CO_2C\underline{H}_2CH_3$); 5.40 (s, 1H, $C\underline{H}(OC_2H_5)_2$); 6.40 (s, 2H, H_2C=C). *^{13}C NMR δ :* 13.40 ($CO_2CH_2\underline{C}H_3$); 14.51 ($(OCH_2\underline{C}H_3)_2$); 61.54 ($CO_2\underline{C}H_2CH_3$); 61.64 ($2CH_3\underline{C}H_2O$); 96.71 ($\underline{C}H(OC_2H_5)_2$); 130.44 ($H_2\underline{C}$=C-); 141.96 ($H_2C$=$\underline{C}$-); 162.62 ($\underline{C}O_2C_2H_5$); 185.64 (C=O). *MS m/e (I%) :* 230(1), 201(5), 185(22), 157(58), 129(68), 103(29), 101(89), 83(100). *IR (KBr) cm^{-1} :* 1750 (C=O ester), 1670 (C=O ketone).

***Tert*-butyl 3-diethoxymethyl-2-oxobut-3-enoate (1c)**
^1H NMR δ : 1.21 (t, J = 7Hz, 6H, $2C\underline{H}_3CH_2$); 1.44 (s, 9H, $C(C\underline{H}_3)_3$); 3.56 (q, J = 7Hz, 4H, $(OC\underline{H}_2CH_3)_2$); 5.41 (s, 1H, $C\underline{H}(OC_2H_5)_2$); 6.40 (s, 2H, H_2C=C). *^{13}C NMR δ :* 14.79 ($(OCH_2\underline{C}H_3)_2$); 27.45 ($C(\underline{C}H_3)_3$); 61.76 ($2CH_3\underline{C}H_2O$); 83.72 ($\underline{C}(CH_3)_3$); 96.73 ($\underline{C}H(OC_2H_5)_2$); 130.50 ($H_2\underline{C}$=C-); 142.21 ($H_2C$=$\underline{C}$-); 157.63 ($\underline{C}O_2t$.Bu); 186.35 (C=O). *MS m/e (I%) :* 213(1), 185(1), 157(14), 129(13), 103(3), 101(19), 83(34), 57(100). *IR (KBr) cm^{-1} :* 1745 (C=O ester), 1685 (C=O ketone).

General procedure for the [3+3] cyclocondensation : synthesis of 2-methylenetetrahydrothiazines (3)
To a solution of 5 mmoles of thioamide **2**, obtained as described in the literature[2f], in 30 mL of CH_2Cl_2 were added successively 10 mmoles of vinylic ketoester **1** and 5 mmoles of triethylamine. The solution was stirred for 3 h at room temperature. After

evaporation of the solvent, the residue was purified by a silica gel column (Eluent : EtOAc/Petroleum ether/Triethylamine : 48/50/2).

Methyl 2-(5-diethoxymethyl-4-hydroxy-4-methoxycarbonyl-1,3-perhydrothiazine-2-ylidene)-2-phthalimido ethanoate (3a)

Yield = 65 %. Diastereoisomeric ratio = 80/20. White crystals. mp = 179-180°C (diethyl ether). *^{1}H NMR δ :* 1.17 (t, J = 7Hz, 6H, $CH(OCH_2\underline{C}H_3)_2$); 2.70 (m, 1H, $\underline{C}H$-$CH(OC_2H_5)_2$); 3.57 (q, J = 7Hz, 4H, $CH(O\underline{C}H_2CH_3)_2$); 3.61 and 3.87 (2s, 6H, $2CO_2CH_3$); 4.50 and 4.64 (2d, J = 6.6Hz, 1 H, $C\underline{H}(OC_2H_5)_2$); 7.79 (m, 4H, C_6H_4); 10.66 and 10.87 (2bs, 1H, NH); the signals corresponding to SCH_2 and OH are superimposed with the signals of $CH(OC_2H_5)_2$ and CO_2CH_3. *^{13}C NMR δ :* 14.83; 15.06; 15.22 and 15.45 (CH_3); 23.13 and 24.13 (SCH_2); 41.96 and 43.50 ($\underline{C}H$-$CH(OC_2H_5)_2$); 51.20; 52.73; 53.18 and 53.93 ($CO_2\underline{C}H_3$); 64.14; 65.25 and 65.51 ($CH_3\underline{C}H_2O$); 79,20 et 82.59 (N-$\underline{C}$-OH); 92.35 (N-$\underline{C}$=C-S); 100.77 ($\underline{C}H(OC_2H_5)_2$); 123.54; 123.90; 132.13; 134.11 and 134.47 (C_6H_4); 160.59; 164.40; 165.31; 165.89; 167.94; 168.82 and 170.35 (N-C=$\underline{C}$-S + C=O). *MS m/e (I%) :* 494 ($M^{+\cdot}$, <1), 476(14), 431(42), 399(47), 371(18), 278(10), 230(9), 196(10), 190(41), 185(419), 171(10), 158(26), 132(38), 130(21), 115(16), 104(98), 103(58), 83(49), 76(60), 45(19), 29(100). *IR (KBr) cm^{-1} :* 3349 (OH), 3200 (NH), 1783, 1764, 1748 and 1712 (C=O Phth and C=O esters). *Anal.* Calcd. for $C_{22}H_{26}N_2O_9S$ (494.52): C 53.43, H 5.30, N 5.66 Found : C 53.10, H 5.35, N 5.55

Methyl 2-(4-ethoxycarbonyl-5-diethoxymethyl-4-hydroxy-1,3-perhydrothiazine-2-ylidene)-2-phthalimido ethanoate (3b)

Yield = 68 %. Diastereoisomeric ratio = 80/20. Yellow crystals. mp = 182-183°C (diethyl ether). *^{1}H NMR δ :* 1.16 (t, J = 7Hz, 6H, $CH(OCH_2\underline{C}H_3)_2$); 1.37 (t, J = 7.2Hz, 3H, $CO_2CH_2\underline{C}H_3$); 2.70 (m, 1H, $\underline{C}H$-$CH(OC_2H_5)_2$); 3.52 (q, J = 7Hz, 4H, $CH(O\underline{C}H_2CH_3)_2$); 3.61 (s, 3H, CO_2CH_3); 4.32 (q, J = 7.2Hz, 2H, $CO_2\underline{C}H_2CH_3$); 4.50 and 4.65 (2d, J = 6.4Hz, 1H, $C\underline{H}(OC_2H_5)_2$); 7.83 (m, 4H, C_6H_4); 10.60 (bs, 1H, NH); the signals corresponding to SCH_2 and OH are superimposed with the signals of $CH(OC_2H_5)_2$ and CO_2CH_3. *^{13}C NMR δ :* 13.98; 14.89; 15.22 and 15.35 ($\underline{C}H_3CH_2$); 22.10 and 23.20 (SCH_2); 42.61 and 43.06 ($\underline{C}H$-$CH(OC_2H_5)_2$); 51.23 ($CO_2\underline{C}H_3$); 61.41; 62.84; 63.30; 64.05; 64.83 and 65.18 ($CH_3\underline{C}H_2O$); 79.40 and 79.85 (N-$\underline{C}$-OH); 92.41 (N-$\underline{C}$=C-S); 100.80 and 101.98 ($\underline{C}H(OC_2H_5)_2$); 123.61; 132.23 and 134.15 (C_6H_4); 160.17; 160.72; 165.99; 168.17; 169.99 and 170.20 (N-C=$\underline{C}$-S + C=O). *MS m/e (I%) :* 490(3), 445(11), 413(11), 385(5), 311(6), 230(10), 200(9), 190(18), 185(21), 158(14), 132(14), 129(9), 104(43), 103(100), 85(36), 83(30), 76(29), 75(64). *IR (KBr) cm^{-1} :* 3423 (OH), 3197 (NH), 1786, 1751 and 1723 (C=O Phth and C=O esters). *Anal.* Calcd. for $C_{23}H_{28}N_2O_9S$ (508.55): C 54.32, H 5.55, N 5.51 Found : C 54.86, H 5.50, N 5.43

***Tert*-butyl 2-(5-diethoxymethyl-4-hydroxy-4-methoxycarbonyl-1,3-perhydrothiazine-2-ylidene)-2-phthalimidoethanoate (3c)**

Yield = 50 to 65 %. Diastereoisomeric ratio = 78/22. Yellow crystals. mp = 96-99°C (diethyl ether). *^{1}H NMR δ :* 1.17 (t, J = 7Hz, 6H, $CH(OCH_2\underline{C}H_3)_2$); 1.30 and 1.33 (2s, 9H, *t*.Bu); 2.65 (m, 1H, $\underline{C}H$-$CH(OC_2H_5)_2$); 3.57 (q, J = 7Hz, 4H, $CH(O\underline{C}H_2CH_3)_2$); 3.86 and 3.89 (2s, 3 H, CO_2CH_3); 4.50 and 4.67 (2d, J = 6.7Hz, 1H, $C\underline{H}(OC_2H_5)_2$), 7.81 (m, 4H, C_6H_4); 10.25 and 10.50 (2bs, 1H, NH); the signals corresponding to SCH_2 and OH are superimposed with the signals of $CH(OC_2H_5)_2$ and CO_2CH_3. *^{13}C NMR δ :* 14.83; 15.22 and 15.35 (CH_3); 23.19 (SCH_2); 28.33 ($(\underline{C}H_3)_3C$); 43.13 ($\underline{C}H$-$CH(OC_2H_5)_2$); 53.12 ($CO_2\underline{C}H_3$); 64.31; 65.28 and 65.84 ($CH_3\underline{C}H_2O$): 79.27 and 80.38 (N-$\underline{C}$-OH + $(CH_3)_3\underline{C}$): 89.61 (N-$\underline{C}$=C-S); 100.93 and 102.10 ($\underline{C}H(OC_2H_5)_2$): 123.54; 132.33 and 134.11 (C_6H_4); 159.16; 164.99; 168.24 and 170.61 (N-C=$\underline{C}$-S + C=O). *MS m/e (I%) :* 536($M^{+\cdot}$, 20), 518(6), 480(7), 477(10), 462(11), 431(12), 421(16); 417(24), 399(13), 376(15), 375(72), 331(19), 329(12), 285(40), 264(16), 203(28), 190(10), 160(12), 132(15), 115(13), 104(33), 103(65), 85(100), 76(16), 75(34), 57(61). *IR (KBr) cm^{-1} :* 3400 (OH), 3220 (NH), 1780, 1740, 1730 and 1710 (C=O Phth and C=O esters)

***Tert*-butyl 2-(4-*tert*-butoxycarbonyl-5-diethoxymethyl-4-hydroxy-5-diethoxymethyl-1,3-perhydrothiazine-2-ylidene)-2-phthalimidoethanoate (3d)**

Yield = 63 %. Diastereoisomeric ratio = 60/40. Oil. *^{1}H NMR δ :* 1.15 (t, J = 7Hz, 6H, $(OCH_2\underline{C}H_3)_2$); 1.33 and 1.52 (2s, 18H, $2C(\underline{C}H_3)_3$); 2.70 (m, 1H, $\underline{C}H$-$CH(OC_2H_5)_2$); 3.54 (q, J = 7Hz, 4H, $(O\underline{C}H_2CH_3)_2$); 4.58 and 4.76 (2d, J = 6.6Hz, 1H, $C\underline{H}(OC_2H_5)_2$); 7.82 (m, 4H, C_6H_4); 10.10 and 10.35 (2bs, 1H, NH); the signals corresponding to SCH_2 and OH are superimposed with the signals of $CH(OC_2H_5)_2$. *^{13}C NMR δ :* 14.64; 14.90 and 15.16 (CH_3); 22.22 and 23.42 (SCH_2); 27.58 and 27.98 ($C(\underline{C}H_3)_3$); 42.61 and 43.56 ($\underline{C}H$-$CH(OC_2H_5)_2$); 61.29; 63.30 and 64.67 ($CH_3\underline{C}H_2O$); 79.47; 79.92; 80.51 and 83.92 (N-$\underline{C}$-OH + $\underline{C}(CH_3)_3$); 89.03 and 89.75 (N-$\underline{C}$=C-S); 100.38 and 101.85 ($\underline{C}H(OC_2H_5)_2$); 123.12; 123.22; 132.04 and 133.86 (C_6H_4); 157.73; 159.65; 159.88; 165.02; 167.75; 168.02; 168.90 and 170.06 (N-C=$\underline{C}$-S + C=O). *MS m/e (I%) :* 578($M^{+\cdot}$, <1), 560(<1), 477(5), 431(4), 402(2), 375(22), 331(5), 285(16), 203(4), 104(11), 103(29), 85(100), 76(16), 57(69). *IR (KBr) cm^{-1} :* 3360 (OH), 3220 (NH), 1785, 1760, 1730 and 1740 (C=O Phth and C=O esters).

Methyl 2-(4-ethoxycarbonyl-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene)-2-phthalimidoethanoate (4)

A stream of dry HCl was passed through a solution of tetrahydrothiazine **3b** (0.31 g, 0.61 mmol) in 40 mL of anhydrous CH_3NO_2, cooled at 0°C, under saturation. The mixture was stirred for 1 h at 0°C, the solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography (Eluent : EtOAc/petroleum ether = 50/50) to give 0.22 g of the corresponding compound **4** as a colourless oil. Yield = 93 %.

^{1}H NMR δ : 1,37 (t, J = 7.2Hz, 3H, $C\underline{H}_3CH_2$); 3.45 (d, J = 5.7Hz, 2H, SCH_2); 3.67 (s, 3H, CO_2CH_3); 4.36 (q, J = 7Hz, 2H, $CH_2\underline{C}H_3$); 6.17 (dt, J = 1.2 and 5.7Hz, 1H, N-C=C$\underline{H}$); 7.84 (m, 4H, C_6H_4); 11.61 (bs, 1H, NH). *^{13}C NMR δ :* 14.15

($\underline{C}H_3CH_2$); 23.29 (SCH_2); 51.68 ($CO_2\underline{C}H_3$); 62.22 ($CH_3\underline{C}H_2O$); 90.94 (N-$\underline{C}$=C-S); 106.59 (N-C=$\underline{C}$H); 123.73; 131.99 and 134.30 (C_6H_4); 130.56 (N-$\underline{C}$=CH); 157.24; 161.63; 165.70 and 167.78 (N-C=$\underline{C}$-S + C=O). *MS m/e (I%) :* 388($M^{+\cdot}$, 100), 356(29), 342(13), 314(13), 283(37), 255(14), 230(18), 190(43), 158(33), 132(51), 130(15), 104(99), 76(42). *IR (KBr) cm^{-1}:* 3185 (NH), 1785 and 1723 (C=O).

Methyl 2-(5-diethoxymethyl-4-ethoxy-4-ethoxycarbonyl-1,3-perhydrothiazine-2-ylidene)-2-phthalimido ethanoate (5)

To a solution of tetrahydrothiazine **3b** (0.2 g, 0.39 mmol) in 30 mL of anhydrous ethanol was added a spatule of 4Å molecular sieves. The reaction was saturated at 0°C with a stream of dry HCl under saturation, then stirred at 0°C for 4 h. The solution was filtered through celite, then concentrated and the residue was chromatographed on a silica gel column (Eluent : EtOAc/petroleum ether/triethylamine = 50/48/2) to afford 0.151 g of colourless oil. Yield = 72 %.

^1H NMR δ : 1.14; 1.18; 1.22 and 1.36 (4t, J = 7Hz, 12H, $C\underline{H}_3CH_2$); 3.64 (s, 3H, CO_2CH_3); 2.80 to 3.90 (m, 9H, SCH_2 + C$\underline{H}$-CH($OC\underline{H}_2CH_3$)$_2$ + $OC\underline{H}_2CH_3$); 4.28 and 4.36 (2 q, J = 7Hz, 2H, $CO_2C\underline{H}_2CH_3$); 4.59 (d, J = 8.2Hz, 1H, C$\underline{H}$(OC_2H_5)$_2$); 7.83 (m, 4H, C_6H_4); 10.92 (bs, 1H, NH). *^{13}C NMR δ :* 13.91; 14.42; 14.94 and 15.30 (CH_3); 24.01 (SCH_2); 41.58 (C$\underline{H}$-CH(OC_2H_5)$_2$); 51.00 ($CO_2\underline{C}H_3$); 58.40; 61.91; 63.54 and 65.19 ($CH_3\underline{C}H_2O$); 82.40 (N-$\underline{C}$-OC_2H_5); 88.02 (N-$\underline{C}$=C-S); 100.61 ($\underline{C}$H(OC_2H_5)$_2$); 123.35; 132.01 and 133.96 (C_6H_4); 160.63; 165.67; 167.85 and 168.11(N-C=$\underline{C}$-S + C=O). *MS m/e (I%) :* 536($M^{+\cdot}$, 11), 492(2), 463(11), 445(4), 419(18), 385(14), 357(9), 343(8), 190(10), 158(6), 132(8), 104(20), 103(100), 85(10), 76(7), 75(30), 47(27). *IR (KBr) cm^{-1} :* 3182 (NH), 1787, 1744 and 1725 (C=O).

General procedure for the synthesis of 5-formyl-3,6-dihydro-2*H*-1,3-thiazines (6)

To a solution of 3 mmoles of tetrahydrothiazine **3** in 60 mL of acetone were added successively 0.5 mL of water and 0.5 mL of 48% aqueous solution of hydrobromic acid in acetone (0.1 mL/5 mL). The mixture was stirred at reflux for 3 h. The reaction was followed by TLC. The solution was then concentrated under reduced pressure, dissolved in EtOAc and washed successively with a 5% aqueous solution of $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by silica gel chromatography (Eluent : CH_2Cl_2/EtOAc = 96/4).

Methyl 2-(5-formyl-4-methoxycarbonyl-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene)-2-phthalimidoethanoate (6a)

Yield = 92 %. Yellow crystals. mp = 111-113°C (methanol). *^1H NMR δ :* 3.67 (s, 2H, SCH_2); 3.72 (s, 3H, CO_2CH_3); 4.07 (s, 3H, CO_2CH_3); 7.86 (m, 4H, C_6H_4); 10.40 (s, 1H, CHO); 12.25 (bs, 1H, NH). *^{13}C NMR δ :* 20.27 (SCH_2); 52.28 and 54.00 ($CO_2\underline{C}H_3$); 95.79 (N-$\underline{C}$=C-S); 117.36 (N-$\underline{C}$=C-CHO); 123.89; 131.90 and 134.50 (C_6H_4); 138.70 (N-C=$\underline{C}$-CHO); 155.90 (N-C=$\underline{C}$-S); 161.14; 165.63 and 167.10 (C=O); 187.95 (CHO). *MS m/e (I%) :* 402($M^{+\cdot}$, 82), 370(25), 355(9), 341(21), 338(30), 313(19), 283(19), 230(10), 190(43), 158(15), 132(48), 104(100), 76(40). *IR (KBr) cm^{-1} :* 3480 (NH), 1720 and 1780 (C=O). *Anal.* Calcd. for $C_{18}H_{14}N_2O_7S$ (402.38) : C 53.73, H 3.51, N 6.96 Found : C 53.41, H 3.62, N 6.78

Methyl 2-(4-ethoxycarbonyl-5-formyl-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene)-2-phthalimidoethanoate (6b)

Yield = 95 %. Yellow crystals. mp = 136-138°C (methanol). *^1H NMR δ :* 1.47 (t, J = 7Hz, 3H, $C\underline{H}_3CH_2$); 3.67 (s, 2H, SCH_2); 3.71 (s, 3H, CO_2CH_3); 4.52 (q, J = 7Hz, 2H, $CH_3C\underline{H}_2$); 7.86 (m, 4H, C_6H_4); 10.45 (s, 1H, CHO); 12.27 (bs, 1H, NH). *^{13}C NMR δ :* 14.03 ($\underline{C}H_3CH_2$); 20.30 (SCH_2); 52.21 ($CO_2\underline{C}H_3$); 63.82 ($CH_3\underline{C}H_2O$); 95.39 (N-$\underline{C}$=C-S); 117.17 (N-$\underline{C}$=C-CHO); 123.93; 131.67 and 134.47 (C_6H_4); 139.15 (N-C=$\underline{C}$-CHO); 155.91 (N-C=$\underline{C}$-S); 160.72; 165.67 and 167.20 (C=O); 187.85 (CHO). *MS m/e (I%) :* 416($M^{+\cdot}$, 30), 384(6), 370(4), 355(37), 338(11), 327(10), 190(11), 158(12), 132(23), 104(100), 76(50). *IR (KBr) cm^{-1} :* 3420(NH); 1780 and 1720 (C=O). *Anal.* Calcd. for $C_{19}H_{16}N_2O_7S$ (416.41) : C 54.80, H 3.87, N 6.73 Found : C 54.77, H 3.97, N 6.62

***Tert*-butyl 2-(5-formyl-4-methoxycarbonyl-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene)-2-phthalimidoethanoate (6c)**

Yield = 85 %. Oil. *^1H NMR δ :* 1.38 (s, 9H, *t*.Bu); 3.65 (s, 2H, SCH_2); 4.05 (s, 3H, CO_2CH_3); 7.87 (m, 4H, C_6H_4); 10.39 (s, 1H, CHO); 12.21 (bs, 1H, NH). *^{13}C NMR δ:* 20.36 (SCH_2); 28.13 (($\underline{C}H_3$)$_3$C); 53.93 ($CO_2\underline{C}H_3$); 82.68 ((CH_3)$_3\underline{C}$); 98.04 (N-$\underline{C}$=C-S); 117.10 (N-$\underline{C}$=C-CHO); 123.87; 132.13 and 134.44 (C_6H_4); 139.13 (N-C=$\underline{C}$-CHO); 154.35 (N-C=$\underline{C}$-S); 161.57; 163.33 and 167.36 (C=O); 187.82 (CHO). *MS m/e (I%) :* 444($M^{+\cdot}$, 12), 390(8), 388(100), 360(19), 341(13), 313(17), 312(40), 256(18), 203(19), 190(17), 160(25), 132(19), 104(33), 76(13). *IR (KBr) cm^{-1} :* 3480 (NH), 1787 and 1724 (C=O). *Anal.* Calcd. for $C_{21}H_{20}N_2O_7S$ (444.56) : C 56.75, H 4.54, N 6.30 Found : C 56.76, H 4.49, N 6.20

***Tert*-butyl 2-(4-*tert*-butoxycarbonyl-5-formyl-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene)-2-phthalimido ethanoate (6d)**

Yield = 74 %. Yellow crystals. mp = 174-175°C (methanol). *^1H NMR δ :* 1.33 (s, 9H, *t*.Bu); 1.62 (s, 9H, *t*.Bu); 3.60 (s, 2H, SCH_2); 7.82 (m, 4H, C_6H_4); 10.42 (s, 1H, CHO); 12.29 (bs, 1H, NH). *^{13}C NMR δ :* 20.10 (SCH_2); 27.85 (2($\underline{C}H_3$)$_3$C); 82.17 ((CH_3)$_3\underline{C}$); 85.97 ((CH_3)$_3\underline{C}$); 97.23 (N-$\underline{C}$=C-S); 116.19 (N-$\underline{C}$=C-CHO); 123.58; 131.84 and 134.25 (C_6H_4); 140.23 (N-C=$\underline{C}$-CHO); 154.35 (N-C=$\underline{C}$-S); 159.33; 164.37 and 167.17 (C=O); 187.86 (CHO). *MS m/e (I%) :* 486($M^{+\cdot}$, 4), 430(6), 375(10), 374(53), 357(7), 312(18), 284(18), 256(10), 203(21), 189(25), 160(18), 158(13), 132(24), 104(68), 76(28), 57(100). *IR (KBr) cm^{-1} :* 3294 (NH), 1785 and 1725 (C=O). *Anal.* Calcd. for $C_{24}H_{26}N_2O_7S$ (486.54) : C 59.25, H 5.39, N 5.76 Found : C 58.98, H 5.35, N 5.78

Methyl 2-(5-chloro-4-ethoxycarbonyl-5-formyl-4-methoxy-5,6-dihydro-*4H*-1,3-thiazine-2-yl)-2-methoxy-2-*o*-methoxycarbonylbenzamidoethanoate (8)

To a solution of 5-formyl-3,6-dihydro-2*H*-1,3-thiazine **6b** (0.22 g, 0.53 mmol) in 30 mL of dry THF were added at -70°C 1 mL of lithium methylate (1M in methanol), then *tert*-butylhypochlorite (0.11 g; 1 mmol). The reaction mixture was stirred for 2 h, poured in cooled water and extracted with EtOAc. The organic layer was dried ($MgSO_4$), then the solvent was evaporared affording after chromatography on silica gel (Eluent : EtOAc/petroleum ether = 50/50) 0.148 g of colourless oil. Yield = 53 %. Diastereoisomeric ratio = 76/24.

^1H NMR δ : 1.25 (t, J = 7Hz, 3H, $C\underline{H}_3CH_2$); 3.42 (m, 2H, SCH_2); 3.48 and 3.52 (2s, 6H, CH_3O); 3.87 (s, 6H, $2CO_2CH_3$); 4.30 (q, J = 7Hz, 2H, $CH_3C\underline{H}_2$); 7.50 to 8.00 (m, 4 H, C_6H_4); 8.10 (bs, 1H, NH); 9.72 and 9.77 (2s, 1H, CHO). *^{13}C NMR* δ : 14.02 (CH_3); 29.50 (SCH_2); 51.78; 52.63; 53.21 and 53.77 ($2CH_3O$ + $2CO_2\underline{C}H_3$); 63.04 ($O\underline{C}H_2CH_3$); 64.37 ($\underline{C}$(Cl)CHO); 88.06 and 89.26 (N-$\underline{C}$-OCH_3 + N-$\underline{C}$-$CO_2C_2H_5$); 127.28; 130.24; 130.44; 131.77 and 136.81 (C_6H_4); 166.61; 166.90; 167.10 and 167.94 (C=O); 190.06 (CHO). *MS m/e (I%)* : 544/546($M^{+\cdot}$, <1), 514/516(<1), 485/487(3/1), 471/473(6/3), 443(4), 280(3), 248(6), 174(8), 163(100), 104(8). *IR (KBr) cm^{-1}* : 3360 (NH), 1770 and 1720 (C=O esters).

Methyl 2-(5-chloro-4-ethoxycarbonyl-5-formyl-4-methoxy-5,6-dihydro-*4H*-1,3-thiazine-2-yl)-2-chloro-2-phthalimidoethanoate (7)

This compound **7**, isolated as a colourless oil, was the precursor of the compound **8**. Diastereoisomeric ratio = 63/37. *^1H NMR* δ : 1.10 and 1.29 (2t, J = 7Hz, 3H, $C\underline{H}_3CH_2$); 3.25 and 3.30 (2s, 3H, CH_3O); 3.20 to 3.80 (m, 2H, SCH_2); 3.82 (s, 3H, CO_2CH_3); 4.26 (q, J = 7Hz, 2H, $CO_2C\underline{H}_2CH_3$); 7.86 (m, 4H, C_6H_4); 9.70 and 9.72 (2s, 1H, CHO). *MS m/e (I%)* : 516/518/520($M^{+\cdot}$, <1), 457(8), 445(47), 443(65), 415(8), 399(16), 349(20), 216(13), 190(15), 174(100), 132(21), 104(63), 76(42). *IR (KBr) cm^{-1}* : 1790, 1765 and 1740 (C=O).

Methyl 2-[5-(1,3-dioxan-2-yl)-4-ethoxycarbonyl-3,6-dihydro-*2H*-1,3-thiazine-2-ylidene]-2-phthalimido ethanoate (9)

A solution of 2 mmoles of 5-formyl-3,6-dihydro-2*H*-1,3-thiazine **6b** (0.84 g) in 50 mL of anhydrous benzene containing 6 mmoles of 1,3-propanediol and a catalytic amount of *p*-toluenesulfonic acid was stirred at reflux for 16 h. Water was eliminated using a Dean and Stark separator. The solution was washed with an aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (Eluent : EtOAc/petroleum ether/triethylamine = 48/50/2) to afford 0.77 g of colourless oil. Yield = 81 %.

^1H NMR δ : 1.44 (t, J = 7.2Hz, 3H, $C\underline{H}_3$-CH_2); 2.06 (m, 2H, $OCH_2C\underline{H}_2CH_2O$); 3.57 (s, 2H, SCH_2); 3.66 (s, 3H, CO_2CH_3); 4.05 (m, 4H, $OC\underline{H}_2CH_2C\underline{H}_2O$); 4.41 (q, J = 7.2Hz, 2H, $CH_3C\underline{H}_2$); 6.19 (s, 1H, O-$C\underline{H}$-O); 7.83 (m, 4H, C_6H_4); 11.80 (bs, 1H, NH). *^{13}C NMR* δ : 14.05 ($\underline{C}H_3CH_2$); 22.67 and 25.69 (SCH_2 + $OCH_2\underline{C}H_2CH_2O$); 51.55 ($CO_2\underline{C}H_3$); 62.48 ($\underline{C}H_2CH_3$); 67.07 ($O\underline{C}H_2CH_2\underline{C}H_2O$); 91.27 (N-$\underline{C}$=C-S); 97.16 (O-$\underline{C}$H-O); 120.77 and 128.06 (N-$\underline{C}$=$\underline{C}$-CH); 123.67; 132.10 and 134.21 (C_6H_4); 159.03; 161.08; 165.73 and 167.58 (N-C=$\underline{C}$-S + C=O). *MS m/e (I%)* : 474($M^{+\cdot}$, 54), 443(4), 415(6), 401(18), 369(42), 355(24), 230(14), 190(35), 158(19), 132(24), 104(47), 87(100), 76(17). *IR (KBr) cm^{-1}* : 3190 (NH), 1787 and 1730 (C=O). *Anal.* Calcd. for $C_{22}H_{22}N_2O_8S$ (474.49) : C 55.69, H 4.67, N 5.90 Found : C 55.85, H 4.80, N 5.81

General procedure for the synthesis of 2-methylene-3,6-dihydro-*2H*-1,3-thiazines (10)

To a solution of 2.5 mmoles of 5-formyl-3,6-dihydro-2*H*-1,3-thiazine **6** in 60 mL of dry CH_2Cl_2 were added 8 mmoles of 1,2-ethanedithiol (or 1,3-propanedithiol) and 0.06 mL of boron trifluoride etherate. The reaction mixture was stirred for 4 h at room temperature under nitrogen atmosphere, then washed successively with 20 mL of 5% aqueous solution of NaOH and 20 mL of water. The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and the residue was chromatographed on silica gel (Eluent : EtOAc/petroleum ether = 40/60).

Methyl 2-[4-methoxycarbonyl-5-(1,3-dithiolan-2-yl)-3,6-dihydro-*2H*-1,3-thiazine-2-ylidene]-2-phthalimido ethanoate (10a)

Yield = 97 %. Oil. *^1H NMR* δ : 3.33 (s, 4H, $CH(SC\underline{H}_2)_2$); 3.59 (s, 2H, $SC\underline{H}_2$); 3.66 (s, 3H, CO_2CH_3); 3.96 (s, 3H, CO_2CH_3); 6.82 (s, 1H, $C\underline{H}(SCH_2)_2$); 7.84 (m, 4H, C_6H_4); 11.78 (bs, 1H, NH). *^{13}C NMR* δ : 25.44 (S-$\underline{C}H_2$-C=C); 40.59 ($CH(S\underline{C}H_2)_2$); 51.10; 51;36 and 52.34 ($2CO_2CH_3$ + $\underline{C}H(SCH_2)_2$); 91.92 (N-$\underline{C}$=C-S); 123.61; 132.72 and 134.08 (C_6H_4); 123.83 and 126.96 (N-$\underline{C}$=$\underline{C}$-CH); 158.74 (N-C=$\underline{C}$-S); 161.60; 166.42 and 167.62 (C=O). *MS m/e (I%)* : 478($M^{+\cdot}$, 11), 446(7), 418(6), 386(8), 262(12), 230(15), 190(16), 158(16), 156(12), 132(14), 130(13), 105(42), 104(100), 76(80). *IR (KBr) cm^{-1}* : 3480 (NH), 1786, 1754 and 1723 (C=O). *Anal.* Calcd. for $C_{20}H_{18}N_2O_6S_3$ (478.56) : C 50.20, H 3.79, N 5.85 Found : C 51.50, H 3.77, N 5.79

Methyl 2-[4-ethoxycarbonyl-5-(1,3-dithiolan-2-yl)-3,6-dihydro-*2H*-1,3-thiazine-2-ylidène]-2-phthalimido ethanoate (10b)

Yield = 95 %. Yellow crystals. mp = 110-113°C (methanol). *^1H NMR* δ : 1.43 (t, J = 7.2Hz, 3H, $C\underline{H}_3CH_2$); 3.32 and 3.33 (2s, 4H, $CH(SC\underline{H}_2)_2$); 3.59 (s, 2H, SCH_2); 3.65 (s, 3H, CO_2CH_3); 4.41 (q, J = 7.2Hz, 2H, $CH_3C\underline{H}_2$); 6.83 (s, 1H, $C\underline{H}(SCH_2)_2$); 7.87 (m, 4H, C_6H_4); 11.78 (bs, 1H, NH). *^{13}C NMR* δ : 14.12 ($\underline{C}H_3CH_2$); 25.47 (S-$\underline{C}H_2$-C=C); 40.72 ($CH(S\underline{C}H_2)_2$); 50.94 and 51.62 (CO_2CH_3 + $\underline{C}H(SCH_2)_2$); 62.61 ($CH_3\underline{C}H_2$); 91.01 (N-$\underline{C}$=C-S); 123.71; 132.10 and 134.24 (C_6H_4); 123.25 and 127.22 (N-$\underline{C}$=$\underline{C}$-CH); 158.74 (N-C=$\underline{C}$-S); 161.54; 165.73 and 167.62 (C=O). *MS m/e (I%)* : 492($M^{+\cdot}$, 23), 460(5), 446(12), 418(16), 387(10), 386(17), 359(8), 262(24), 230(28), 202(12), 190(30), 158(31), 132(18), 130(20), 105(32), 104(100), 76(58). *IR (KBr)*

cm^{-1} : 3485 (NH), 1780, 1730 and 1710 (C=O). *Anal.* Calcd. for $C_{21}H_{20}N_2O_6S_3$ (492.58) : C 51.21, H 4.09, N 5.69 Found : C 51.23, H 4.18, N 5;69

Tert-butyl 2-[4-methoxycarbonyl-5-(1,3-dithiolan-2-yl)-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene]-2-phthalimidoethanoate (10c)

Yield = 71 %. Oil. ^1H *NMR* δ : 1.36 (s, 9H, *t*.Bu); 3.32 (s, 4H, CH(SC$\underline{H}_2$)$_2$); 3.57 (s, 2H, SC$\underline{H}_2$); 3.95 (s, 3H, CO_2CH_3); 6.79 (s, 1H, C$\underline{H}$(SCH$_2$)$_2$); 7.85 (m, 4H, C_6H_4); 11.72 (bs, 1H, NH). ^{13}C *NMR* δ : 25.47 (S$\underline{C}$H$_2$-C=C); 28.13 (($\underline{C}$H$_3$)$_3$C); 40.69 (CH(S$\underline{C}$H$_2$)$_2$); 51.07 and 53.88 (CO_2CH_3 + $\underline{C}$H(SCH$_2$)$_2$); 81.22 ((CH$_3$)$_3\underline{C}$); 92.96 (N-$\underline{C}$=C-S); 123.54; 132.07 and 134.18 (C_6H_4); 123.02 and 127.02 (N-C=$\underline{C}$-CH); 157.34 (N-C=$\underline{C}$-S); 162.32; 164.69 and 167.75 (C=O). *MS m/e (I%)* : 520($M^{+\cdot}$, 23), 464(66), 447(6), 432(24), 420(23), 404(22), 388(94), 386(11), 360(100), 332(41), 327(18), 300(10), 248(14), 230(14), 204(44), 190(20), 160(48), 156(21), 105(25), 104(39), 76(17). *IR (KBr)* cm^{-1} : 3440 (NH), 1780, 1760 and 1720 (C=O). *Anal.* Calcd. for $C_{23}H_{24}N_2O_6S_3$ (520.64) : C 53.06, H 4.65, N 5.38 Found : C 52.76, H 4.41, N 5.45

Tert-butyl 2-[4-_tert_-butoxycarbonyl-5-(1,3-dithiolan-2-yl)-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene]-2-phthalimidoethanoate (10d)

Yield = 72 %. Oil. ^1H *NMR* δ : 1.34 (s, 9H, *t*.Bu); 1.62 (s, 9H, *t*.Bu); 3.31 and 3.32 (s, 4H, CH(SC$\underline{H}_2$)$_2$); 3.55 (s, 2H, SC$\underline{H}_2$); 6.87 (s, 1H, C$\underline{H}$(SCH$_2$)$_2$); 7.83 (m, 4H, C_6H_4); 11.85 (bs, 1H, NH). ^{13}C *NMR* δ : 25.40 (S$\underline{C}$H$_2$-C=C); 28.03 and 28.10 (($\underline{C}$H$_3$)$_3$C); 40.56 (CH(S$\underline{C}$H$_2$)$_2$); 51.03 ($\underline{C}$H(SCH$_2$)$_2$); 80.88 and 84.41 (2(CH$_3$)$_3\underline{C}$); 92.44 (N-$\underline{C}$=C-S); 123.51; 132.16 and 134.11 (C_6H_4); 121.43 et 128.45 (N-$\underline{C}$=$\underline{C}$-CH); 157.44 (N-C=$\underline{C}$-S); 160.52; 164.82 and 167.85 (C=O). *MS m/e (I%)* : 562($M^{+\cdot}$, 1), 505(8), 450(29), 432(18), 406(14), 388(27), 360(39), 332(20), 248(6), 230(8), 204(31), 190(11), 167(47), 158(11), 156(19), 148(9), 130(10), 105(24), 104(34), 76(17), 41(100). *IR (KBr)* cm^{-1} : 3440 (NH), 1785, 1760 and 1720 (C=O). *Anal.* Calcd. for $C_{26}H_{30}N_2O_6S_3$ (562.72) : C 55.50, H 5.37, N 4.98 Found : C 55.57, H 5.28, N 5.22

Methyl 2-[4-methoxycarbonyl-5-(1,3-dithian-2-yl)-3,6-dihydro-2*H*-1,3-thiazine-2-ylidene]-2-phthalimido ethanoate (10e)

Yield = 73 %. Oil. ^1H *NMR* δ : 2.03 (m, 2H, SCH$_2$C$\underline{H}_2$CH$_2$S); 2.88 (m, 4 H, SC$\underline{H}_2$CH$_2$C$\underline{H}_2$S); 3.60 (s, 2H, SC$\underline{H}_2$); 3.66 (s, 3H, CO_2CH_3); 3.97 (s, 3H, CO_2CH_3); 6.52 (s, 1H, S-C$\underline{H}$-S); 7.84 (m, 4H, C_6H_4); 11.85 (bs, 1H, NH). ^{13}C *NMR* δ : 24.82 and 25.63 (S$\underline{C}$H$_2$-C=C + SCH$_2\underline{C}$H$_2$CH$_2$S); 30.44 (S$\underline{C}$H$_2$CH$_2\underline{C}$H$_2$S); 47.33 (S-$\underline{C}$H-S); 51.39 and 52.37 (2$CO_2\underline{C}$H$_3$); 91.98 (N-$\underline{C}$=C-S); 123.61; 132.62 and 134.11 (C_6H_4); 122.63 and 126.96 (N-$\underline{C}$=$\underline{C}$-CH); 158.78 (N-C=$\underline{C}$-S); 161.05, 166.32 and 167.62 (C=O). *MS m/e (I%)* : 492($M^{+\cdot}$, 95), 460(61), 354(56), 298(17), 230(22), 190(58), 119(18), 104(100), 76(44). *IR (KBr)* cm^{-1} : 3480 (NH), 1780, 1750 and 1720 (C=O).

4-Methoxycarbonyl-5-(1,3-dithiolan-2-yl)-2-phthalimidomethyl-6*H*-1,3-thiazine (11a)

These compounds **11**, isolated as colourless oil, resulted from the decarboxylation of *tert*-butyl esters **10c,d**.

^1H *NMR* δ : 3.26 (s, 4H, CH(SC$\underline{H}_2$)$_2$); 3.52 (s, 5H, SC$\underline{H}_2$ + CO_2CH_3); 4.62 (s, 2H, C$\underline{H}_2$-C=N); 6.41 (s, 1H, C$\underline{H}$(SCH$_2$)$_2$); 7.74 (m, 4H, C_6H_4). ^{13}C *NMR* δ : 24.88 (S$\underline{C}$H$_2$); 40.82 (CH(S$\underline{C}$H$_2$)$_2$); 44.50 ($\underline{C}$H$_2$-C=N); 51.43 and 52.08 ($CO_2\underline{C}$H$_3$ + $\underline{C}$H(SCH$_2$)$_2$); 123.48; 132.26 and 134.12 (C_6H_4); 126.01 and 135.90 (N-$\underline{C}$=$\underline{C}$-CH); 161.08; 164.82 and 167.65 (C=N + C=O). *MS m/e (I%)* : 420($M^{+\cdot}$, 44), 388(100), 360(66), 332(28), 327(19), 300(12), 204(62), 160(89), 156(19), 133(14), 132(5), 105(17), 104(15), 76(11). *IR (KBr)* cm^{-1} : 1770, 1720 and 1710 (C=O). *Anal.* Calcd. for $C_{18}H_{16}N_2O_4S_3$ (420.52) : C 51.41, H 3.84, N 6.66 Found : C 51.40, H 3.76, N 6.57

4-_Tert_-butoxycarbonyl-5-(1,3-dithiolan-2-yl)-2-phthalimidomethyl-6*H*-1,3-thiazine (11b)

^1H *NMR* δ : 1.16 (s, 9H, *t*.Bu); 3.24 and 3.25 (2s, 4H, CH(SC$\underline{H}_2$)$_2$); 3.52 (s, 2H, SC$\underline{H}_2$); 4.58 (s, 2H, C$\underline{H}_2$-C=N); 6.25 (s, 1H, C$\underline{H}$(SCH$_2$)$_2$); 7.73 (m, 4H, C_6H_4). ^{13}C *NMR* δ : 24.71 (S$\underline{C}$H$_2$); 27.84 (($\underline{C}$H$_3$)$_3$C); 40.78 (CH(S$\underline{C}$H$_2$)$_2$); 44.14 ($\underline{C}$H$_2$-C=N); 51.88 ($\underline{C}$H(SCH$_2$)$_2$); 81.91 ((CH$_3$)$_3\underline{C}$); 123.57; 132.45 and 134.08 (C_6H_4); 137.91 and 141.85 (N-$\underline{C}$=$\underline{C}$-CH); 159.55; 163.91 and 167.58 (C=N + C=O). *MS m/e (I%)* : 462($M^{+\cdot}$,1), 406(21), 388(26), 360(30), 332(17), 214(9), 204(53), 160(100), 156(15), 133(15), 132(8), 105(21), 104(24), 77(20), 76(18).

General procedure for the synthesis of 6*H*-1,3-thiazines (12) and (13)

To a solution of 1.5 mmole of compound **9** or **10** in dry THF were added at -70°C 3 mL of lithium methylate (1M in methanol) and 3 mmoles of *tert*-butylhypochlorite. The reaction mixture was stirred at -70°C for 1 h 1/2, then poured in cooled water and extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and the residue was purified by silica gel chromatography (Eluent : EtOAc/petroleum ether = 60/40) to afford the compound **12** or **13**.

Methyl 2-[5-(1,3-dioxan-2-yl)-4-ethoxycarbonyl-6*H*-1,3-thiazine-2-yl]-2-methoxy-2-*o*-methoxycarbonyl benzamidoethanoate (12)

Yield = 84 %. Foam. ^1H *NMR* δ : 1.20 (t, J = 7.2Hz, 3H, C$\underline{H}_3$CH$_2$); 2.10 (m, 2H, OCH$_2$C$\underline{H}_2$CH$_2$O); 3.39 and 3.83 (dd, J = 15.8Hz, 2H, SCH$_2$); 3.44 (s, 3H, CH$_3$O); 3.86 and 3.87 (2s, 6H, 2CO_2CH_3); 4.12 (m, 4H, OC$\underline{H}_2$-CH$_2$C$\underline{H}_2$O); 4.23 (q, J = 7.2Hz, 2H, CH$_3$C$\underline{H}_2$O); 6.06 (s, 1H, O-C$\underline{H}$-O); 7.28 to 7.90 (m, 4H, C_6H_4); 8,23 (bs, 1H, NH). ^{13}C *NMR* δ : 13.86 ($\underline{C}$H$_3$CH$_2$); 22.58 and 25.63 (SCH$_2$ + OCH$_2\underline{C}$H$_2$CH$_2$O); 51.59; 52.47 and 53.48 (CH$_3$O); 61.32 (CH$_3\underline{C}$H$_2$O); 66.95

($O\underline{C}H_2\underline{C}H_2O$); 87.11 (N-$\underline{C}(OCH_3)CO_2CH_3$); 97.42 (O-CH-O); 124.75; 127.42; 130.02; 130.22; 131.52; 135.75 and 136.66 (N-$\underline{C}$=$\underline{C}$ + C_6H_4); 163.46; 164.34; 166.84; 167.04 and 167.88 (C=N + C=O). *MS m/e (I%) :* 536($M^{+\cdot}$, <1), 504(5), 490(2), 472(3), 471(3), 357(11), 342(4), 341(4), 174(2), 163(100), 135(4), 133(5), 87(17), 77(8). *IR (KBr) cm^{-1} :* 3359 (NH), 1771, 1732 (C=O). *Anal.* Calcd. for $C_{24}H_{28}N_2O_{10}S$ (536.57) : C 53.73, H 5.26, N 5.22 Found : C 53.78, H 5.09, N 5.09

Methyl 2-[4-methoxycarbonyl-5-(1,3-dithiolan-2-yl)-*6H*-1,3-thiazine-2-yl]-2-methoxy-2-*o*-methoxycarbonyl benzamidoethanoate (13a)

Yield = 75 %. Oil. *^1H NMR δ :* 3.39 (s, 4H, CH($S\underline{C}H_2$)$_2$); 3.47 (s, 3H, OCH_3); 3.62 and 3.71 (2s, 2H, $S\underline{C}H_2$); 3.78 (s, 3H, CO_2CH_3); 3.87 (s. 6H. $2CO_2CH_3$); 6.54 (s. 1H. $C\underline{H}(SCH_2)_2$); 7.56 to 7.91 (m. 4H. C_6H_4); 8.17 (bs. 1H. NH). *^{13}C NMR δ :* 24.75 ($S\underline{C}H_2$); 40.85 (CH($S\underline{C}H_2$)$_2$); 50.94; 51.68; 52.27; 52.40 and 53.47 ($3CO_2\underline{C}H_3$ + CH_3O + $\underline{C}H(SCH_2)_2$); 87.04 (N-$\underline{C}$-OCH_3); 127.41; 128.94; 129.91; 130.31; 130.37; 131.48; 134.44 and 136.42 (N-$\underline{C}$=$\underline{C}$ + C_6H_4); 162.38; 164.26; 166.80; 167.00 and 167.75 (C=N + C=O). *MS m/e (I%) :* 540($M^{+\cdot}$, <1), 508(2), 361(6), 346(3), 248(3), 216(8), 163(100), 156(5), 135(5), 133(7), 105(9), 104(8), 77(13), 76(7). *IR (KBr) cm^{-1} :* 3340 (NH), 1760, 1735 and 1730 (C=O). *Anal.* Calcd. for $C_{22}H_{24}N_2O_8S_3$ (540.62) : C 48.88, H 4.47, N 5.18 Found : C 47.65, H 4.30, N 5.15

Methyl 2-[4-ethoxycarbonyl-5-(1,3-dithiolan-2-yl)-*6H*-1,3-thiazine-2-yl]-2-methoxy-2-*o*-methoxycarbonyl benzamidoethanoate (13b)

Yield = 76% for the previous method.

This compound was also synthesised using the transacetalisation reaction of *6H*-1,3-thiazine **16b** :

To a solution of 0.5 mmole of *6H*-1,3-thiazine in 15 mL of dry CH_2Cl_2 were added 0.5 mL of 1,2-ethanedithiol and 0.02 mL of boron trifluoride etherate. The reaction mixture was stirred at room temperature for 6 h under nitrogen atmosphere. The solution diluted with 40 mL of CH_2Cl_2 was washed successively with 20 mL of 5% aqueous solution of NaOH and 20 mL of water. The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and the residue was chromatographed on silica gel (Eluent : EtOAc/petroleum ether = 40/60) to afford a colourless oil. Yield = 80 %.

^1H NMR δ : 1.10 (t, J = 7Hz, 3H, $C\underline{H}_3CH_2$); 3.30 (s, 4H, CH($S\underline{C}H_2$)$_2$); 3.39 (s, 3H, CH_3O); 3.61 and 3.70 (2s, 2H, $S\underline{C}H_2$); 3.79 and 3.80 (2s, 6H, $2CO_2CH_3$); 4.14 (q, J = 7Hz, 2H, $CH_3C\underline{H}_2$); 6.48 (s, 1H, $C\underline{H}(SCH_2)_2$); 7.30 to 7.80 (m, 4H, C_6H_4); 8.14 (bs, 1H, NH). *^{13}C NMR δ :* 13.99 ($\underline{C}H_3CH_2$); 24.95 ($S\underline{C}H_2$); 41.05 (CH($S\underline{C}H_2$)$_2$); 51.10; 51.88; 52.63 and 53.70 ($2CO_2\underline{C}H_3$ + CH_3O + $\underline{C}H(SCH_2)_2$); 61.57 ($CH_3\underline{C}H_2O$); 87.21 (N-$\underline{C}$-OCH_3); 127.48; 129.11; 130.18; 130.47; 131.71; 134.76 and 136.78 (C_6H_4 + N-$\underline{C}$=$\underline{C}$); 162.19; 163.98; 167.04 and 168.04 (C=N + C=O). *MS m/e (I%) :* 554($M^{+\cdot}$, 1), 522(6), 418(3), 375(8), 361(4), 248(5), 230(11), 174(5), 163(100), 156(9), 135(6), 133(7), 105(11), 104(12), 77(12), 76(9). *IR (KBr) cm^{-1} :* 3343 (NH), 1770, 1728 and 1702(C=O). *Anal.* Calcd. for $C_{23}H_{26}N_2O_8S_3$ (554.65) : C 49.81 H 4.72 N 5.05 Found : C 49.88 H 4.85 N 5.05

***Tert*-butyl 2-[4-methoxycarbonyl-5-(1,3-dithiolan-2-yl)-*6H*-1,3-thiazine-2-yl]-2-methoxy-2-*o*-methoxy carbonylbenzamidoethanoate (13c)**

Yield = 76 % . Oil. *^1H NMR δ :* 1.50 (s, 9H, *t*.Bu); 3.38 and 3.39 (2s, 4H, CH($S\underline{C}H_2$)$_2$); 3.48 (s, 3H, CH_3O); 3.57 and 3.68 (2s, 2H, SCH_2); 3.77 and 3.87 (2s, 6H, $2CO_2CH_3$); 6.54 (s, 1H, $C\underline{H}(SCH_2)_2$); 7.40 to 7.90 (m, 4H, C_6H_4); 8.07 (bs, 1H, NH). *^{13}C NMR δ :* 24.82 ($S\underline{C}H_2$); 27.67 (($\underline{C}H_3$)$_3$C); 40.86 (CH($S\underline{C}H_2$)$_2$); 51.14; 51.82; 52.21 and 52.47 ($2CO_2\underline{C}H_3$ + CH_3O + $\underline{C}H(SCH_2)_2$); 83.60 ((CH_3)$_3\underline{C}$); 87.37 (N-$\underline{C}$-OCH_3); 127.39; 128.33; 130.02; 130.38; 131.48; 134.93 and 137.11 (C_6H_4 + N-$\underline{C}$=$\underline{C}$); 163.78; 164.57; 164.96; 167.07 and 167.62 (C=N + C=O). *MS m/e (I%) :* 582($M^{+\cdot}$, <1), 550(1), 450(9), 418(4), 303(8), 190(6), 174(3), 163(100), 156(4), 135(6), 133(7), 130(7), 105(10), 104(5), 77(17), 76(6). *IR (KBr) cm^{-1} :* 3350 (NH), 1759, 1730 (C=O). *Anal.* Calcd. for $C_{25}H_{30}N_2O_8S_3$(582.71) : C 51.53, H 5.19, N 4.81 Found : C 50.08, H 4.95, N 4.75

***Tert*-butyl 2-[4-*tert*-butoxycarbonyl-5-(1,3-dithiolan-2-yl)-*6H*-1,3-thiazine-2-yl]-2-methoxy-2-*o*-methoxy carbonylbenzamidoethanoate (13d)**

Yield = 27 %. Foam. *^1H NMR δ :* 1.31 and 1.43 (2s, 18H, 2*t*.Bu); 3.29 (s, 4H, CH($S\underline{C}H_2$)$_2$); 3.41 (s, 3H, CH_3O); 3,45 and 3.59 (2s, 2H, $S\underline{C}H_2$); 3.79 (s, 3H, CO_2CH_3); 6.41 (s, 1H, $C\underline{H}(SCH_2)_2$); 7.30 to 7.80 (m, 4H, C_6H_4); 8.08 (bs, 1H, NH). *^{13}C NMR δ :* 24.84 ($S\underline{C}H_2$-C=C); 27.81 and 28.04 ($2(\underline{C}H_3)_3C$); 40.91 (CH($S\underline{C}H_2$)$_2$); 51.36; 51.88 and 52.53 (CH_3O + $CO_2\underline{C}H_3$ + $\underline{C}H(SCH_2)_2$); 82.42 and 83.50 ($2(CH_3)_3\underline{C}$); 87.30 (N-$\underline{C}$-OCH_3); 126.86; 127.35; 130.05; 130.18; 131.70; 136.39 and 137.50 (C_6H_4 + N-$\underline{C}$=$\underline{C}$); 162.67; 163.26 164.92; 166.93 and 167.88 (C=N + C=O). *MS m/e (I%) :* 624($M^{+\cdot}$, <1), 592(<1), 536(1), 480(2), 436(3), 217(3), 190(3), 174(3), 163(100), 156(4), 133(6), 105(9), 104(5), 77(12), 76(7). *IR (KBr) cm^{-1} :* 3350 (NH), 1760, 1730 and 1715 (C=O).

Methyl 2-[4-methoxycarbonyl-5-(1,3-dithian-2-yl)-*6H*-1,3-thiazine-2-yl]-2-methoxy-2-*o*-methoxycarbonyl benzamidoethanoate (13e)

Yield = 40 %. Oil. *^1H NMR δ :* 2.00 (m, 2H, $SCH_2C\underline{H}_2CH_2S$); 2.90 (m, 4H, $SC\underline{H}_2CH_2C\underline{H}_2S$); 3.47 (s, 3H, OCH_3); 3.43 and 3.84 (dd, J = 16.8Hz, 2H, SCH_2); 3.78 and 3.87 (2s, 9H, $3CO_2CH_3$); 6.41 (s, 1H, S-C$\underline{H}$-S); 7.40 to 7.90 (m, 4H, C_6H_4); 8.16 (bs, 1H, NH). *^{13}C NMR δ :* 24.50 and 25.25 ($S\underline{C}H_2$ + $SCH_2\underline{C}H_2CH_2S$); 30.06 and 30.52 ($SCH_2CH_2\underline{C}H_2S$); 47.69 (S-$\underline{C}$H-S); 51.79; 52.24; 52.44 and 53.54 (CH_3O + $3CO_2\underline{C}H_3$); 87.08 (N-$\underline{C}$-OCH_3); 127.42; 129.96; 130,31; 131.45; 134.28 and 136.43 (C_6H_4 + N-$\underline{C}$=$\underline{C}$); 163.82; 166.84; 167.00 and 167.82 (C=N + C=O). *MS m/e (I%) :* 554($M^{+\cdot}$, 1), 522(8), 490(3), 458(3),

375(10), 360(5), 359(5), 247(5), 230(9), 163(100), 133(5), 104(5), 77(8). *IR (KBr) cm^{-1} :* 3368 (NH), 1762, 1734 and 1700 (C=O). *Anal.* Calcd. for $C_{23}H_{26}N_2O_8S_3$ (554.65) : C 49.81, H 4.72, N 5.05 Found : C 48.32, H 4.73, N 4.95

Methyl 2-(5-diethoxymethyl-4-hydroxy-4-methoxycarbonyl-5,6-dihydro-*4H*-1,3-thiazine-2-yl)-2-methoxy-2-*o*-methoxycarbonylbenzamidoethanoate (14a)

This compound **14a**, isolated as an oil, was obtained using the same experimental conditions described for **8** for the methoxylation reaction of the tetrahydrothiazine **3a**. Yield = 96 %.

It was also synthesised using the [3+3] cyclocondensation reaction between the thioamide **2d** and the vinylic ketoester **1a** as described for the compound **15**. Yield = 69 %. Diastereoisomeric ratio = 52/48.

^{1}H NMR δ : 1.13 and 1.21 (2t, J = 7Hz, 6H, $CH(OCH_2\underline{C}H_3)_2$); 2.40 (m, 1H, $C\underline{H}$-$CH(OC_2H_5)_2$); 3.36 and 3.42 (2s, 3H, CH_3O); 3.46 (m, 4H, $CH(OC\underline{H}_2CH_3)_2$); 3.73 and 3.80 (2s, 3H, CO_2CH_3); 3.87 (s, 6H, $2CO_2CH_3$); 4.60 (m, 1H, $\underline{C}H(OC_2H_5)_2$); 7.26 to 7.90 (m, 4H, C_6H_4); 7.95 and 8.07 (2bs, 1H, NH); the signals corresponding to SCH_2 and OH are superimposed with the signals of $CH(OC_2H_5)_2$ and CO_2CH_3. *^{13}C NMR δ :* 14.76 and 15.38 ($2\underline{C}H_3CH_2$); 21.92 (SCH_2); 38.77 and 41.28 ($\underline{C}H$-$CH(OC_2H_5)_2$); 50.68; 51.39; 52.57; 52.92 and 53.51 (CH_3O + $3CO_2\underline{C}H_3$); 61.90; 64.60 and 64.83 ($CH_3\underline{C}H_2O$); 81.61 and 84.38 (N-$\underline{C}$-OH); 87.21 and 87.47 (N-$\underline{C}$-OCH_3); 101.59 and 102.63($\underline{C}H(OC_2H_5)_2$); 127.51; 127.74; 129.99; 131.77; 136.78 and 136.98 (C_6H_4); 163.52; 164.17; 165.90; 167.00; 167.85; 171.00 and 172.92 (C=N + C=O). *MS m/e (I%) :* 557(M+1, <1), 526(1), 497(1), 280(7), 263(2), 248(3), 204(2), 174(2), 163(100), 135(4), 133(4), 118(5), 115(6), 104(5), 103(11), 83(16), 77(10), 76(5). *IR (KBr) cm^{-1} :* 3441 (OH), 3329 (NH), 1742 and 1728 (C=O). *Anal.* Calcd. for $C_{24}H_{32}N_2O_{11}S$ (556.58) : C 51.79, H 5.80, N 5.03 Found : C 50.42, H 5.64, N 4.96

Methyl 2-(4-ethoxycarbonyl-5-diethoxymethyl-4-hydroxy-5,6-dihydro-*4H*-1,3-thiazine-2-yl)-2-methoxy-2-*o*-methoxycarbonylbenzamidoethanoate (14b)

This compound **14b** was obtained using the same experimental conditions described for **8** for the methoxylation reaction of the tetrahydrothiazine **3b**. Yield = 94 %. Diastereoisomeric ratio = 55/45.

^{1}H NMR δ : 1.13; 1.21 and 1.29 (3t, J = 7Hz, 9H, $\underline{C}H_3CH_2$); 2.50 (m, 1H, $C\underline{H}$-$CH(OC_2H_5)_2$); 3.38 and 3.44 (2s, 3H, CH_3O); 3.50 (m, 4H, $CH(OC\underline{H}_2CH_3)_2$); 3.86 and 3.87 (2s, 6H, 2 CO_2CH_3); 4.19 (q, J = 7Hz, 2H, $CO_2C\underline{H}_2CH_3$); 4.60 (m, 1H, $C\underline{H}(OC_2H_5)_2$); 7.40 to 7.90 (m, 4H, C_6H_4); 8.03 and 8.13 (2bs, 1H, NH). *^{13}C NMR δ :* 14.02; 14.73 and 15.42 ($3\underline{C}H_3CH_2$); 22.02 (SCH_2); 38.67 and 41.28 ($\underline{C}H$-$CH(OC_2H_5)_2$); 50.68; 51.39; 52.56 and 53.54 (CH_3O + $2CO_2\underline{C}H_3$); 62.03; 62.78 and 64.36 ($3CH_3\underline{C}H_2O$); 81.42 and 84.28 (N-$\underline{C}$-OH); 87.47 (N-$\underline{C}$-OCH_3); 101.59 and 102.60 ($\underline{C}H(OC_2H_5)_2$); 127.64; 128.10; 130.44; 132.13; 137.11 and 137.46 (C_6H_4); 163.05; 164.16; 167.30; 167.46; 168.22; 168.37; 170.97 and 172.76 (C=N + C=O). *MS m/e (I%) :* 571(M+1, <1), 540(3), 497(7), 465(3), 451(4), 419(2), 389(2), 280(4), 272(4), 185(3), 174(2), 163(100), 157(5), 135(4), 133(4), 104(4), 103(13), 85(23), 77(7). *IR (KBr) cm^{-1} :* 3450 (OH), 3320 (NH), 1760 and 1730 (C=O).

Methyl 2-(4-ethoxycarbonyl-5-diethoxymethyl-4-hydroxy-5,6-dihydro-*4H*-1,3-thiazine-2-yl)-2-methoxy-2-phthalimidoethanoate (15)

To a solution of thioamide **10c** (1.5 g, 4.8 mmol) in 40 mL of dry THF were added DABCO (0.54 g, 4.9 mmol) and 3 g of crude vinylic ketoester **1b**. The reaction mixture was stirred at room temperature for 1 h 1/2, then diluted with EtOAc. The solution was washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried ($MgSO_4$), concentrated and the residue was purified by silica gel chromatography (Eluent : EtOAc/petroleum ether/triethylamine = 50/48/2) to give 1.98 g of white crystals. Yield = 70%. Diastereoisomeric ratio = 43/36/21.

^{1}H NMR δ : 0.95 to 1.40 (3t, J = 7.2Hz, 9H, $3CH_2C\underline{H}_3$); 2.80 (m, 1H, $C\underline{H}$-$CH(OC_2H_5)_2$); 3.45; 3,46 and 3.48 (CH_3O); 3.51 (m, 4H, $CH(O\underline{C}H_2CH_3)_2$); 3.72; 3.78 and 3.80 ($CO_2CH_3$); 4.07 and 4.24 (2q, J = 7.2Hz, 2H, $CO_2C\underline{H}_2CH_3$); 4.57 (m, 1H, $C\underline{H}(OC_2H_5)_2$); 7.71 (m, 4H, C_6H_4); the signals corresponding to SCH_2 and OH are superimposed with the signals of $CH(OC_2H_5)_2$ and CO_2CH_3. *^{13}C NMR δ :* 13.92; 14.60; 14.73 and 15.35 ($\underline{C}H_3CH_2$); 22.05; 22.34 and 22.89 (SCH_2); 38.41; 39.16 and 40.56 ($\underline{C}H$-$CH(OC_2H_5)_2$); 53.08; 53.34; 53.54; 53.66; 53.73 and 53.93 (CH_3O); 60.63; 61.70; 62.12; 64.33; 64.53 and 64.76 ($CH_3\underline{C}H_2O$); 81.38; 82.46; 84.05; 84.27 and 87.98 (N-$\underline{C}$-OH + N-$\underline{C}$-OCH_3); 101.74 and 102.46 ($\underline{C}H(OC_2H_5)_2$); 123.47; 123.70; 131.35 and 134.47 (C_6H_4); 161.11; 162.09; 164.92; 165.28; 166.28; 166.44; 166.70; 170.51 and 172.30 (C=O + C=N). *MS m/e (I%) :* 539(M + 1, <1), 508(1), 493(1), 465(16), 419(26), 389(17), 249(15), 248(41), 215(18), 190(11), 174(32), 163(12, 157(15), 130(30), 104(19), 103(53), 101(18), 85(100), 76(16), 75(35). *IR (KBr) cm^{-1} :* 3480 (OH), 1780 and 1730 (C=O).

Methyl 2-(4-ethoxycarbonyl-5-diethoxymethyl-*6H*-1,3-thiazine-2-yl)-2-methoxy-2-*o*-methoxycarbonyl benzamidoethanoate (16)

A solution of dihydro-*4H*-1,3-thiazine **14b** (0.4 g, 0.70 mmol) in 30 mL of dry pyridine and 0.4 mL of anhydrous methanesulfonyl chloride was stirred at 60°C for 3 h under argon atmosphere. The reaction mixture was concentrated then chromatographed on silica gel (Eluent : EtOAc/petroleum ether/triethylamine = 48/50/2) to give 0.27 g of colourless oil. Yield = 67 %.

^{1}H NMR δ : 1.18; 1.21 and 1.23 (3t, J = 7Hz, 9H, 3 $\underline{C}H_3CH_2$); 3.48 (s, 3H, CH_3O); 3.34 and 3.74 (dd, J = 15,5Hz, 2H, SCH_2); 3.60 (m, 4H, $CH(OC\underline{H}_2CH_3)_2$); 3.87 (s, 6H, 2 CO_2CH_3); 4.22 (q, J = 7Hz, 2H, $CO_2C\underline{H}_2CH_3$); 5.95 (s, 1H, $C\underline{H}(OC_2H_5)_2$); 7.40 to 7.90 (m, 4H, C_6H_4); 8.24 (bs, 1H, NH). *^{13}C NMR δ :* 13.94 ($\underline{C}H_3CH_2$); 15.18 ($2\underline{C}H_3CH_2$); 22.66 (SCH_2); 51.84; 52.56 and 53.63 (CH_3O + $2CO_2\underline{C}H_3$); 61.40 ($CO_2\underline{C}H_2CH_3$); 63.39 (($CH(O\underline{C}H_2CH_3)_2$); 87.23 (N-$\underline{C}$-$OCH_3$); 98.26 ($\underline{C}H(OC_2H_5)_2$); 126.72; 127.47; 130.11; 130.36; 130.50; 131.64; 135.02 and 136.78 (N-$\underline{C}$=$\underline{C}$ + C_6H_4); 163.64; 163.97; 167.03; 167.13 and 168.00 (C=N + C=O). *MS m/e (I%) :* 553(M+1, <1), 507(2), 506(5), 373(3), 313(2), 286(5), 263(18), 248(21), 204(36), 176(10), 163(100), 133(6), 130(5), 103(25), 75(13). *IR (KBr) cm^{-1} :* 3349 (NH), 1772 and 1740 (C=O).

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