Exocyclic–Endocyclic *N*-Acyliminium Ion Equilibration via an Intramolecular α-Thioamidoalkylation in the Synthesis of Fused N,S-Heterocyclic Systems: Some New Parameters[‡][‡‡]

Nicolas Hucher,[a] Anthony Pesquet,[a] Pierre Netchitaïlo,[a] and Adam Daïch*[a]

Dedicated to the memory of our colleague Professor Tong-Kuan Wang[‡‡‡]

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The reactivity of *N*-[aryl(or alkyl)thio(oxo or seleno)alkylamidals **6** bearing the *N*-$(CH_2)_n$-X-$(CH_2)_m$-Ar functionality towards neat TFA has been examined. Substrates of type **6** give, together with the products **11**, **17**, **19**, and **25** of the "expected" π-cyclization process, the "unexpected" products **12**, **18**, and **26** resulting from a new tandem heteroamidoalkylation/isomerization/π-cyclization. The composition of the final isomeric mixture depends on the temperature of the reaction, with a high selectivity in favor of the "expected" π-cyclization product **11** as a thermodynamic isomer. Furthermore, the results demonstrate again the relevance of TFA catalysis and support two reaction pathways involving the formation of an aza-sulfonium cation **A** as a valuable intermediate which undergoes the π-cyclization process alone or in tandem with the thiocyclization/isomerization to give the cyclized products cited above. For the latter tandem reaction, we have established clearly that the *n* value should be equal to 1, the process can be performed independently for both the succinimide and phthalimide series, the reaction depends on the nucleophilicity of the heteroatom, and can be generalized to other heterocycles. Only the role of the benzene substitution has still to be totally elucidated.

Introduction

In the framework of our interest in intramolecular cationic cyclizations based on the formation and cleavage of a thioether linkage for the preparation of complex *N*,*S*-containing heterocycles,[1] we have recently demonstrated that α-hydroxy lactams **1** (n = 0, 1) are effective precursors, in acidic media, of the tricyclic N,S-acetals **2** and **3** (Scheme 1).[2–4] These cyclized products are the result of the exclusive intramolecular attack of the sulfur atom onto the endocyclic *N*-acyliminium ion intermediates, followed by either deprotonation or dealkylation (R = H, Me, Bzl; Scheme 1).

More recently, to exploit fully this remarkable thiophilicity for cationic initiation reactions[5–7] to form *N*-acyl-N,S-acetals, we investigated the behavior of 2,3-dihydro-3-hydroxy-2-(phenylthiomethyl)-1*H*-isoindol-1-one (**4**, R = H) with acids, and observed an "unexpected" mixture of two thiazines **I** and **II** in the reaction with trifluoroacetic acid (neat TFA, room temp., 4 h). To explain these results, the mechanism shown in Scheme 2 was postulated.[4] Thus, [1,3]benzothiazine (**I**) is accessible from the classical endocyclic *N*-acyliminium ion **B**, while [1,3]benzothiazine (**II**) suggests the formation of the exocyclic acyliminium ion **C**, which is in equilibrium with **B** via the cyclic azasulfonium cation **A**. The latter is the consequence of a novel intramolecular α-thioamidoalkylation of the intermediate **B**. During these studies, we demonstrated that only TFA among the Brönsted acids can operate as a proton source.[8] Also, with another acid the bis(phenylthio) derivative **5** was isolated, and, again, its treatment with TFA at reflux led to **I** and **II**. Finally, the substitution at the angular C atom has already been investigated; in each case the formation of both benzothiazines of type **I** and **II** was claimed (Scheme 2).[9]

In this context, we wish to present herein our findings from a related study dealing with the examination of the influence of several other factors on the reactivity of an α-

[‡] Preliminary results in this area, including part of this work, were presented at the American Chemical Society National Meeting, Poster 367, San Francisco, CA, March 26–30, 2000.
[‡‡] For the preceding paper in the series see ref.[4]
[a] URCOM, EA 3221, UFR des Sciences & Techniques de l'Université du Havre,
25 rue Philippe Lebon, B. P. 540, 76058 Le Havre Cedex, France
Fax: +33-02-3274-4391
E-mail: adam.daich@univ-lehavre.fr
[‡‡‡] Deceased on January 2, 2004 in Le Havre.

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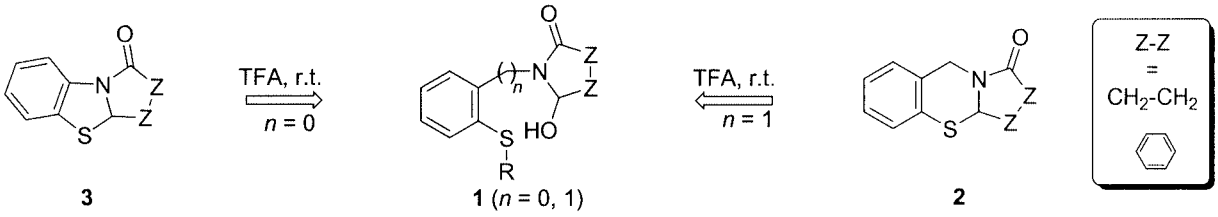
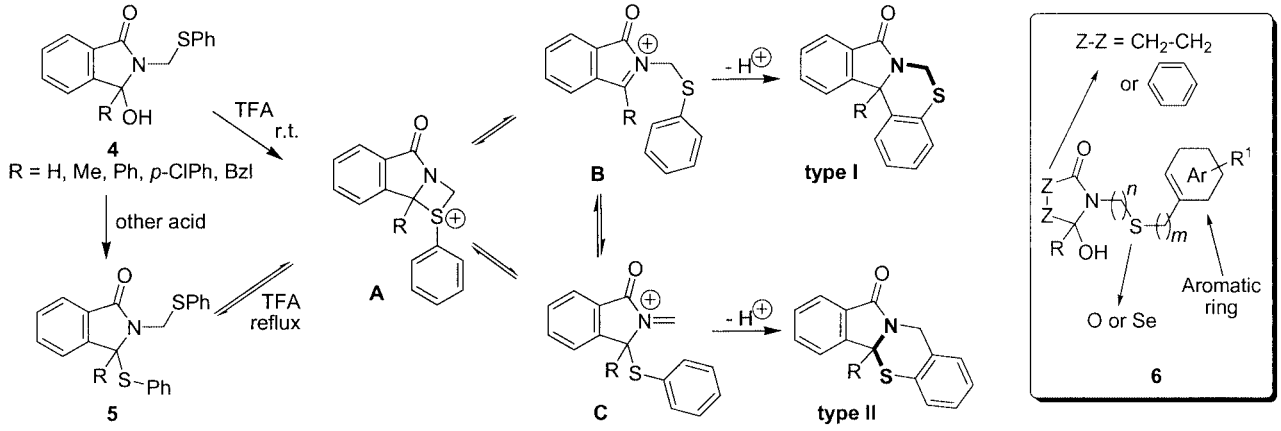


Scheme 1. Heterocyclization with the sulfur atom as internal nucleophile.



Scheme 2. The mechanism of the tandem intramolecular sulfuration/isomerization/π-cationic cyclization process.

hydroxy lactam precursor of type **6** during the cyclization process (Scheme 2) in order to shed further light on the course of this tandem intramolecular sulfuration/isomerization/cationic cyclization process, and to gain insight into the mechanistic aspects of this cascade reaction.

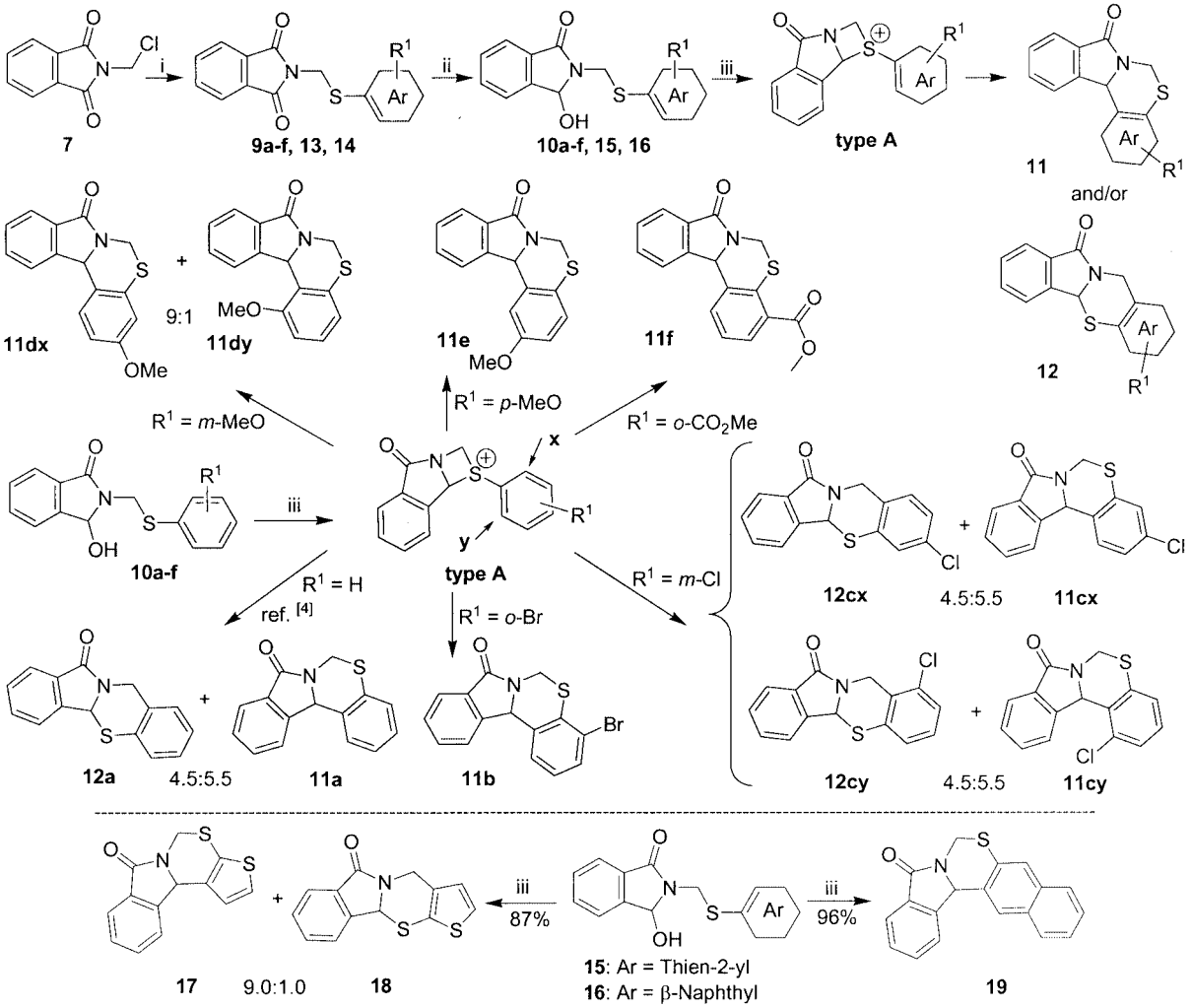
Results and Discussion

As indicated above, we have developed a set of efficient and practical conditions that use neat TFA in a precise ratio to the hydroxy lactam substrate (2 mL of TFA for 1 mmol of reactant) and have demonstrated their efficiency in obtaining benzo[1,3]thiazines of types **I** and **II**.[4] In order to collect additional information on the role of the aromatic ring in the cyclization step, three aromatic nuclei with a set of substituents having different electron-donating and electron-withdrawing properties on the benzene ring were chosen.

Influence of the Benzene Substitution and the Aromatic Ring on the Cyclization Process

First, the synthesis of the requisite hydroxy lactams **10b–f** was accomplished in a three-step sequence, as outlined in Scheme 3. Thus, commercially available 1-chloromethylphthalimide (**7**) was *S*-alkylated with a slight excess of substituted thiophenol **8** in an alkaline medium (yield: 54–88%). Regioselective reduction of the resultant imides **9** was performed with a large excess of $NaBH_4$ (4 to 6 equiv.) in analogy to our reports for **9a**[4] to afford **10b–f** in excellent yields (81 to 99%; see Table 1). In some cases, to avoid the poor solubility of the starting imides **9** and the laborious work-up encountered during these processes, a small quantity of THF was added as co-solvent. In the next step, the five α-hydroxy lactams **10b–f** examined were found to react under the conditions outlined above to give the cyclized products in moderate to excellent yields (Scheme 3, Table 1).

From these results, it seems that the nature and the position of the substitution on the benzene ring have an interesting effect on the reaction profile of our cyclization protocol. In general, two different processes occur: for **10c**, the reaction furnishes a mixture of two kinds of thiazines (**11** and **12**) by the well-established tandem reaction, as for **10a** (see the postulated mechanism in Scheme 2). Interestingly, for the *m*-chloro substitution, in addition to the classical inseparable couple **11cx/12cx** (5.5:4.5), the regioisomers **11cy/12cy** were obtained in similar proportions. These two couples were separated by chromatography on a silica gel column with a mixture of CH_2Cl_2/hexane as eluting solvents. In the second process, for hydroxy lactams **10b** and **10d–f**, no isomerization is observed and, consequently, only the "expected" benzo[1,3]thiazines of type **I** (**11b** and **11d–f**) are obtained by intramolecular arylation of an endocyclic *N*-acyliminium ion of type **B** (see Scheme 2). Furthermore, while substituents at the *ortho* position of the benzene ring of **10b** (R^1 = *o*-Br) and **10f** (R^1 = *o*-CO_2Me) were found to have a very strong influence on both the regiochemical outcome and yields (95 and 94% yields, respectively) of the reaction, substitution at the *meta* and *para* positions gives only mediocre yields (8 and 19% yields, respectively), although with total regiocontrol in favor of the π-cyclization process without the isomerization of the *N*-acyliminium ion



Scheme 3. Reagents and conditions: (i) MeONa, DMF, 1.5 equiv. of substituted thiophenol (**8**; see text for phthalimidals in thiophene and naphthalene series **15** and **16**, respectively), room temp., 5 h; (ii) 4 to 6 equiv. of $NaBH_4$, MeOH, 0 °C, 30 min to 1 h; (iii) neat TFA, room temp., 3 h.

Table 1. Effect of the benzene substitution and the aromatic ring on the cyclization process.

	R^1	Aromatic ring	Imides (% yield)	Alcohols (% yield)	Cyclization (% yield)	Products ratio	Regioisomers ratio
a	H	phenyl	**9** (90)	**10** (94)	92[a]	**11**:**12** = 5.5:4.5	–
b	*o*-Br	phenyl	**9** (82)	**10** (89)	95	**11**:**12** = 1.0:0.0	–
c	*m*-Cl	phenyl	**9** (88)	**10** (99)	89[b]	**11**:**12** = 5.5:4.5	**x**:**y** = 1:1
d	*m*-OMe	phenyl	**9** (68)	**10** (81)	8[c][d]	**11**:**12** = 1.0:0.0	**x**:**y** = 9:1
e	*p*-OMe	phenyl	**9** (54)	**10** (98)	19[c]	**11**:**12** = 1.0:0.0	–
f	*o*-CO_2Me	phenyl	**9** (84)	**10** (98)	94	**11**:**12** = 1.0:0.0	–
–	–	thien-2-yl	**13**[15]	**15**[15]	87	**17**:**18** = 9.0:1.0	–
–	–	β-naphthyl	**14**[3]	**16**[3]	96	**19**[e]	–

[a] A mixture of thiazines **11a** and **12a** was obtained, see ref.[4]. [b] Four products were obtained, see Scheme 3 for details. [c] The substituted thiophenol **8** resulting from the cleavage of the thioether linkage was also isolated. [d] Two regioisomers of thiazine **11d** were isolated in a 9:1 ratio, see Scheme 3 for details. [e] Only one product was obtained.

intermediate. This fact can be explained, not by the influence of the methoxy group, but by the higher sensitivity of the thioether linkage in these acid conditions. The *m*-methoxythiophenol and *p*-methoxythiophenol isolated as the major products from the reaction are in agreement with this hypothesis. In addition, for the *m*-methoxy hydroxy lactam derivative **10d**, the cyclization reaction occurs at the two free *ortho* positions to give the 3-methoxy- and 1-methoxy[6,12-*b*]-dihydroisoindolo[2,1-*c*][1,3]benzothiazines **11dx** and **11dy** in a 9.0:1.0 ratio (Scheme 3).

In an effort to further define the scope of the cyclization process, especially the effect of the nucleophilicity of the π-aromatic nucleus, the elaboration of other aromatic models, substituted by naphthyl or thienyl groups on the aromatic

moiety, was explored in the same reaction protocol demonstrated above (Scheme 2 and Scheme 3). Thus, the requisite 2-(thien-2′-yl-thiomethyl)phthalimidal **15** was obtained in two steps, as described in the literature, by successive *S*-alkylation and chemoselective borohydride reduction.[15] The use of the same protocol in the naphthalene series led to hydroxy lactam derivative **16**, via the sulfide imide **14** (94%),[3] in a yield of 99%.

The hydroxy lactam **16** was treated with neat TFA according to the well-established cyclization protocol given above. The examination of the TLC of the reaction mixture indicated the presence of only one product, which, after a classical work-up, was identified as **19**, resulting from the π-cyclization of the endocyclic *N*-acyliminium ion intermediate. This reaction occurs cleanly and affords the cyclic thiazine **19** as the sole reaction product in an excellent yield of 96%. In contrast to the results obtained in the benzene series, where thiazines **11** and **12** were obtained as a mixture from hydroxy lactams **10**, no isomerization takes place. This fact can be explained by the steric repulsion in the case of an alternative cyclization at the α-naphthyl position. Furthermore the regioselectivity of electrophilic attack at naphthalene rings is a matter of kinetic and thermodynamic control. The cyclized product obtained here (**19**) is certainly the thermodynamic isomer.

Although the presence of the naphthyl nucleus instead of the phenyl one (in the *N*-acyliminium ion precursor **16**) seems to facilitate only the π-cyclization process in a total regiocontrol, there is no discernible preference between the phenyl and thienyl groups. In fact, in the latter case hydroxy lactam **15** in the thiophene series gives N,S-acetals **17** and **18** in 87% yield in up to a 9.0:1.0 ratio. In this process, the tandem intramolecular sulfuration/isomerization/π-cationic cyclization occurs as in the benzene series, although with a much better selectivity for the π-cationic cyclization of the endocyclic *N*-acyliminium intermediate **B** (9.0:1.0 ratio instead of 5.5:4.5 ratio).

Temperature Effects

According to our protocol with TFA as the cyclization promoter at ambient temperature to give benzothiazines **11a** and **12a** in a 5.5:4.5 ratio,[4] the reaction was tested again with **10a** as the *N*-acyliminium ion precursor model at two other temperatures (Scheme 2, Table 2).

Table 2. Effect of the temperature on the product ratio.

Entry	*T* [°C]	Time [h]	Thiazine **11a**[a]	Thiazine **12a**[a]	% Yield
1	–20[b]	240	4.5	5.5	92
2	20	3	5.5	4.5	90
3	72	1.5	7.0	3.0	84

[a] The ratio was determined by ^{1}H NMR spectroscopy. [b] With CH_2Cl_2 as solvent.

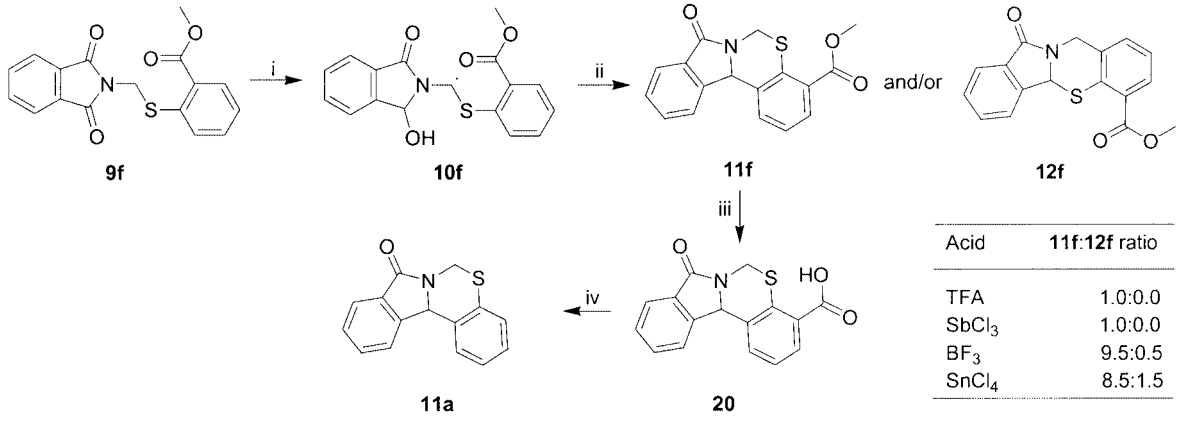
The reaction was carried out under the standard conditions (neat TFA) until complete disappearance of α-hydroxy lactam **10a** (the reaction was monitored by TLC with CH_2Cl_2 as eluent). As can be seen from Table 2, both series of data at ambient temperature (20 °C) and 72 °C show a high selectivity in favor of **11a** as the thermodynamic product, in contrast to that performed at –20 °C. In the case of the run conducted at –20 °C, the reaction needed an additional co-solvent (CH_2Cl_2) and consequently a much longer reaction time (240 h) was necessary for complete reaction. This effect has also been observed in our earlier reports.[4] Because the increase of the reaction temperature (≥80 °C) is limited by the decomposition of **10a**, and taking into account that we have already investigated successfully the thioamidoalkylation to give **12a**,[2,4] our attention turned to synthesizing **11a**.

Indeed, according to the sequential method shown in Scheme 4, **11f**, obtained by a π-cationic cyclization of **10f** upon treatment with TFA, was hydrolyzed into **20** under standard conditions (K_2CO_3, MeOH/H_2O, 5:1, reflux, 3 h, 96%). Interestingly, in a parallel reaction with **10f** and a Lewis acid catalyst, only a limited effect was observed during the cyclization (See table in Scheme 4) since the maximum proportion of **12f** never exceeds 15% of the benzothiazine mixture (2 equiv. of $SnCl_4$, CH_2Cl_2, room temp., 24 h, 86%). When submitted to decarboxylation in the presence of quinoline and a catalytic amount of copper at 150 °C,[10] **20** yielded the expected benzothiazine **11a** in 78% yield.

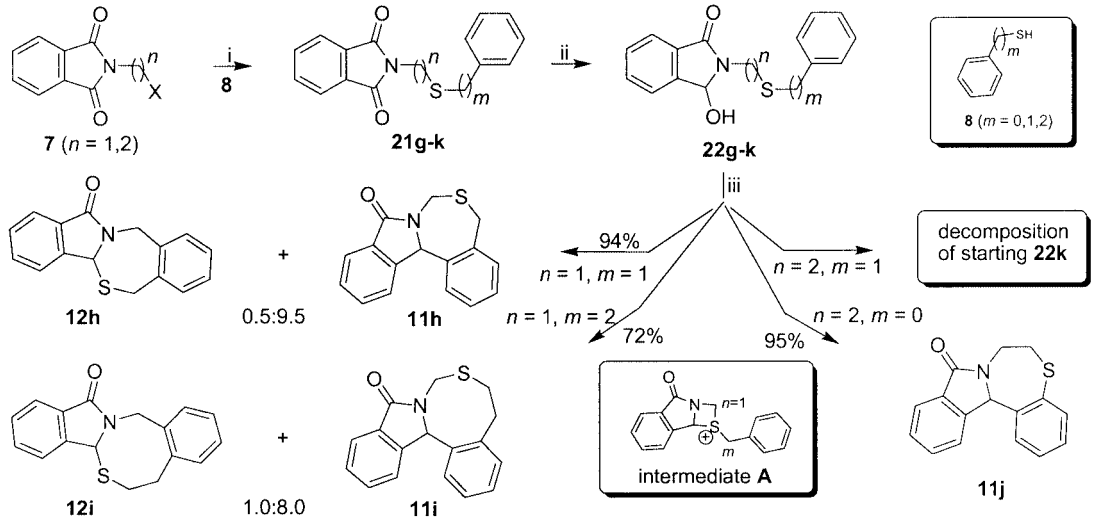
Effect of the Chain Length [N-$(CH_2)_n$-S and S-$(CH_2)_m$-Ar] on the Cyclization Process

We next examined the role of the *n* and *m* spacers on the rearrangement/cyclization step. Thus, as depicted in Scheme 5, the required hydroxy lactams **22g**–**k** were synthesized conveniently by the successive *S*-alkylation of **7** (*n* = 1, 2; 69 to 81% yield) and borohydride reduction of the resulting imides **21g**–**k** (60 to 91% yield; Table 3). Hydroxy lactam **22h** (*n* = *m* = 1), upon treatment under the conditions cited above (neat TFA, room temp., 24 h), gave a mixture of the cyclized benzo[1,3]thiazepine products **11h** (95%) and **12h** (5%) in a good yield of 94%. Under the same conditions, **22i** (*n* = 1, *m* = 2) furnished similarly the two benzo[1,4]thiazocines **11i** and **12i** in an 8:1 ratio, although in only 72% yield. In contrast, **22j** led to benzo[1,4]thiazepine **11j** as the sole reaction product in an excellent yield of 95%; **22k** decomposed totally.

From these results it seems that only the spacer *n* exerts a pivotal role on the cyclization reaction. In fact, in all cases when *n* = 1 the tandem intramolecular sulfuration/isomerization/π-cationic cyclization process is effective (see reaction of hydroxy lactams **22h**,**i** in Scheme 5). In addition, irrespective of the *m* value, the reaction failed to give the corresponding benzothiazoline (**12g**) and benzo[1,4]thiazepine (**12j**) products when *n* = 0 and *n* = 2, respectively (**12g** has already been described by us in the preceding paper).[4] In these cases only the products resulting from the classical π-cyclization were isolated. The formation of the cyclic cation species (type **A** with *n* = 1), as the key step to the "unex-



Scheme 4. Conditions and reagents: (i) 4 equiv. of $NaBH_4$, MeOH, 0 °C, 35 min; (ii) See conditions in table; (iii) K_2CO_3, MeOH/H_2O, 5:1, reflux, 3 h; (iv) Cu, quinoline, 150 °C, 3.5 h.



Scheme 5. Conditions and reagents: (i) MeONa, DMF, 1.5 equiv. of thiol derivative **8**, room temp., 5 h; (ii) 4 to 6 equiv. of $NaBH_4$, MeOH, 0 °C, 30 to 45 min; (iii) neat TFA, 24 h.

Table 3. Effect of the *n* and *m* spacers on the cyclization process.

	n	*m*	% Yield of imide **21**	% Yield of alcohol **22**
g	0	0	–[a]	60[b]
h	1	1	81	90
i	1	2	72	82
j	2	0	69	91
k	2	1	77	83

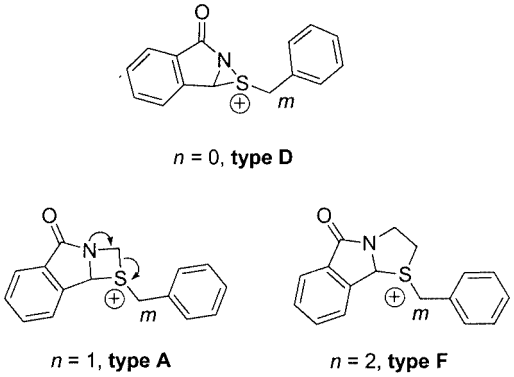
[a] Imide **21g** was purchased from Aldrich. [b] The cyclized product **22g** was accompanied by an appreciable tar.[4]

pected" product **12**, can be related to the fact that only this species can furnish the exocyclic *N*-acyliminium ion of type **C** because of the nitrogen lactam electron-donating effect. This fact cannot occur when $n = 0$ (cation of type **D**) and $n = 2$ (cation of type **F**), as shown in Scheme 6.

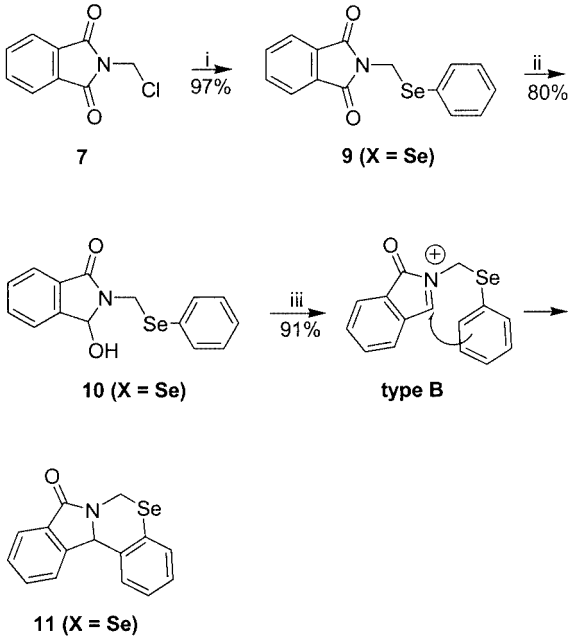
Effect of the Heteroatom Nucleophilicity on the Cyclization Reaction

In order to consider the impact of the heteroatom nucleophilicity on the cyclization transposition step, instead of the sulfur atom two heteroatoms (oxygen, less nucleophilic, and selenium, more nucleophilic) were chosen. For comparison reasons, hydroxy lactams of type **10** with X = Se were considered (Scheme 7).

We have demonstrated previously that treatment of hydroxy lactams **10** (X = O) and **10a** (X = S) with TFA (neat TFA, room temp., 24 h, 86%),[11] under similar conditions, gives isoindolo[1,3]benzoxazines **11** (X = O), as a single isomer in good yield (86%),[11] and a mixture of isoindolo[1,3] benzothiazines **11a** and **12a**, respectively, in only a short time (3 h).[4] In this context, *N*-phenylselenomethylamidal **10** (X = Se) was prepared as outlined in Scheme 7 in an



Scheme 6. Azasulfonium ions as potential intermediates in the tandem cyclization process.



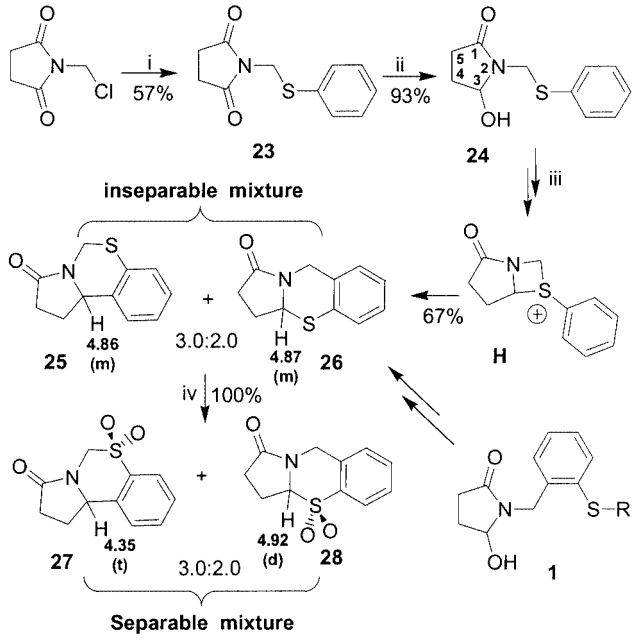
Scheme 7. Influence of the heteroatom on the cyclization: (i) 1.1 equiv. of selenophenol, MeONa, DMF, 12 h; (ii) 5 equiv. of $NaBH_4$, MeOH, 0 °C, 45 min; (iii) neat TFA, room temp., 3 h.

overall yield of 77.5% and treated with TFA according to our standard cyclization protocol. This type of functionality has never been studied in the literature and this is the first study of its behavior in an acid medium. After the work-up of the reaction only the isoindolo[1,3]benzoselenazine **11** (X = Se) was isolated in a very good yield of 91%.

Finally, since no traces of isoindolo[1,3]benzoselenazine **12** (X = Se), the regional isomer of **11** (X = Se), were detected in the reaction medium (the crude mixture of the reaction was also analyzed by GS-MS prior the final work-up), it is clear that the heteroatom nucleophilicity is a crucial factor in the tandem cyclization/transposition process observed in the sulfur series.

Role of the *N*-Acyliminium Aromaticity on the Cyclization Reaction

Taking into account that *N*-acyliminium ions derived from phthalimide derivatives are more stable than those generated from succinimides and related five- and six-membered rings,[12] we decided to investigate the behavior of (phenylthiomethyl)succinamidal (**24**) as an *N*-acyliminium ion precursor (Scheme 8).



Scheme 8. Effect of the nature of the *N*-acyliminium species: (i) 1.0 equiv. of thiophenol, NaH, DMF, 5 h; (ii) 6 equiv. of $NaBH_4$, MeOH, 0 °C, 35 min; (iii) neat TFA, room temp., 2 h; (iv) 2.2 equiv. of *m*-CPBA, CH_2Cl_2, 0 °C to room temp., 2 min and 1 h.

Thus, alkylation of the known *N*-chloromethylsuccinimide[13] with thiophenol in the presence of NaH as a base gave, after 5 h of reaction in dry DMF at room temp., the desired imide **23** (57% yield). Selective reduction of **23** with a large excess of $NaBH_4$ (6 equiv.) in methanol gave α-hydroxy lactam **24** in an excellent yield (93%). This latter, upon treatment with TFA at room temp., furnished a 3.0:2.0 isomeric mixture of two tricyclic thiolactams **25** and **26** in 67% yield after chromatographic purification. This suggests that the cyclic azasulfonium cation **H**, similar to **A** (Scheme 8), is formed an intermediate. At this stage, it should be pointed out that (i) the regioselectivity of the reaction is in favor of **25** to the detriment of **26** (3.0:2.0 ratio) and is comparable to that observed in the isoindolone series, (ii) the reaction proceeds with lower yield (67%), thus confirming the instability difference evoked between the iminium species in the pyrrolidinone and isoindolone series, and (iii) all attempts to separate the mixture of **25** and **26** failed, although the recovered unreacted mixture contained further unknown impurities. This is due to the instability of these thiolactams.

Compounds **25** and **26** have comparable R_f values in numerous solvents and, consequently, their complete separation failed. Since the minor product has been isolated by us by the linear thiocyclization of an *N*-acyliminium ion,[2,4] and by others by radical cyclization with Bu_3SnH as a promoter,[14] a chemical separation protocol was envisioned, as reported by us for the related thiolactams.[4] Thus, oxidation

of the mixture of **25** and **26** with 2.2 equiv. of *m*-CPBA in dry dichloromethane at room temperature afforded a mixture of sulfones **27** and **28** (100%), which were separated by simple crystallization from dichloromethane (Scheme 8).

The spectroscopic data and microanalysis confirmed the structures of these compounds. For instance, the ^{1}H NMR spectra of **27** and **28** reveal the presence of a triplet for **27** at δ = 4.35 ppm and a doublet for **28** at δ = 4.92 ppm corresponding to the angular proton. The spectra also contain two doublets of an AB system for the methylene group due to the diastereotopic effect, with a coupling constant of 14.0 Hz for **27** and 17.7 Hz for **28,** characteristic of geminal protons. Of particular note for product **27** (Scheme 8), the ^{1}H NMR spectrum shows an "unexpected" important shielding of about 0.51 ppm of the angular proton H-10a compared to the corresponding one in the tricyclic N,S-acetal **25**, while the same proton H-9a in sulfone **28** is barely affected by this oxidation (in this case only a small deshielding effect was observed: $\Delta\delta$ = 0.05 ppm) in spite of the proximity of the sulfur atom. Interestingly, these results are similar to that obtained for sulfones in related isoindolo[1,3] benzothiazines, which show, however, an important deshielding effect.[4] Moreover, the sequence of chemical shifts of the angular protons in sulfides **25** and **26** is inverted compared to the corresponding signals in the related N,S-acetals of the isoindolone series **11a** and **12a** (in the latter the values decrease from **11a** to **12a**).

Conclusions

In conclusion, the obtained results show that the *N*-acyliminium ion precursor in neat TFA at ambient temperature gives two categories of processes involving the cyclic azathionium species (type **A** or type **H**) as the reaction intermediate. From the latter cation, obtained by the intramolecular thioamidoalkylation of the classical endocyclic *N*-acyliminium ion, an isomerization into the "unexpected" exocyclic one occurs that leads to original triheterocyclic systems containing fused six-, seven-, and eight-membered N,S-, and/or N,Se-acetals. Under these acidic conditions, we have found that a value of n = 1 is necessary for the occurrence of the "unexpected" pathway to give **11**:**12**, **17**:**18**, and **25**:**26** ratios that depend on the benzene substitution, the nature of the aryl nucleus, and the nature of the heteroatom. Furthermore, this tandem process seems to be general to nonaromatic *N*-acyliminium ions derived from the succinimide ring. Finally, we anticipate that the novel transformations developed in this project will find further application in synthesis, and the systems currently under investigation in our laboratory will be published soon as a full account.

Experimental Section

General Remarks: Melting points were measured on a Boetius micro hot-stage and are uncorrected. The IR spectra were recorded on a Philips analytical PV 9 800 FT IR spectrophotometer (potassium bromide for solids and without solvent (neat) for liquids). The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 (200 MHz) and Varian VXR-300 (300 MHz) instruments with $CDCl_3$ (δ = 7.24 ppm) or [D_6]DMSO (δ = 2.49 ppm) as solvents; chemical shifts (δ) are expressed in ppm relative to TMS or HMDS as internal standard. Thin layer chromatography (TLC) was performed with silica gel analytical plates Merck 5715 (F_{254}) of 0.25 mm thickness. The detection on TLC plates was performed with UV light at 254 or 365 nm or using iodine vapor. Mass spectral measurements were recorded on an AEI MS 902 S spectrophotometer (70 eV, electron impact). The elemental analyses (C, H, N) were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France.

General Procedure for *S*-Alkylation of *N*-(Chloromethyl)- or *N*-(Bromoethy)lphthalimide (7) and *N*-(Chloromethyl)succinimide: Sodium methoxide (0.1 to 0.15 mol) was added to a stirred solution of aryl mercaptan derivative **8** (0.1 to 0.15 mol) in 40 mL of dry DMF under an atmosphere of dry argon. After stirring for 40 min at room temperature, the halide (0.1 mol) was added slowly dropwise over a period of 5 min. The mixture was then stirred at ambient temperature for 4 to 12 h (monitored by TLC with CH_2Cl_2/cyclohexane as eluent, see text, schemes, and tables for the reaction time) and hydrolyzed with crushed ice. The solution was filtered and the solid was recrystallized from suitable solvent to give the expected imide. If a solid was not formed, the solution was extracted three times with diethyl ether, the organic layer was dried with $MgSO_4$, and concentrated in vacuo. The oily residue was passed through a short celite column and used in the next step without further purification (the products obtained in these cases were, in general, sufficiently pure).

***N*-(2-Bromophenylthiomethyl)phthalimide (9b):** This compound was isolated as a white solid in 82% yield (see ref.[3]) after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 97 °C. IR: $\tilde{\nu}_{max}$ = 1710 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 5.06 (s, 2 H, CH_2), 7.11–7.18 (m, 2 H, benzene), 7.53–7.65 (m, 2 H, benzene), 7.66–7.74 (m, 2 H, phthalimide), 7.78–7.85 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.5 (CH_2), 123.6 (CH_{Ar}), 127.9 (C), 128.0 (CH_{Ar}), 129.6 (CH_{Ar}), 131.9 (C), 133.4 (CH_{Ar}), 134.2 (CH_{Ar}), 134.3 (CH_{Ar} + C), 167 (C=O) ppm. MS (EI): m/z = 348 [M$^+$]. $C_{15}H_{10}BrNO_2S$ (348.22): calcd. C 51.74, H 2.89, N 4.02; found C 51.63, H 2.91, N 3.97.

***N*-(3-Chlorophenylthiomethyl)phthalimide (9c):** This compound was isolated as a white solid in 88% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 101 °C (98 °C from ref.[16]). IR: $\tilde{\nu}_{max}$ = 1719 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 5.05 (s, 2 H, CH_2-S), 7.22 (m, 2 H, benzene), 7.36–7.40 (m, 1 H, benzene), 7.47–7.51 (m, 1 H, benzene), 7.70–7.72 (m, 2 H, phthalimide), 7.81–7.85 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.3 (CH_2), 123.7 (CH_{Ar}), 128 (CH_{Ar}), 130 (CH_{Ar}), 130.1 (CH_{Ar}), 131.8 (CH_{Ar}), 131.85 (C), 134.4 (CH_{Ar}), 134.6 (C), 135.3 (C), 166.9 (C=O) ppm. MS (EI): m/z = 303 [M$^+$]. $C_{15}H_{10}ClNO_2S$ (303.77): calcd. C 59.31, H 3.32, N 4.61; found C 59.19, H 3.21, N 4.68.

***N*-(3-Methoxyphenylthiomethyl)phthalimide (9d):** This compound was isolated as a white solid in 68% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 98 °C. IR: $\tilde{\nu}_{max}$ = 1712 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ = 3.73 (s, 3 H, O-Me), 5.05 (s, 2 H, CH_2-S), 6.77–6.79 (m, 1 H, benzene), 7.03–7.06 (m, 2 H, benzene), 7.16–7.20 (m, 1 H, benzene), 7.67–7.71 (m, 2 H, phthalimide), 7.80–7.83 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.8 (CH_2), 55.3 (CH_3), 114.1 (CH_{Ar}), 116.7 (CH_{Ar}), 123.6 (CH_{Ar}), 124.1 (CH_{Ar}), 129.9

(CH_{Ar}), 131.9 (C), 134.3 (CH_{Ar}), 134.5 (C), 159.8 (C), 166.9 (C=O) ppm. MS (EI): *m*/*z* = 299 [M^+]. $C_{16}H_{13}NO_3S$ (299.35): calcd. C 64.20, H 4.38, N 4.68; found C 64.42, H 4.19, N 4.78.

***N*-(4-Methoxyphenylthiomethyl)phthalimide (9e):** This compound was isolated as a white solid in 54% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 112 °C. IR: $\tilde{\nu}_{max}$ = 1711 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 3.72 (s, 3 H, OMe), 4.88 (s, 2 H, CH_2-S), 6.74 (d, *J* = 8.8 Hz, 2 H, benzene), 7.36 (d, *J* = 8.8 Hz, 2 H, benzene), 7.64–7.68 (m, 2 H, phthalimide), 7.75–7.78 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 43.4 (CH_2), 55.3 (CH_3), 114.6 (CH_{Ar}), 123.4 (C), 123.5 (CH_{Ar}), 131.9 (C), 134.2 (CH_{Ar}), 135.8 (CH_{Ar}), 160.2 (C), 166.9 (C=O) ppm. MS (EI): *m*/*z* = 299 [M^+]. $C_{16}H_{13}NO_3S$ (299.35): calcd. C 64.20, H 4.38, N 4.68; found C 63.95, H 4.41, N 4.61.

***N*-[2-(Methoxycarbonyl)phenylthiomethyl]phthalimide (9f):** This compound was isolated as a white solid in 84% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 112 °C. IR: $\tilde{\nu}_{max}$ = 1702, 1720 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 3.83 (s, 3 H, OMe), 5.13 (s, 2 H, CH_2-S), 7.23–7.26 (m, 2 H, benzene), 7.43–7.48 (m, 1 H, benzene), 7.67–7.72 (m, 3 H, phthalimide + benzene), 7.81–7.85 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.3 (CH_2), 52.3 (CH_3), 123.5 (CH_{Ar}), 126.5 (CH_{Ar}), 130.6 (CH_{Ar}), 130.8 (CH_{Ar}), 131.4 (C), 132 (C), 132.2 (CH_{Ar}), 134.2 (CH_{Ar}), 136.3 (C), 166.8 (C=O), 167.1 (C=O) ppm. MS (EI): *m*/*z* = 327 [M^+]. $C_{17}H_{13}NO_4S$ (327.36): calcd. C 62.37, H 4.00, N 4.28; found C 62.18, H 3.86, N 4.21.

***N*-(Phenylselenomethyl)phthalimide [9 (X = Se)]:** This compound was isolated as a white solid in 97% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 114 °C. IR: $\tilde{\nu}_{max}$ = 1710 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 5.08 (s, 2 H, CH_2–Se), 7.23–7.28 (m, 3 H, benzene), 7.58–7.65 (m, 2 H, benzene), 7.67–7.72 (m, 2 H, phthalimide), 7.77–7.82 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 33.1 (CH_2), 123.5 (CH_{Ar}), 128.2 (CH_{Ar}), 128.4 (C), 129.1 (CH_{Ar}), 132.4 (C), 134.2 (CH_{Ar}), 134.8 (CH_{Ar}), 166.8 (C=O) ppm. MS (EI): *m*/*z* = 316 [M^+]. $C_{15}H_{11}NO_2Se$ (316.22): calcd. C 56.98, H 3.51, N 4.43; found C 56.91, H 3.41, N 4.52.

***N*-(2-Naphthylthiomethyl)phthalimide (14):** This compound was isolated as a white solid in 94% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 111 °C (see ref.[3]). IR: $\tilde{\nu}_{max}$ = 1718 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 5.14 (s, 2 H, CH_2-S), 7.42–7.45 (m, 2 H, naphthalene), 7.55–7.59 (m, 2 H, naphthalene), 7.65–7.69 (m, 2 H, phthalimide), 7.75–7.79 (m, 4 H, phthalimide + naphthalene), 7.96 (s, 1 H, naphthalene) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.9 (CH_2), 123.6 (CH_{Ar}), 126.4 (CH_{Ar}), 126.6 (CH_{Ar}), 127.6 (CH_{Ar}), 127.8 (CH_{Ar}), 128.8 (CH_{Ar}), 129.2 (CH_{Ar}), 130.5 (C), 131.1 (CH_{Ar}), 131.9 (C), 132.6 (C), 133.6 (C), 134.2 (CH_{Ar}), 167 (C=O) ppm. MS (EI): *m*/*z* = 319 [M^+]. $C_{19}H_{13}NO_2S$ (319.38): calcd. C 71.45, H 4.10, N 4.39; found C 71.36, H 4.03, N 4.51.

***N*-(Benzylthiomethyl)phthalimide (21h):** This compound was isolated as a yellow solid in 81% yield after recrystallization from ethanol/water according to the general procedure for the *S*-alkylation. M.p. 118 °C. IR: $\tilde{\nu}_{max}$ = 1724 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 3.89 (s, 2 H, CH_2-S), 4.69 (s, 2 H, N-CH_2-S), 7.07–7.11 (m, 1 H, benzene), 7.29–7.34 (m, 2 H, benzene), 7.38–7.42 (m, 2 H, benzene), 7.68–7.71 (m, 2 H, phthalimide), 7.80–7.85 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.6 (CH_2), 38.7 (CH_2), 123.5 (CH_{Ar}), 127.1 (CH_{Ar}), 128.5 (CH_{Ar}), 129.1 (CH_{Ar}), 132 (C), 134.2 (CH_{Ar}), 137.9 (C), 167.6 (C=O) ppm. MS (EI): *m*/*z* = 283 [M^+]. $C_{16}H_{13}NO_2S$ (283.35): calcd. C 67.82, H 4.62, N 4.94; found C 67.95, H 4.94, N 5.03.

***N*-(Phenethylthiomethyl)phthalimide (21i):** This compound was isolated as a yellow solid in 72% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 105 °C. IR: $\tilde{\nu}_{max}$ = 1711 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 2.92 (s, 4 H, CH_2-CH_2-S), 4.75 (s, 2 H, N-CH_2-S), 7.23–7.28 (m, 5 H, benzene), 7.70–7.76 (m, 2 H, phthalimide), 7.82–7.87 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 33.8 (CH_2), 36.3 (CH_2), 39 (CH_2), 123.6 (CH_{Ar}), 126.4 (CH_{Ar}), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 132 (C), 134.3 (CH_{Ar}), 140.1 (C), 167.6 (C=O) ppm. MS (EI): *m*/*z* = 297 [M^+]. $C_{17}H_{15}NO_2S$ (297.38): calcd. C 68.66, H 5.08, N 4.71; found C 68.75, H 4.97, N 4.66.

***N*-(2-Phenylthioethyl)phthalimide (21j):** This compound was isolated as a yellow oil in 69% yield according to the general procedure for the *S*-alkylation. IR: $\tilde{\nu}_{max}$ = 1712 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 3.19 (t, *J* = 7.0 Hz, 2 H, C–CH_2–S), 3.90 (t, *J* = 7.0 Hz, 2 H, N-CH_2-C), 7.19–7.23 (m, 2 H, benzene), 7.36–7.41 (m, 3 H, benzene), 7.64–7.71 (m, 2 H, phthalimide), 7.74–7.82 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.6 (CH_2), 37.5 (CH_2), 123.3 (CH_{Ar}), 126.4 (CH_{Ar}), 129 (CH_{Ar}), 129.6 (CH_{Ar}), 132 (C), 134 (CH_{Ar}), 134.9 (C), 168 (C=O) ppm. MS (EI): *m*/*z* = 283 [M^+]. $C_{16}H_{13}NO_2S$ (283.35): calcd. C 67.82, H 4.62, N 4.94; found C 67.78, H 4.42, N 4.78.

***N*-(2-Benzylthioethyl)phthalimide (21k):** This compound was isolated as a yellow solid in 77% yield after recrystallization from ethanol according to the general procedure for the *S*-alkylation. M.p. 45 °C. IR: $\tilde{\nu}_{max}$ = 1710 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 2.68 (t, *J* = 7.0 Hz, 2 H, C-CH_2-S), 3.76 (s, 2 H, CH_2-S), 3.84 (t, *J* = 7.0 Hz, 2 H, N-CH_2-C), 7.25–7.31 (m, 5 H, benzene), 7.67–7.71 (m, 2 H, phthalimide), 7.80–7.84 (m, 2 H, phthalimide) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.1 (CH_2), 35.5 (CH_2), 36.7 (CH2), 123.4 (CH_{Ar}), 127.1 (CH_{Ar}), 128.6 (CH_{Ar}), 129.0 (CH_{Ar}), 132.1 (C), 134.0 (CH_{Ar}), 137.9 (C), 168.2 (C=O) ppm. MS (EI): *m*/*z* = 297 [M^+]. $C_{17}H_{15}NO_2S$ (297.38): calcd. C 68.66, H 5.08, N 4.71; found C 68.91, H 5.12, N 4.61.

***N*-(Phenylthiomethyl)succinimide (23):** This compound was isolated as an colorless oil in 57% yield after filtration through celite according to the general procedure for the *S*-alkylation by using NaH as base. IR: $\tilde{\nu}_{max}$ = 1710 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 2.62 (s, 4 H, succinimide), 4.80 (s, 2 H, CH_2-S), 7.26–7.31 (m, 3 H, benzene), 7.41–7.46 (m, 2 H, benzene) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.5 (CH_2), 42.7 (CH_2), 128.3 (CH), 128.9 (CH), 129.2 (CH), 136.1 (C), 177.2 (CO) ppm. MS (EI): *m*/*z* = 221 [M^+]. $C_{11}H_{11}NO_2S$ (221.28): calcd. C 59.71, H 5.01, N 6.33; found C 59.58, H 4.83, N 6.04.

General Procedure for Reduction of Imides: Sodium borohydride (60 mmol, 4–6 equiv.) was added in portions to a solution of the imide obtained above (10 mmol) in dry methanol (30 mL) at 0–5 °C. After complete addition of sodium borohydride the mixture was allowed to react whilst stirring for the required time (monitored by TLC with CH_2Cl_2 as eluent). The unreacted sodium borohydride was destroyed by careful addition of 5% HCl solution and basified with a saturated $NaHCO_3$ aqueous solution. After evaporation of the solvent under reduced pressure, the residue was diluted with cold water (30 mL) and allowed to stir at room temperature for an additional hour. The resulting solid was filtered off and recrystallized from dry ethanol to give pure ω-carbinol lactam in good to excellent yield. For oily products, the solution was extracted with CH_2Cl_2 and the organic layer was washed with water, brine, dried with $MgSO_4$, and concentrated in vacuo at room tem-

perature to give the desired ω-carbinol lactam in pure form and comparable yield to the solid.

2-(2-Bromophenylthiomethyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (10b): This compound was isolated as a white solid in 89% yield after recrystallization from ethanol according to the general procedure for the reduction. M.p. 159 °C. IR: $\tilde{\nu}_{max}$ = 1702 (C=O), 3341 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.42 (d, J = 11.3 Hz, 1 H, OH), 4.53 (d, J = 14.0 Hz, 1 H, CH_2), 5.23 (d, J = 14.0 Hz, 1 H, CH_2), 6.01 (d, J = 11.3 Hz, 1 H, CH), 7.00–7.12 (m, 1 H, benzene), 7.18–7.26 (m, 1 H, benzene), 7.50–7.54 (m, 6 H, benzene + isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 42.6 (CH_2), 80.5 (CH), 123.6 (CH_{Ar}), 123.6 (CH_{Ar}), 125.5 (C), 128.1 (CH_{Ar}), 128.4 (CH_{Ar}), 130.0 (CH_{Ar}), 130.7 (C), 131.3 (CH_{Ar}), 132.9 (CH_{Ar}), 133.2 (CH_{Ar}), 134.8 (C), 143.6 (C), 166.9 (C=O) ppm. MS (EI): m/z = 350 [M^+]. $C_{15}H_{12}BrNO_2S$ (350.24): calcd. C 51.44, H 3.45, N 4.00; found C 51.53, H 3.29, N 4.11.

2-(3-Chlorophenylthiomethyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (10c): This compound was isolated as a white solid in 99% yield after recrystallization from ethanol according to the general procedure for the reduction. M.p. 134 °C. IR: $\tilde{\nu}_{max}$ = 1690 (C=O), 3323 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.60 (d, J = 11.6 Hz, 1 H, OH), 4.47 (d, J = 14.0 Hz, 1 H, CH_2), 5.09 (d, J = 14.0 Hz, 1 H, CH_2), 5.93 (d, J = 11.6 Hz, 1 H, CH), 7.13–7.19 (m, 2 H, benzene), 7.23–7.29 (m, 2 H, benzene), 7.45–7.51 (m, 1 H, isoindole), 7.56–7.62 (m, 3 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 43.0 (CH_2), 80.4 (CH), 123.6 (CH_{Ar}), 123.7 (CH_{Ar}), 127.4 (CH_{Ar}), 128.5 (CH_{Ar}), 130.1 (CH_{Ar}), 130.2 (CH_{Ar}), 130.3 (CH_{Ar}), 130.6 (C), 133.0 (CH_{Ar}), 134.7 (C), 135.7 (C), 143.5 (C), 166.9 (C=O) ppm. MS (EI): m/z = 305 [M^+]. $C_{15}H_{12}ClNO_2S$ (305.79): calcd. C 58.92, H 3.96, N 4.58; found C 58.86, H 4.01, N 4.71.

3-Hydroxy-2-(3-methoxyphenylthiomethyl)-2,3-dihydro-1*H*-isoindol-1-one (10d): This compound was isolated as a white solid in 81% yield after recrystallization from ethanol according to the general procedure for the reduction. M.p. 131 °C. IR: $\tilde{\nu}_{max}$ = 1680 (C=O), 3274 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.69 (s, 3 H, CH_3), 3.75 (d, J = 11.0 Hz, 1 H, OH), 4.46 (d, J = 14.0 Hz, 1 H, CH_2), 5.08 (d, J = 14.0 Hz, 1 H, CH_2), 5.93 (d, J = 11.0 Hz, 1 H, CH), 6.69 (dd, J = 1.8 and 7.0 Hz, 1 H, benzene), 6.95 (dd, J = 1.8 and 7.0 Hz, 1 H, benzene), 6.96 (s, 1 H, benzene), 7.12 (t, J = 7.0 Hz, 1 H, benzene), 7.43–7.48 (m, 1 H, isoindole), 7.52–7.57 (m, 3 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 42.8 (CH_2), 55.3 (CH_3), 80.5 (CH), 113.5 (CH_{Ar}), 115.2 (CH_{Ar}), 122.5 (CH_{Ar}), 123.4 (CH_{Ar}), 123.6 (CH_{Ar}), 129.8 (CH_{Ar}), 129.9 (CH_{Ar}), 130.7 (C), 132.8 (CH_{Ar}), 134.8 (C), 143.7 (C), 159.9 (C), 167.0 (C=O) ppm. MS (EI): m/z = 301 [M^+]. $C_{16}H_{15}NO_3S$ (301.37): calcd. C 63.77, H 5.02, N 4.65; found C 63.68, H 4.93, N 4.72.

3-Hydroxy-2-(4-methoxyphenylthiomethyl)-2,3-dihydro-1*H*-isoindol-1-one (10e): This compound was isolated as a white solid in 98% yield after recrystallization from ethanol according to the general procedure for the reduction. M.p. 125 °C. IR: $\tilde{\nu}_{max}$ = 1680 (C=O), 3340 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.70 (s, 3 H, OMe), 4.05 (d, J = 11.0 Hz, 1 H, OH), 4.32 (d, J = 13.7 Hz, 1 H, CH_2), 4.87 (d, J = 13.7 Hz, 1 H, CH_2), 4.90 (d, J = 11.0 Hz, 1 H, CH), 6.72 (d, J = 8.9 Hz, 2 H, benzene), 7.27 (d, J = 8.9 Hz, 2 H, benzene), 7.45–7.48 (m, 2 H, isoindole), 7.53–7.59 (m, 2 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.0 (CH_2), 55.3 (CH_3), 80.5 (CH), 114.8 (CH_{Ar}), 123.5 (CH_{Ar}), 123.58 (CH_{Ar}), 123.6 (C), 130.0 (CH_{Ar}), 130.9 (C), 132.7 (CH_{Ar}), 134.5 (CH_{Ar}), 143.5 (C), 159.7 (C), 166.6 (C=O) ppm. MS (EI): m/z = 301 [M^+]. $C_{16}H_{15}NO_3S$ (301.37): calcd. C 63.77, H 5.02, N 4.65; found C 63.43, H 5.15, N 4.81.

3-Hydroxy-2-[2-(methoxycarbonyl)phenylthiomethyl]-2,3-dihydro-1*H*-isoindol-1-one (10f): This compound was isolated as a yellow solid in 98% yield after recrystallization from ethanol/water according to the general procedure for the reduction. M.p. 135 °C. IR: $\tilde{\nu}_{max}$ = 1674, 1709 (C=O), 3325 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.81 (s, 3 H, CH_3), 4.28 (d, J = 9.9 Hz, 1 H, OH), 4.63 (d, J = 14.0 Hz, 1 H, CH_2), 5.38 (d, J = 14.0 Hz, 1 H, CH_2), 6.05 (d, J = 9.9 Hz, 1 H, CH), 7.17 (t, J = 7.3 Hz, 1 H, benzene), 7.36–7.41 (m, 2 H, benzene), 7.54–7.59 (m, 2 H, isoindole), 7.63–7.71 (m, 2 H, isoindole), 7.85 (d, J = 7.1 Hz, 1 H, benzene) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.5 (CH_2), 52.3 (CH_3), 80.5 (CH), 123.4 (CH_{Ar}), 123.6 (CH_{Ar}), 125.4 (CH_{Ar}), 128.3 (CH_{Ar}), 129.0 (C), 129.9 (CH_{Ar}), 130.9 (C), 131.2 (CH_{Ar}), 132.7 (CH_{Ar}), 137.6 (C), 143.7 (C), 167.1 (C=O), 167.2 (C=O) ppm. MS (EI): m/z = 329 [M^+]. $C_{17}H_{15}NO_4S$ (329.38): calcd. C 61.99, H 4.59, N 4.25; found C 62.07, H 4.61, N 4.12.

3-Hydroxy-2-(phenylselenomethyl)-2,3-dihydro-1*H*-isoindol-1-one [10 (X = Se)]: This compound was isolated as a yellow solid in 80% yield after recrystallization from ethanol according to the general procedure for the reduction. M.p. 112 °C. IR: $\tilde{\nu}_{max}$ = 1678 (C=O), 3290 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.97 (d, J = 11.8 Hz, 1 H, OH), 4.54 (d, J = 12.1 Hz, 1 H, CH_2–Se), 5.08 (d, J = 12.1 Hz, 1 H, CH_2–Se), 5.85 (d, J = 11.8 Hz, 1 H, CH), 7.18–7.25 (m, 3 H, benzene), 7.39–7.44 (m, 2 H, benzene), 7.48–7.61 (m, 4 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.4 (CH_2), 80.9 (CH), 123.3 (CH_{Ar}), 123.6 (CH_{Ar}), 127.8 (CH_{Ar}), 128.6 (C), 129.3 (CH_{Ar}), 129.8 (CH_{Ar}), 130.7 (C), 132.8 (CH_{Ar}), 133.8 (CH_{Ar}), 143.7 (C), 166.8 (C=O) ppm. MS (EI): m/z = 318 [M^+]. $C_{15}H_{13}NO_2Se$ (318.24): calcd. C 56.61, H 4.12, N 4.40; found C 56.49, H 4.09, N 4.22.

3-Hydroxy-2-(2-naphthylthiomethyl)-2,3-dihydro-1*H*-isoindol-1-one (16): This compound was isolated as a yellow solid in 99% yield after recrystallization from ethanol/water according to the general procedure for the reduction. M.p. 168 °C. IR: $\tilde{\nu}_{max}$ = 1682 (C=O), 3302 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.15 (d, J = 11.3 Hz, 1 H, OH), 4.63 (d, J = 14.0 Hz, 1 H, CH_2), 5.31 (d, J = 14.0 Hz, 1 H, CH_2), 5.97 (d, J = 11.3 Hz, 1 H, CH), 7.39–7.75 (m, 10 H, isoindole + naphthalene), 7.87 (s, 1 H, naphthalene) ppm. ^{13}C NMR ($CDCl_3$): δ = 42.9 (CH_2), 80.5 (CH), 123.5 (CH_{Ar}), 123.6 (CH_{Ar}), 126.2 (CH_{Ar}), 126.6 (CH_{Ar}), 127.4 (CH_{Ar}), 127.7 (CH_{Ar}), 128.0 (CH_{Ar}), 128.8 (CH_{Ar}), 129.3 (CH_{Ar}), 129.9 (CH_{Ar}), 130.7 (C), 130.9 (C), 132.2 (C), 132.8 (CH_{Ar}), 133.6 (C), 143.6 (C), 166.9 (C=O) ppm. MS (EI): m/z = 321 [M^+]. $C_{19}H_{15}NO_2S$ (321.40): calcd. C 71.01, H 4.70, N 4.36; found C 70.89, H 4.65, N 4.41.

2-(Benzylthiomethyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (22h): This compound was isolated as a white solid in 90% yield after recrystallization from ethanol according to the general procedure for the reduction. M.p. 120 °C. IR: $\tilde{\nu}_{max}$ = 1686 (C=O), 3264 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.63 (d, J = 13.7 Hz, 1 H, S-CH_2), 3.74 (d, J = 13.7 Hz, 1 H, S-CH_2), 3.87 (d, J = 11.0 Hz, 1 H, OH), 4.07 (d, J = 14.2 Hz, 1 H, N-CH_2-S), 4.71 (d, J = 14.2 Hz, 1 H, N-CH_2-S), 5.87 (d, J = 11.0 Hz, 1 H, CH), 7.08–7.29 (m, 5 H, benzene), 7.36–7.40 (m, 1 H, isoindole), 7.50–7.56 (m, 3 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.9 (CH_2), 40.8 (CH_2), 80.3 (CH), 123.3 (CH_{Ar}), 123.5 (CH_{Ar}), 126.9 (CH_{Ar}), 128.4 (CH_{Ar}), 128.8 (CH_{Ar}), 129.8 (CH_{Ar}), 130.7 (C), 132.7 (CH_{Ar}), 138.0 (C), 143.7 (C), 167.5 (C=O) ppm. MS (EI): m/z = 285 [M^+]. $C_{16}H_{15}NO_2S$ (285.37): calcd. C 67.34, H 5.30, N 4.91; found C 67.43, H 5.25, N 4.78.

3-Hydroxy-2-(2-phenethylthiomethyl)-2,3-dihydro-1*H*-isoindol-1-one (22i): This compound was isolated as a yellow oil in 82% yield after filtration through a short celite column according to the general procedure for the reduction. IR: $\tilde{\nu}_{max}$ = 1673 (C=O), 3318 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.56–2.98 (m, 4 H, S-CH_2-CH_2), 4.08 (d, J = 14.0 Hz, 1 H, N-CH_2-S), 4.75 (d, J = 14.0 Hz, 1 H, N-CH_2-

S), 5.91 (s, 1 H, CH), 7.12–7.17 (m, 5 H, benzene), 7.40–7.47 (m, 1 H, isoindole), 7.54–7.59 (m, 3 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.6 (CH_2), 35.2 (CH_2), 40.5 (CH_2), 80.7 (CH), 122.3 (CH_{Ar}), 122.8 (CH_{Ar}), 124.7 (CH_{Ar}), 127.3 (CH_{Ar}), 127.5 (CH_{Ar}), 128.0 (CH), 129.6 (C), 132.2 (CH_{Ar}), 138.9 (C), 142.9 (C), 166.6 (C=O) ppm. MS (EI): *m*/*z* = 299 [M$^+$]. $C_{17}H_{17}NO_2S$ (299.39): calcd. C 68.20, H 5.72, N 4.68; found C 68.00, H 5.39, N 4.49.

3-Hydroxy-2-[(2-phenylthio)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (22j): This compound was isolated as a yellow solid in 91% yield after recrystallization from diethyl ether/hexane according to the general procedure for the reduction. M.p. <30 °C. IR: $\tilde{\nu}_{max}$ = 1674 (C=O), 3325 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.08 (t, *J* = 7.0 Hz, 2 H, N-CH_2), 3.49 (t, *J* = 7.0 Hz, 2 H, S-CH_2), 5.73 (s, 1 H, CH), 7.09–7.39 (m, 5 H, benzene), 7.44–7.54 (m, 4 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.9 (CH_2), 39.1 (CH_2), 82.5 (CH), 123.3 (CH_{Ar}), 123.5 (CH_{Ar}), 126.4 (CH_{Ar}), 129.1 (CH_{Ar}), 129.9 (CH_{Ar}), 131.1 (CH_{Ar}), 132.5 (C), 135.1 (CH_{Ar}), 144.0 (C), 167.8 (C=O) ppm. MS (EI): *m*/*z* = 285 [M$^+$]. $C_{16}H_{15}NO_2S$ (285.37): calcd. C 67.34, H 5.30, N 4.91; found C 67.09, H 5.19, N 4.69.

2-(2-Benzylthioethyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (22k): This compound was isolated as a yellow oil in 83% yield after a short celite column filtration according to the general procedure for the reduction. IR: $\tilde{\nu}_{max}$ = 1671 (C=O), 3316 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.66 (t, *J* = 6.7 Hz, 2 H, N-CH_2-C), 3.41–3.85 (m, 4 H, S-CH_2-C and S-CH_2), 5.90 (s, 1 H, CH), 7.14–7.75 (m, 9 H, benzene + isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.7 (CH_2), 36.2 (CH_2), 40.5 (CH_2), 79.7 (CH), 121.3 (CH_{Ar}), 123.2 (CH_{Ar}), 124.2 (CH_{Ar}), 126.8 (CH_{Ar}), 127.0 (CH_{Ar}), 127.9 (CH), 128.9 (C), 133.2 (CH_{Ar}), 138.5 (C), 142.5 (C), 167.4 (C=O) ppm. MS (EI): *m*/*z* = 299 [M$^+$]. $C_{17}H_{17}NO_2S$ (299.39): calcd. C 68.20, H 5.72, N 4.68; found C 67.96, H 5.32, N 4.51.

5-Hydroxy-1-(phenylthiomethyl)pyrrolidin-2-one (24): This compound was isolated as a yellow oil in 93% yield according to the general procedure for the reduction. IR: $\tilde{\nu}_{max}$ = 1674 (C=O), 3325 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.66–2.29 (m, 4 H, pyrrolidinone), 4.37 (d, *J* = 14.0 Hz, 1 H, CH_2), 4.74 (d, *J* = 6.0 Hz, 1 H, OH), 5.13 (d, *J* = 14.0 Hz, 1 H, CH_2), 5.35–5.41 (m, 1 H, CH), 7.19–5.28 (m, 3 H, benzene), 7.37–5.45 (m, 2 H, benzene) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.4 (CH_2), 29.2 (CH_2), 43.7 (CH_2), 113.7 (CH), 127.9 (CH), 128.1 (CH), 129.0 (CH), 136.8 (C), 175.1 (C=O) ppm. MS (EI): *m*/*z* = 223 [M$^+$]. $C_{11}H_{13}NO_2S$ (223.30): calcd. C 59.17, H 5.87, N 6.27; found C 59.02, H 5.38, N 6.12.

General Procedure for Cyclization of Hydroxy Lactams. Method A: Neat TFA (20 mL) was added to a stirred solution of the hydroxy lactam (10 mmol), obtained by standard borohydride reduction of the imide as indicated above. After 2–3 h of reaction at room temperature whilst stirring, the reaction mixture was diluted with water (45 mL) and neutralized on cooling with 5% NaOH aqueous solution. The solution was extracted twice with CH_2Cl_2 (25 mL) and separated. The organic layer was washed with water, brine, separated, dried with $MgSO_4$, and the solvents evaporated in vacuo. The resulting crude residue was purified by chromatography [SiO_2, CH_2Cl_2/hexane (4:1)] or recrystallized from the indicated solvent to give the tricyclic product.

Method B (for the hydroxy lactam 10f only): Lewis acid ($SbCl_3$, $BF_3{\cdot}Et_2O$, or $SnCl_4$; 2 equiv.) was added in three portions to a stirred and cold (ice bath) solution of hydroxy lactam **10f** (10 mmol) in 15 mL of dry CH_2Cl_2. After complete addition the mixture was allowed to react at ambient temperature for 24–240 h. After hydrolysis on cooling with 10% NaOH solution and separation, the organic layer was separated, washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude solid was recrystallized from a mixture of ethanol/water to give the cyclized product **11f** in pure form in a similar yield to that obtained with method A. The minor product **12f** has never been isolated but its ^{1}H NMR spectrum was deduced from that of the mixture.

4-Bromo-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzothiazin-8-one (11b): This compound was isolated as a white solid in 95% yield after recrystallization from ethanol according to the general procedure for the cyclization. M.p. 185 °C. IR: $\tilde{\nu}_{max}$ = 1715 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.55 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.37 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.85 (s, 1 H, CH), 7.07–7.11 (m, 1 H, benzene), 7.41–7.46 (m, 2 H, benzene), 7.59–7.66 (m, 2 H, isoindole), 7.69–7.76 (m, 1 H, isoindole), 7.79–7.86 (m, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.4 (CH_2), 59.5 (CH), 123.4 (CH_{Ar}), 123.9 (C), 124.2 (CH_{Ar}), 126.0 (CH_{Ar}), 126.3 (CH_{Ar}), 129.0 (CH_{Ar}), 131.6 (CH_{Ar}), 131.8 (C), 132.5 (CH_{Ar}), 133.6 (C), 134.1 (C), 143.9 (C), 167.9 (CO) ppm. MS (EI): *m*/*z* = 332 [M$^+$]. $C_{15}H_{10}BrNOS$ (332.22): calcd. C 54.23, H 3.03, N 4.22; found C 54.06, H 3.01, N 3.97.

1-Chloro-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzothiazin-8-one (11cx), 4-Chloro-5,11b-dihydroisoindolo[1,2-*b*][1,3]benzothiazin-8-one (12cx), 3-Chloro-6,12b-dihydroisoindolo[2,1-*c*][1,3]-benzothiazin-8-one (11cy), and 2-Chloro-5,11b-dihydroisoindolo[1,2-*b*][1,3]benzothiazin-8-one (12cy): These products were separated by chromatography on a silica gel column into two parts, each containing an inseparable mixture of two positional isomers **11cx/12cx** and **11cy/12cy** (89% yield) in a 5.5:4.5 ratio according to the general procedure for the cyclization; they were characterized by ^{1}H NMR spectroscopy and GC-MS analysis.

Major Product 11cx of the Isomeric Couple 11cx/12cx: ^{1}H NMR ($CDCl_3$): δ = 4.60 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.30 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.79 (s, 1 H, CH), 7.08–7.26 (m, 2 H, benzene), 7.45–7.62 (m, 3 H, isoindole), 7.75 (d, *J* = 7.9 Hz, 1 H, benzene), 7.91 (t, *J* = 7.6 and 7.9 Hz, 1 H, isoindole) ppm.

Minor Product 12cx of the Isomeric Couple 11cx/12cx: ^{1}H NMR ($CDCl_3$): δ = 4.55 (d, *J* = 17.5 Hz, 1 H, CH_2), 5.27 (d, *J* = 17.5 Hz, 1 H, CH_2), 5.81 (s, 1 H, CH), 7.08–7.26 (m, 2 H, benzene), 7.45–7.62 (m, 3 H, isoindole), 7.75 (d, *J* = 7.9 Hz, 1 H, benzene), 7.91 (t, *J* = 7.6 and 7.9 Hz, 1 H, isoindole) ppm.

Major Product 11cy of the Isomeric Couple 11cy/12cy: ^{1}H NMR ($CDCl_3$): δ = 4.30 (d, *J* = 12.1 Hz, 1 H, CH_2), 5.49 (d, *J* = 12.1 Hz, 1 H, CH_2), 6.45 (s, 1 H, CH), 7.00–7.15 (m, 1 H, benzene), 7.25–7.35 (m, 1 H, benzene), 7.40–7.67 (m, 3 H, isoindole), 7.75–7.90 (m, 1 H, benzene), 8.05 (d, *J* = 7.9 Hz, 1 H, isoindole) ppm.

Minor Product 12cy of the Isomeric Couple 11cy/12cy: ^{1}H NMR ($CDCl_3$): δ = 4.55 (d, *J* = 18.5 Hz, 1 H, CH_2), 5.45 (d, *J* = 18.5 Hz, 1 H, CH_2), 5.79 (s, 1 H, CH), 7.00–7.15 (m, 1 H, benzene), 7.25–7.35 (m, 1 H, benzene), 7.40–7.67 (m, 3 H, isoindole), 7.75–7.90 (m, 1 H, benzene), 8.05 (d, *J* = 7.9 Hz, 1 H, isoindole) ppm. MS (EI) (mixture): *m*/*z* = 287 [M$^+$].

1-Methoxy-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzothiazin-8-one (11dx) and 3-Methoxy-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzothiazin-8-one (11dy): These products were obtained as an inseparable mixture of two isomers (8% yield) in a 9:1 ratio according to the general procedure for the cyclization and were characterized by ^{1}H NMR spectroscopy and GC-MS analysis.

Major Isomer 11dx: ^{1}H NMR ($CDCl_3$): δ = 3.74 (s, 3 H, CH_3), 4.61 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.29 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.80 (s, 1 H, CH), 7.48–7.89 (m, 7 H, benzene + isoindole) ppm.

Minor Isomer 11dy: ^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 3 H, CH_3), 4.37 (d, *J* = 12.4 Hz, 1 H, CH_2), 5.44 (d, *J* = 12.4 Hz, 1 H, CH_2), 6.29

(s, 1 H, CH), 7.48–7.89 (m, 7 H, benzene + isoindole) ppm. MS (EI) (mixture): *m*/*z* = 283 [M$^+$].

2-Methoxy-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzothiazin-8-one (11e): This compound was isolated as a white solid in 19% yield after recrystallization from ethanol according to the general procedure for the cyclization. M.p. 171 °C. IR: $\tilde{\nu}_{max}$ = 1697 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.65 (s, 3 H, CH_3), 4.52 (d, J = 12.4 Hz, 1 H, CH_2), 5.35 (d, J = 12.4 Hz, 1 H, CH_2), 5.84 (s, 1 H, CH), 7.07 (s, 1 H, benzene), 7.40–7.45 (m, 2 H, benzene), 7.59–7.65 (m, 2 H, isoindole), 7.70–7.76 (m, 1 H, isoindole), 7.78–7.84 (m, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.9 (CH_2), 82.0 (CH), 114.8 (C), 119.2 (CH_{Ar}), 121.2 (C), 123.7 (CH_{Ar}), 123.8 (CH_{Ar}), 129.9 (CH_{Ar}), 130.3 (CH_{Ar}), 131.3 (CH_{Ar}), 132.3 (C), 132.4 (CH_{Ar}), 140.5 (C), 151.1 (C), 167.5 (CO) ppm. MS (EI): *m*/*z* = 283 [M$^+$]. $C_{16}H_{13}NO_2S$ (283.35): calcd. C 67.82, H 4.62, N 4.94; found C 67.78, H 4.60, N 4.91.

Methyl 8-Oxo-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzothiazin-4-carboxylate (11f): This compound was isolated as a white solid in 94% yield after recrystallization from ethanol/water according to the general procedure for the cyclization. M.p. 196 °C. IR: $\tilde{\nu}_{max}$ = 1702, 1703 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 4.42 (d, J = 12.4 Hz, 1 H, CH_2), 5.37 (d, J = 12.4 Hz, 1 H, CH_2), 5.86 (s, 1 H, CH), 7.38–7.44 (m, 1 H, benzene), 7.51–7.55 (m, 2 H, benzene), 7.67–7.72 (m, 2 H, isoindole), 7.80–7.86 (m, 2 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.4 (CH_2), 52.3 (CH_3), 59.9 (CH), 123.4 (CH_{Ar}), 124.1 (CH_{Ar}), 124.9 (CH_{Ar}), 128.9 (CH_{Ar}), 129.9 (C), 130.2 (CH_{Ar}), 130.9 (CH_{Ar}), 132.2 (CH_{Ar}), 132.3 (C), 133.3 (C), 136.7 (C), 143.7 (C), 166.2 (CO), 168.0 (CO) ppm. MS (EI): *m*/*z* = 311 [M$^+$]. $C_{17}H_{13}NO_3S$ (311.36): calcd. C 65.58, H 4.21, N 4.50; found C 65.66, H 4.00, N 4.67.

Methyl 7-Oxo-5,11b-dihydroisoindolo[1,2-*b*][1,3]benzothiazin-1-carboxylate (12f): This product was not isolated in pure form but its ^{1}H NMR spectroscopic data were deduced from the ^{1}H NMR spectrum of the mixture. ^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 4.73 (d, J = 14.1 Hz, 1 H, S-CH_2), 5.82 (d, J = 14.1 Hz, 1 H, S-CH_2), 6.81 (s, 3 H, CH), 7.11–7.23 (m, 4 H, benzene), 7.37–7.78 (m, 3 H, isoindole), 7.81–7.89 (m, 1 H, isoindole) ppm. MS (EI) (mixture): *m*/*z* = 311 [M$^+$].

5,7-Dihydroisoindolo[2,1-*d*][2,4]benzothiazepin-9(13*bH*)-one (11h): This product was obtained as a mixture (**11h**:**12h**, 9.5:0.5, 94% yield) according to the general cyclization protocol. It was isolated in pure form as a white solid after recrystallization from ethanol. M.p. 209 °C. IR: $\tilde{\nu}_{max}$ = 1703 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.78 (d, J = 15.0 Hz, 1 H, S-CH_2), 4.23 (d, J = 15.0 Hz, 1 H, S-CH_2), 4.59 (d, J = 15.1 Hz, 1 H, N-CH_2-S), 5.22 (d, J = 15.1 Hz, 1 H, N-CH_2-S), 5.90 (s, 1 H, CH), 7.11–7.23 (m, 4 H, benzene), 7.37–7.48 (m, 3 H, isoindole), 7.81–7.89 (m, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.1 (CH_2), 46.0 (CH_2), 65.3 (CH), 122.5 (CH_{Ar}), 123.8 (CH_{Ar}), 127.9 (CH_{Ar}), 128.3 (CH_{Ar}), 128.6 (CH_{Ar}), 129.2 (CH_{Ar}), 130.3 (CH_{Ar}), 131.8 (C), 131.9 (CH_{Ar}), 135.4 (C), 139.8 (C), 142.2 (C), 166.6 (CO) ppm. MS (EI): *m*/*z* = 267 [M$^+$]. $C_{16}H_{13}NOS$ (267.35): calcd. C 71.88, H 4.90, N 5.24; found C 71.66, H 4.79, N 5.11.

5,13-Dihydroisoindolo[1,2-*c*][2,4]benzothiazepin-7(11*bH*)-one (12h): This product was not isolated in pure form but its ^{1}H NMR spectroscopic data were deduced from the ^{1}H NMR spectrum of the mixture. ^{1}H NMR ($CDCl_3$): δ = 3.70 (d, J = 15.5 Hz, 1 H, S-CH_2), 4.19 (d, J = 15.5 Hz, 1 H, S-CH_2), 4.68 (d, J = 16.3 Hz, 1 H, N-CH_2-S), 5.26 (d, J = 16.3 Hz, 1 H, N-CH_2-S), 6.12 (s, 1 H, CH), 7.11–7.23 (m, 4 H, benzene), 7.37–7.78 (m, 3 H, isoindole), 7.81–7.89 (m, 1 H, isoindole) ppm. MS (EI) (mixture): *m*/*z* = 267 [M$^+$].

5,6,8,14b-Tetrahydroisoindolo[2,1-*c*][3,5]benzothiazocin-10-one (11i): This product was obtained as a mixture (**11i**:**12i**, 8:1, 72% yield) according to the general cyclization protocol. It was isolated in pure form as a white solid after recrystallization from ethanol. M.p. 215 °C. IR: $\tilde{\nu}_{max}$ = 1704 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.77–2.95 (m, 1 H, S–CH_2–C), 3.07–3.32 (m, 3 H, S–CH_2–C), 4.50 (d, J = 13.7 Hz, 1 H, N-CH_2-S), 4.97 (s, 1 H, CH), 5.25 (d, J = 13.7 Hz, 1 H, N-CH_2-S), 7.09–7.25 (m, 4 H, benzene), 7.39–7.49 (m, 3 H, isoindole), 7.74 (d, J = 8.1 Hz, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.4 (CH_2), 37.0 (CH_2), 40.8 (CH_2), 64.7 (CH), 123.0 (CH_{Ar}), 123.9 (CH_{Ar}), 127.5 (CH_{Ar}), 128.7 (2CH_{Ar}), 130.0 (CH_{Ar}), 130.9 (CH_{Ar}), 131.3 (C), 131.4 (CH_{Ar}), 134.0 (C), 139.5 (C), 142.2 (C), 165.5 (CO) ppm. MS (EI): *m*/*z* = 281 [M$^+$]. $C_{17}H_{15}NOS$ (281.38): calcd. C 72.57, H 5.37, N 4.98; found C 72.49, H 5.41, N 5.02.

5,11b,13,14-Tetrahydroisoindolo[1,2-*d*][3,5]benzothiazocin-7-one (12i): This product was not isolated in pure form but its ^{1}H NMR spectroscopic data were deduced from the ^{1}H NMR spectrum of the mixture. ^{1}H NMR ($CDCl_3$): δ = 2.71–3.02 (m, 4 H, S-CH_2-CH_2), 4.20 (d, J = 13.7 Hz, 1 H, N-CH_2), 5.33 (d, J = 13.7 Hz, 1 H, N-CH_2), 5.68 (s, 1 H, CH), 7.10–7.27 (m, 4 H, benzene), 7.44–7.73 (m, 3 H, isoindole), 7.87–8.83 (m, 1 H, isoindole) ppm. MS (EI) (mixture): *m*/*z* = 281 [M$^+$].

6,7-Dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13*bH*)-one (11j): This compound was isolated as a yellow solid in 95% yield after recrystallization from ethanol according to the general procedure for the cyclization. M.p. 200 °C. IR: $\tilde{\nu}_{max}$ = 1702 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.92–3.25 (m, 2 H, N-CH_2-CH_2), 3.82–4.15 (m, 2 H, S-CH_2-CH_2), 6.20 (s, 1 H, CH), 6.86–6.92 (m, 1 H, benzene), 7.15–7.27 (m, 2 H, benzene), 7.39–7.64 (m, 4 H, benzene + isoindole), 7.91 (d, J = 7.8 Hz, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 32.7 (CH_2), 42.7 (CH_2), 63.6 (CH), 124.2 (CH_{Ar}), 124.3 (CH_{Ar}), 127.4 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 131.5 (CH_{Ar}), 132.8 (C), 134.0 (CH_{Ar}), 136.1 (C), 139.2 (C), 143.4 (C), 168.8 (CO) ppm. MS (EI): *m*/*z* = 267 [M$^+$]. $C_{16}H_{13}NOS$ (267.35): calcd. C 71.88, H 4.90, N 5.24; found C 71.93, H 4.94, N 5.27.

6,12b-Dihydroisoindolo[2,1-*c*][1,3]benzoselenazin-8-one [11 (X = Se)]: This compound was isolated as a yellow solid in 91% yield after recrystallization from ethanol according to the general procedure for the cyclization. M.p. 175 °C. IR: $\tilde{\nu}_{max}$ = 1703 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.54 (d, J = 16.9 Hz, 1 H, CH_2), 5.27 (d, J = 16.9 Hz, 1 H, CH_2), 6.12 (s, 1 H, CH), 7.14–7.36 (m, 4 H, benzene), 7.47–7.72 (m, 3 H, isoindole), 7.89 (d, J = 7.3 Hz, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.1 (CH_2), 52.1 (CH), 122.6 (CH_{Ar}), 124.1 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (C), 127.8 (CH_{Ar}), 128.9 (CH_{Ar}), 129.1 (CH_{Ar}), 130.4 (CH_{Ar}), 131.1 (C), 131.3 (C), 132.1 (CH_{Ar}), 143.8 (C), 166.9(CO) ppm. MS (EI): *m*/*z* = 300 [M$^+$]. $C_{15}H_{11}NOSe$ (300.22): calcd. C 60.01, H 3.69, N 4.67; found C 60.09, H 3.72, N 4.69.

Pyrrolidino[2,1-*c*][1,3]benzothiazin-8-one (25) and Pyrrolidino[2,1-*d*][1,3]benzothiazin-7-one (26): These products were obtained as an inseparable mixture (67% yield) in a 3:2 ratio according to the general procedure for the cyclization and were characterized by ^{1}H NMR spectroscopy and GC-MS analysis.

Major Isomer 25: 1.85–2.03 (m, 1 H, pyrrolidine), 2.38–2.72 (m, 3 H, pyrrolidine), 4.30 (d, J = 11.6 Hz, 1 H, N-CH_2), 4.86 (m, 1 H, CH), 5.04 (d, J = 11.6 Hz, 1 H, N-CH_2), 7.07–7.11 (m, 4 H, benzene) ppm. MS (EI) (mixture of **25** and **26**): *m*/*z* = 205 [M$^+$].

Minor Isomer 26: This product was obtained as the sole reaction product from the hydroxy lactam **1** by the direct thiocyclization. M.p. 68 °C (dry ethanol). IR: $\tilde{\nu}_{max}$ = 1698 (C=O) cm^{-1}. ^{1}H NMR

($CDCl_3$): δ = 1.85–2.05 (m, 1 H, pyrrolidine), 2.35–2.70 (m, 3 H, pyrrolidine), 4.23 (d, J = 17.0 Hz, 1 H, N-CH_2), 4.85–4.92 (m, 1 H, CH), 5.04 (d, J = 17.0 Hz, 1 H, N-CH_2), 7.06–7.20 (m, 4 H, benzene) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.7 (CH_2), 28.9 (CH_2), 46.8 (CH_2), 62.9 (CH), 126.0 (CH_{Ar}), 126.7 (CH_{Ar}), 127.9 (CH_{Ar}), 127.3 (CH_{Ar}), 136.2 (C), 137.2 (C), 171.9 (CO) ppm. MS (EI): m/z = 205 [M^+]. $C_{11}H_{11}NOS$ (205.28): calcd. C 64.36, H 5.40, N 6.82; found C 64.15, H 5.22, N 6.69.

5,11b-Dihydrothieno[3′,2′:5,6]thiazino[4,3-*a*]isoindol-7-one (17) and 4,10b-Dihydrothieno[2′,3′:5,6]thiazino[2,3-*a*]isoindol-6-one (18): These products were obtained as a mixture (87% yield) in a 9:1 ratio according to the general procedure for the cyclization and were characterized by ^{1}H NMR spectroscopy and GC-MS analysis.

Major Isomer 17: This compound was isolated in pure form by fractional crystallization from dry ethanol and has identical characteristics to those reported previously.[15] M.p. 168 °C (166 °C from ref.[15]) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.2 (CH_2), 58.1 (CH), 123.4 (CH_{Ar}), 124.2 (CH_{Ar}), 124.3 (CH_{Ar}), 125.6 (C), 126.3 (C), 126.6 (CH_{Ar}), 129.1 (CH_{Ar}), 131.2 (C), 132.7 (CH_{Ar}), 143.9 (C), 167.5 (CO) ppm. MS (EI): m/z = 259 [M^+]. $C_{13}H_9NOS_2$ (259.01): calcd. C 60.20, H 3.50, N 5.40; found C 60.42, H 3.22, N 5.29.

Minor Isomer 18: The NMR characteristics of this product were extracted from the spectra of the mixture. ^{1}H NMR ($CDCl_3$): δ = 4.63 (d, J = 17.2 Hz, 1 H, N-CH_2), 5.48 (d, J = 17.2 Hz, 1 H, N-CH_2), 5.89 (s, 1 H, CH), 6.81 (d, J = 5.6 Hz, 1 H, $H_{\beta\text{-thiophene}}$), 7.31 (d, J = 5.6 Hz, 1 H, $H_{\alpha\text{-thiophene}}$), 7.31 (dd, J = 7.0 Hz, 1 H, benzene), 7.64 (dt, J = 1.6, 7.0 and 7.8 Hz, 1 H, benzene), 7.77 (d, J = 7.8 Hz, 1 H, benzene), 7.88 (d, J = 7.0 Hz, 1 H, benzene) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.6 (CH_2), 58.5 (CH), 122.7 (CH_{Ar}), 124.2 (CH_{Ar}), 124.3 (CH_{Ar}), 124.6 (CH_{Ar}), 125.9 (C), 126.1 (C), 129.6 (CH_{Ar}), 132.1 (C), 132.3 (CH_{Ar}), 145.1 (C), 167.0 (CO) ppm. MS (EI): m/z = 259 [M^+].

8,14b-Dihydroisoindolo[2,1-*c*]naphtho[1,2-*e*][1,3]thiazin-10-one (19): This compound was isolated as a white solid in 96% yield after recrystallization from ethanol according to the general procedure for the cyclization. M.p. 196 °C. IR: $\tilde{\nu}_{max}$ = 1716 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.46 (d, J = 12.4 Hz, 1 H, CH_2), 5.54 (d, J = 12.4 Hz, 1 H, CH_2), 6.82 (s, 1 H, CH), 7.21 (d, J = 8.6 Hz, 1 H, naphthalene), 7.35–7.41 (m, 2 H, naphthalene), 7.58–7.63 (m, 4 H, naphthalene + isoindole), 7.81–7.85 (m, 2 H, isoindole), 8.32–8.39 (m, 1 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 42.7 (CH_2), 58.1 (CH), 123.0 (CH_{Ar}), 124.0 (CH_{Ar}), 124.2 (CH_{Ar}), 124.6 (CH_{Ar}), 125.6 (C), 126.7 (CH_{Ar}), 127.4 (CH_{Ar}), 127.9 (CH_{Ar}), 128.8 (CH_{Ar}), 129.2 (CH_{Ar}), 131.8 (CH_{Ar}), 132.2 (C), 132.3 (C), 132.5 (C), 132.8 (CH_{Ar}), 145.1 (C), 169.7 (CO) ppm. MS (EI): m/z = 303 [M^+]. $C_{19}H_{13}NOS$ (303.39): calcd. C 75.22, H 4.32, N 4.62; found C 75.13, H 4.27, N 4.71.

6,12b-Dihydro-8-oxoisoindolo[2,1-*c*][1,3]benzothiazin-4-carboxylic Acid (20): A mixture of isoindolobenzothiazino ester **11f** (1 g, 3.21 mmol), potassium carbonate (1.04 g, 7.5 mmol), water (5 mL), and methanol (25 mL) was stirred under reflux for 3 h. After cooling, the solution was concentrated under reduced pressure. Water and CH_2Cl_2 (30 mL) were added and the organic layer was discarded. The aqueous phase was washed again with CH_2Cl_2 and acidified on cooling with 10% HCl solution to pH 3. The solution was extracted with CH_2Cl_2 several times. After removal of the solvent, the residue was recrystallized from dry ethanol/diethyl ether to give 0.91 g (96% yield) of the expected compound **20**, which melts at 175 °C (decomposition). IR: $\tilde{\nu}_{max}$ = 3340 (OH), 1713, 1708 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.31 (br. s, 1 H, OH), 4.56 (d, J = 13.2 Hz, 1 H, CH_2), 5.31 (d, J = 13.2 Hz, 1 H, CH_2), 5.91 (s, 1 H, CH), 7.36–7.43 (m, 1 H, benzene), 7.50–7.56 (m, 2 H, benzene), 7.69–7.77 (m, 2 H, isoindole), 7.83–7.91 (m, 2 H, isoindole) ppm. ^{13}C NMR ($CDCl_3$): δ = 43.4 (CH_2), 58.2 (CH), 122.4 (CH_{Ar}), 123.5 (CH_{Ar}), 124.3 (CH_{Ar}), 127.2 (CH_{Ar}), 130.1 (C), 130.2 (CH_{Ar}), 131.5 (CH_{Ar}), 132.1 (CH_{Ar}), 132.4 (C), 133.6 (C), 136.9 (C), 143.3 (C), 166.6 (CO), 171.1 (CO) ppm. MS (EI): m/z = 253 [$M^+ - CO_2$]. $C_{16}H_{11}NO_3S$ (297.05): calcd. C 64.63, H 3.73, N 4.71; found C 64.19, H 3.55, N 4.67.

Copper/Quinoline Decarboxylation of Tricyclic Acid 20 into 11a: Finely powdered copper (0.2 g) was added to a stirred solution of tricyclic benzothiazine acid **20** (1 g, 3.37 mmol) in 20 mL of freshly distilled quinoline. The mixture was allowed to react whilst heating at 150 °C for 3.5 h. After cooling, the solution was diluted with a mixture of water/CH_2Cl_2 (1:1, 60 mL) and acidified carefully with 10% HCl solution. After decantation and separation, the organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure to give **11a** in 78% yield. This product is identical to that described in our earlier paper.[4] ^{13}C NMR ($CDCl_3$): δ = 41.3 (CH_2), 59.6 (CH), 123.6 (CH_{Ar}), 124.1 (CH_{Ar}), 124.9 (CH_{Ar}), 126.1 (CH_{Ar}), 127.0 (CH_{Ar}), 127.6 (CH_{Ar}), 128.8 (CH_{Ar}), 129.4 (CH_{Ar}), 131.8 (C), 132.0 (C), 132.2 (CH_{Ar}), 132.4 (C), 144.0 (C), 167.9 (CO) ppm. MS (EI): m/z = 253 [M^+]. $C_{15}H_{11}NOS$ (253.06): calcd. C 71.12, H 4.38, N 5.53; found C 71.03, H 4.25, N 5.42.

***m*-CPBA Oxidation of the Mixture of Pyrrolidino[1,3]benzothiazines 25 and 26:** *m*-Chloroperbenzoic acid (86% pure, 1 g, 5.35 mmol) in dry CH_2Cl_2 was added portionwise, over a period of 5 min, with vigorous stirring to a cold solution (–5 to 0 °C) of the mixture of thiazines **25** and **26** (500 mg, 2.43 mmol) in dry CH_2Cl_2 (20 mL). After 10 min of reaction at this temperature the mixture was allowed to stir for an additional hour at ambient temperature. The reaction was hydrolyzed carefully with a saturated solution of $NaHCO_3$ and separated. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give, in quantitative yield, **27** and **28** in a 3:2 ratio. Recrystallization of the residue from dry CH_2Cl_2 or dry ethanol afforded pure sulfone **27**. Sulfone **28** was isolated in pure form from the mother liquor after concentration in vacuo and recrystallization from a mixture of CH_2Cl_2 and hexane (3:2).

Pyrrolidino[2,1-*d*][1,3]benzothiazin-7-one *S*,*S*-Dioxide (27): This product was obtained as a white solid after recrystallization from ethanol. M.p. 193 °C (decomposition). IR: $\tilde{\nu}_{max}$ = 1709 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$/[D_6]DMSO, 1:1): δ = 1.52–1.87 (m, 4 H, pyrrolidine), 3.92 (d, J = 14.0 Hz, 1 H, N-CH_2), 4.35 (t, J = 8.6 Hz, 1 H, CH), 4.53 (d, J = 14.0 Hz, 1 H, N-CH_2), 6.61–6.88 (m, 4 H, benzene) ppm. ^{13}C NMR ($CDCl_3$/[D_6]DMSO, 1:1): δ = 25.9 (CH_2), 28.5 (CH_2), 54.5 (CH), 56.8 (CH_2), 121.4 (CH_{Ar}), 124.7 (CH_{Ar}), 126.4 (CH_{Ar}), 131.4 (CH_{Ar}), 135.4 (C), 137.1 (C), 171.5 (CO) ppm. MS (EI): m/z = 239 [M^+]. $C_{11}H_{13}NO_3S$ (239.30): calcd. C 55.21, H 5.48, N 5.85; found C 55.03, H 5.72, N 5.57.

Pyrrolidino[2,1-*c*][1,3]benzothiazin-8-one *S*,*S*-Dioxide (28): This product was obtained as a white solid after recrystallization from ethanol/water. M.p. 188 °C (decomposition). IR: $\tilde{\nu}_{max}$ = 1711 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$/[D_6]DMSO, 1:1): δ = 2.42–2.68 (m, 2 H, pyrrolidine), 2.73–2.93 (m, 2 H, pyrrolidine), 4.39 (d, J = 17.7 Hz, 1 H, N-CH_2), 4.92 (d, J = 8.6 Hz, 1 H, CH), 5.38 (d, J = 17.7 Hz, 1 H, N-CH_2), 7.25–7.59 (m, 4 H, benzene) ppm. ^{13}C NMR ($CDCl_3$/[D_6]DMSO, 1:1): δ = 14.5 (CH_2), 27.0 (CH_2), 39.9 (CH_2), 70.5 (CH), 122.2 (CH_{Ar}), 125.7 (CH_{Ar}), 126.5 (CH_{Ar}), 131.2 (CH_{Ar}), 132.6 (C), 135.7 (C), 172.2 (CO) ppm. MS (EI): m/z = 239 [M^+]. $C_{11}H_{13}NO_3S$ (239.30): calcd. C 55.21, H 5.48, N 5.85; found C 55.12, H 5.68, N 5.49.

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[9] The products were obtained in excellent yields of 85% (R = Me), 92% (R = Ph), 98% (R = *p*-ClPh), and 92% (R = Bzl). In the case of methyl and benzyl groups, the thiazines **I** and **II** were accompanied by the methylidene and benzylidene derivatives as the consequence of the dehydration of the α-alkyl-α-hydroxy lactams **4** (R = Me, Bzl).

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