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Synthesis of tricyclic isoindoles and thiazolo[3,2-*c*][1,3]benzoxazines

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Abstract—The thermolysis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids in Ac_2O led to novel 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles and chiral (9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles were obtained on FVP. Starting from L-cysteine methyl ester (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo[3,2-*c*][1,3]benzoxazines were obtained as single stereoisomers. The thermolysis of (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylic acid in Ac_2O gave 5-acetyl-2-phenyl-2,3-dihydrothiazole. The structures of methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate **1a** and methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **9** were determined by X-ray crystallography.

1. Introduction

The study of 1,3-dipolar cycloaddition of münchnones as an approach to chiral pyrrolo[1,2-*c*]thiazoles is an area of our current research interests.[1] In this context we became interested in exploiting the possibility of preparing 1,3-thiazolidine-4-carboxylic acids fused to five- and six-membered ring systems which could be used as potential münchnone precursors.

In a preliminary communication, we described the thermolysis (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo-[2,3-*a*]isoindole-3-carboxylic acids in acetic anhydride where no evidence for the generation of mesoionic species was observed. However, this study led to the development of a synthetic methodology to 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles.[2] In this paper we report full details of the work on the synthesis and reactivity of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids as well as of 5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo[3,2-*c*][1,3]benzoxazine derivatives.

2. Results and discussion

The reaction of L-cysteine methyl ester with 2-carboxybenzaldehyde was carried out following the general procedure reported earlier for the synthesis of thiazolidines.[3] The product was purified simply by recrystallisation. This resulted in the direct diastereoselective synthesis of methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydro-thiazolo[2,3-*a*]isoindole-3-carboxylate **1a** in 71% yield (Scheme 1).

The structure of **1a** was confirmed by X-ray crystallography (Fig. 1). The absolute structure was determined by a Flack analysis (898 Friedel pairs, η=0.01(3)) that unambiguously assigns the *R*,*S* configuration to the chiral centers C3 and C9b.

Compound **1a** was converted into the corresponding acid **2a** in 91% yield ($[\alpha]_D^{25}=-343$, c=0.1, EtOH) by the reaction with lithium iodide in ethyl acetate and treatment with aqueous HCl (Scheme 1).

Compound **2a** can also be prepared as described by Oliver et al. directly from the reaction of 2-carboxybenzaldehyde with cysteine hydrochloride in the presence of pyridine.[4] This procedure gave 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a** in 58% yield.

The reactivity of compound **2a** as a münchnone precursor was studied. Attempts were made to promote cyclodehydration by heating at reflux a solution of compound **2a** in acetic anhydride in the presence of dimethyl acetylenedicarboxylate. However, the expected 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole was not obtained even when prolonged heating was used.

Keywords: Diastereoselectivity; Thiazolo[2,3-*a*]isoindoles; 3-Methylene-2,5-oxazolo[2,3-*a*]isoindoles; [1.3]Thiazolo[3,2-*c*][1,3]benzoxazines.
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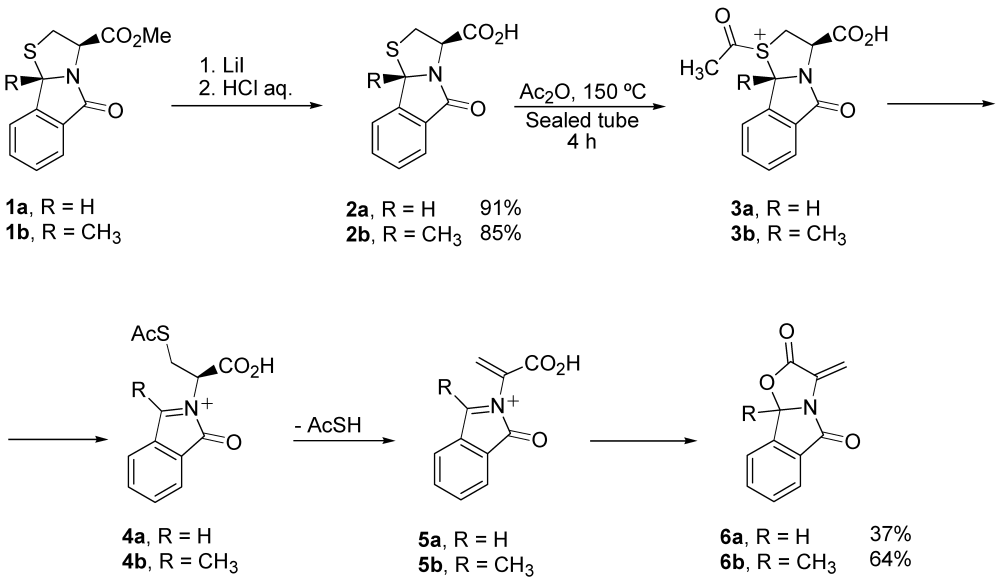


Scheme 1.

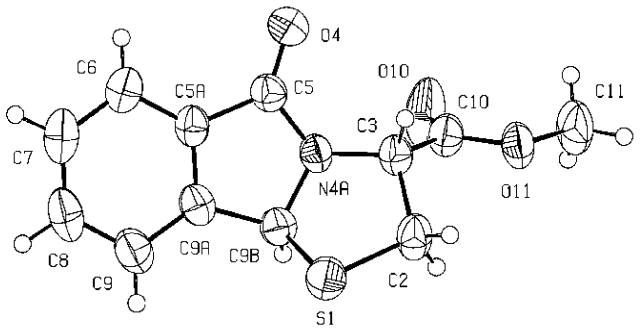


Figure 1. X-ray structure of compound **1a**.

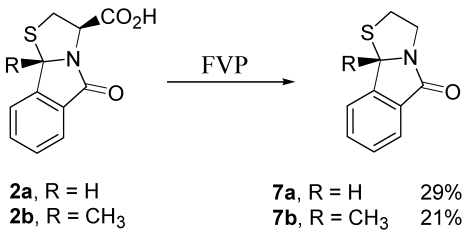
Based on the structure of methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate **1a**, determined by X-ray crystallography, we can explain this unsuccessful result. This tricyclic compound has a rigid structure and is characterized by having a value of 122.42° for the C5–N4A–C-3 bond angle (Fig. 1 and Table 1). A similar bond angle is expected for (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a**. The C-5, N-4A and C-3 atoms would be part of the mesoionic ring and a significant structure distortion had to occur in order to allow its formation. Thus, the generation of a münchnone from compound **2a** is not a favourable process.

Table 1. Bond angles (°) for compound **1a**

C2–S1–C9B	88.93(12)	C5–N4A–C9B	111.93(19)
C9B–N4A–C3	115.55(18)	N4A–C9B–C9A	103.77(19)
N4A–C9B–S1	104.45(16)	N4A–C5–C5A	106.3(2)
C3–C2–S1	106.91(17)	C9A–C5A–C5	108.9(2)
N4A–C3–C2	107.12(19)	C5A–C9A–C9B	108.6(2)
C5–N4A–C3	122.42(19)	C9A–C9B–S1	115.57(18)

Nevertheless, we carried out the reaction of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a** with acetic anhydride and dimethyl acetylenedicarboxylate in a sealed tube. The solution was heated at 150 °C for 4 h. Although no 1,3-dipolar cycloadduct was obtained, 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole **6a** was isolated in 37% yield which (Scheme 1). The structure of **6a** was determined by X-ray crystallography.[2]

The mechanism proposed for the formation of compound **6a** is outlined in Scheme 2. The process can be regarded as involving the formal elimination of the elements of SH from (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a** leading to *N*-acyliminium ion **5a** followed by a 5-*endo*-trig cyclization. It represents the synthesis of an isoindole derivative (**6a**), a new member to a class of compounds having a significant number of applications.[5]



Scheme 2.

In order to determine the scope of this route to 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles we prepared (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2b** (Scheme 1). The reaction of L-cysteine methyl ester with 2-acetylbenzoic acid was carried out in presence of sodium acetate in refluxing toluene for 5 h giving (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate **1b** in 75% yield with the value of $[\alpha]_D^{25}=-328.7$ (c=1.75, CH_2Cl_2). Compound **2b** was obtained from **1b** in 85% yield.

We carried out the reaction of (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2b** with acetic anhydride in a sealed tube (Scheme 1). The solution was heated at 150 °C for 4 h. In a process

analogous to that described for the synthesis of oxazolo[2,3-*a*]isoindole derivative **6a**, compound **2b** was converted into the tricyclic isoindole derivative 9b-methyl-3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole **6b** in 64% yield. When the reaction of **2b** with acetic anhydride was performed in the presence of dimethyl acetylenedicarboxylate (sealed tube, 150 °C, 4 h) compound **6b** was isolated in lower yield (40%) but no 1,3-dipolar cycloadduct was formed.

The flash vacuum pyrolysis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids **2a** and **2b** was also studied (Scheme 2). We found that on FVP (600 °C/3×10^{-2}–4×10^{-2} mbar) these compounds undergo decarboxylation to the corresponding chiral (9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles (**7a** and **7b**) in moderate yields.

Compounds **7a** and **7b** have been prepared before from the reaction of carboxybenzaldehyde or 2-acetylbenzoic acid with 2-aminoethanethiol. However, they were obtained as racemic mixtures.[4,6,7] Some 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles substituted at C-9 with aryl and heteroaromatic groups have also been prepared as racemic mixtures although the separation of both enantiomers can be achieved by chromatography on cellulose triacetate.[5b]

Our synthetic procedure is particularly interesting since it allows the synthesis of (9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles directly as single enantiomers.

We then went on to investigate the possibility of preparing a tricyclic compound having a thiazolidine ring fused to a six-membered ring which should be a better münchnone precursor in terms of structural requirements than 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles **2a** and **2b**. We defined 5-oxo-2,3-dihydro-10b*H*-[1,3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylic acid **11** as our target molecule (Scheme 3). The chemistry of [1,3]thiazolo[3,2-*c*][1,3]benzoxazines is an area of considerable interest since some derivatives show biological activity namely immunoacitvating action which makes this synthesis more appealing.[8]

The synthetic strategy is outlined in Scheme 3. Thiazolidine **8** was prepared by condensing L-cysteine methyl ester hydrochloride with salicylaldehyde in presence of potassium hydrogen carbonate. Our approach to construct the six-membered ring was to react methyl 2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **8** with phosgene. The reaction was carried out at room temperature and after 6 h a product was isolated in 67% yield. Although it was expected to obtain directly the cyclization product, the characterisation data allow us to conclude that we were in the presence of methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **9**. This showed $[\alpha]_D^{25}$=+197 (*c*=0.1, EtOH). Thus, the reaction conditions used led to a diastereoselective N-acylation of thiazolidine **8**.

It is known that NMR spectra of *N*-acylthiazolidines at ambient temperature are usually complicated by the existence of rotamers.[1,9] In agreement with this we found that the ^{1}H and ^{13}C NMR spectra of thiazolidine **9** recorded at room temperature, showed two sets of signals.

The structure of methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **9** was confirmed by X-ray crystallography (Fig. 2). The absolute structure was determined by a Flack analysis (1358 Friedel pairs, η=−0.16(9)) that unambiguously assigns the *R*,*R* configuration to the chiral centers C2 and C4.

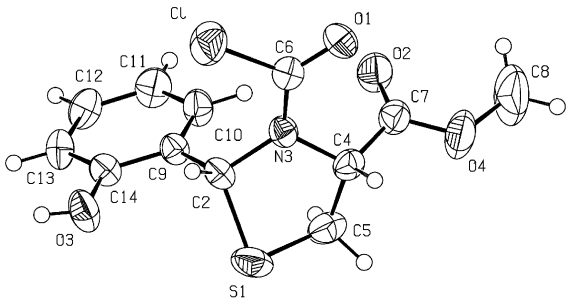
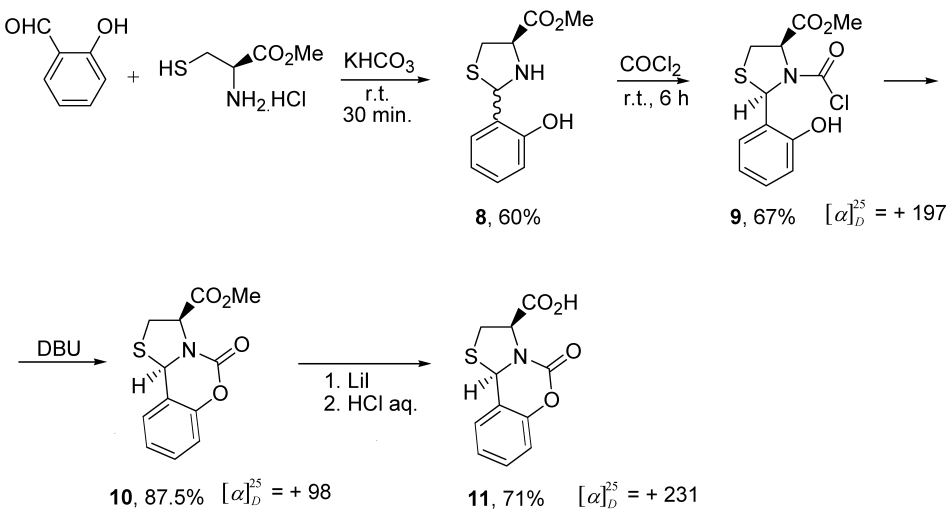


Figure 2. X-ray structure of compound **9**.

The thiazolidine ring adopts a twisted conformation around atom N3. The puckering parameters as defined by Cremer and Pople[10] are q_2=0.503(3) Å, ϕ_2=346.0(4)°, the φ_2 value



Scheme 3.

for the pure twisted conformation being 342°. There is an approximate C_2 axis running through N3 and the middle of the S1–C5 bond, the C_2 asymmetry parameter being 4.2(3)°. The exocyclic angles around the N3 atom show a large asymmetry; the sum of the valence angles around this atom is 358.9° indicating an insignificant degree of pyramidalization.

The least-squares planes of the hydroxyphenyl group and thiazolidine ring make an angle of 48.6(1)°. The methyl carboxylate substituent is in bissectional position with respect to the ring plane. The torsion angle O2–C7–C4–C5 is 86.0(4)°. The chlorocarbonyl group is planar but slightly titled with respect to the least squares plane defined by atoms N3, C2, C4 and C6 (the torsion angle C2–N3–C6–Cl is −4.5(4)°).

We studied the thermolysis of (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **9** as a way to the corresponding cyclization product. However, even when a solution of **9** in sulpholane was heated at reflux did not lead to the desired product. The synthesis of methyl (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylate **10** (87.5%) was achieved when thiazolidine **9** was treated with DBU (with DBN **10** was obtained in 76% yield). This new tricyclic compound **10** was obtained as single stereoisomer with $[\alpha]_D^{25}=+98$ (Scheme 3).

The (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylic acid **11** was obtained in 71% yield by reacting compound **10** with lithium iodide in ethyl acetate followed by treatment with aqueous HCl (Scheme 3).

Attempts to generate the corresponding münchnone from 5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo[3,2-*c*][1,3]benzoxazine derivative **11** in presence of DMAD did not lead to positive results. However, the thermolysis of **11** in acetic anhydride, carried out in a sealed tube, led to the synthesis of 5-acetyl-2-phenyl-2,3-dihydrothiazole **14** in low yield (Scheme 4). The formation of this product can be rationalised as involving a double decarboxylation giving **12** which is converted into 2,3-dihydrothiazole **13** through prototropy. Acylation of this intermediate gives compound **14**.

3. Conclusion

In conclusion, we report a synthetic methodology to new tricyclic isoindole derivatives, 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles through the thermolysis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids in acetic anhydride.

Chiral (9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles (**7a** and **7b**) were also obtained from the flash vacuum pyrolysis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids.

The diastereoselective synthesis of (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1,3]thiazolo[3,2-*c*][1,3]benzoxazines (**10** and **11**) was accomplished and the thermolysis of **11** in acetic anhydride gave 5-acetyl-2-phenyl-2,3-dihydrothiazole **14**.

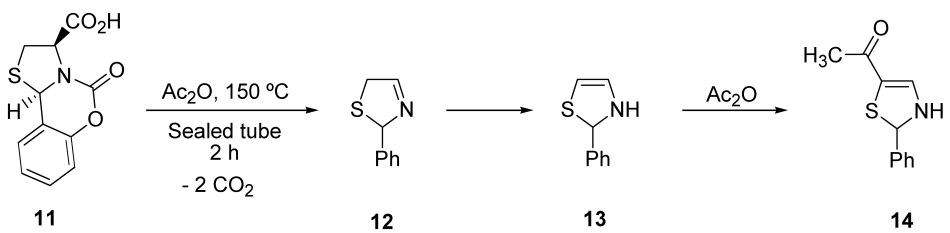
The work provided a range of isoindoles and thiazolobenzoxazines, compounds with potential biological activity.[5,8]

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker AMX300 instrument operating at 300 MHz. ^{13}C spectra were recorded on a Bruker AMX300 instrument operating at 75.5 MHz. The solvent is deuteriochloroform except where indicated otherwise. IR spectra were recorded on a Perkin–Elmer 1720X FTIR spectrometer. Mass spectra were recorded on a HP GC 6890/MSD5973 instrument under electron impact (EI) except where indicated otherwise. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Microanalyses were performed in the University of Coimbra using a EA 1108-CHNS-O Fisons instrument or in the University of Liverpool using a Carlo-Erba elemental analyser. Mp were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

4.1.1. Methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate (1a). L-Cysteine methyl ester hydrochloride (3.45 g, 20 mmol) was dissolved in water (15 mL) and potassium hydrogen carbonate (2.0 g, 20 mmol) was added following the addition of a solution of the 2-carboxybenzaldeyde (3.3 g, 22 mmol) in ethanol (15 mL). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with dichloromethane. The organic phase was dried and the solvent was evaporated off giving the methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate **1a** as a white solid (3.48 g, 71%). Mp 83.2–85.8 °C (from ethyl ether), lit.[6] 83–86 °C. ν_{max}



11 12 13 14

Scheme 4.

(KBr) 1745 and 1710 cm^{-1}; δ_H 3.59–3.70 (2H, m), 3.83 (3H, s), 5.25 (1H, dd, *J*=4.9, 7.1 Hz), 6.08 (1H, s), 7.48–7.63 (3H, m, Ar-H), 7.81–7.83 (1H, m, Ar-H); *m/z* 249 (M^+, 100%), 221 (8), 190 (83), 162 (44) and 146 (12). Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.72; H, 4.44; N, 5.64; S, 12.48%. $[\alpha]_D^{25}=-400.5$ (*c*=2.3, CH_2Cl_2).

4.1.2. Methyl (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate (1b). L-Cysteine methyl ester hydrochloride (0.865 g, 5 mmol) and sodium acetate (1.23 g, 15 mmol) were dissolved in toluene (50 mL) and a solution of 2-acetylbenzoic acid (0.825 g, 5 mmol) in toluene (50 mL) was added. The reaction mixture was at reflux for 5 h. The solution was washed with water, dried and the solvent was evaporated off. The crude product was purified by flash chromatography [hexane–ethyl acetate (1:1)]. Compound **1b** was obtained as a white solid (0.98 g, 74.5%). Mp 128.8–132.1 °C (from ethyl ether), lit.[6] 113–116 °C. ν_{max} (KBr) 1753 and 1695 cm^{-1}; δ_H 1.96 (3H, s, CO_2Me), 3.83 (1H, dd, *J*=8.7 Hz), 3.85 (3H, s), 3.95 (1H, dd, *J*=6.5 Hz), 5,15 (1H, dd, *J*=6.5, 8.7 Hz), 7.48–7.54 (2H, m, ArH), 7.60–7.63 (1H, m, ArH), 7.80–7.82 (1H, m, ArH). $[\alpha]_D^{25}=-328.7$ (*c*=1.75, CH_2Cl_2).

4.2. General procedure for the synthesis of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids 2a and 2b

The (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-a]isoindole-3-carboxylate (**1a** or **1b**) (1 mmol) and LiI (4 mmol) were dissolved in ethyl acetate (1.3 mL). The reaction mixture was protected from light and heated at reflux for 6 h. Water was added (5 mL) and the solution was acidified with HCl 1 M and extracted with ethyl acetate. The organic phase was washed with water and with saturated aqueous solution of NaCl. The organic solvent was evaporated off. To the residue a saturated aqueous solution of $NaHCO_3$ was added and the solution was washed with dichloromethane. The aqueous solution was acidified with concentrated HCl and extracted with ethyl acetate. The organic phase was dried and the solvent was evaporated off giving the desired product.

4.2.1. (3*R*,9b*S*)-5-Oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid 2a. The title compound was obtained as a white solid (91%). Mp 156.1–157.9 °C (from ethyl ether), lit.[4] 161–162 °C. δ_H ($CDCl_3$/DMSO-d_6) 3.71 (1H, dd, *J*=7.4, 12.0 Hz), 3.81 (1H, dd, *J*=6.6, 12.0 Hz), 5.03 (1H, approx. t, *J*=7.0 Hz), 6.06 (1H, s), 7.51–7.58 (3H, m, Ar-H), 7.85–7.88 (1H, m, Ar-H); *m/z* [compound **2a** treated with CH_2N_2] 249 [(M^+−H), 100%], 221 (5) and 190 (95). Anal. Calcd for $C_{11}H_9NO_3S$: C, 56.16; H, 3.86; N, 5.95; S, 13.63. Found: C, 55.87; H, 3.92; N, 5.81; S, 13.92%. $[\alpha]_D^{25}=-343$ (*c*=0.1, EtOH).

4.2.2. (3*R*,9b*S*)-9b-Methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid 2b. The title compound was obtained as a white solid (85%). Mp 162.3–164.9 °C (from ethyl ether). δ_H 1.97 (3H, s), 3.88 (1H, dd, *J*=8.5, 12.3 Hz), 4.05 (1H, dd, *J*=7.8, 12.3 Hz), 5.01 (1H, approx. t, *J*=8.2 Hz), 7.50–7.56 (2H, m, ArH), 7.63–7.69 (1H, m, ArH), 7.81–7.84 (1H, m, ArH). Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.69; H, 4.42; N, 5.33; S, 12.33%. $[\alpha]_D^{25}=-363$ (*c*=0.1, MeOH).

4.3. General procedure for the synthesis of 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles 6a and 6b

A solution of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid (**2a** or **2b**) (3 mmol) in Ac_2O (5 mL) was heated, in a sealed tube, at 150 °C for 4 h. The reaction was cooled to room temperature and was diluted with dichloromethane (50 mL). The organic phase was washed with saturated aqueous solution of $NaHCO_3$ and with water, dried ($MgSO_4$) and evaporated off. The crude product was purified by flash chromatography [ethyl acetate–hexane (1:2)].

4.3.1. 3-Methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole 6a. The title compound was obtained as a white solid (37%). Mp 174.2–176.0 °C (from ethyl ether). δ_H 5.93 (1H, d, *J*=1.4 Hz), 5.96 (1H, d, *J*=1.4 Hz), 6.51 (1H, s), 7.68–7.79 (3H, m, Ar-H), 7.95–7.97 (1H, Ar-H); δ_C 88.0, 107.9, 125.1, 125.5, 130.1, 131.7, 131.9, 134.4, 141.1, 165.2, 169.3; *m/z* 201 (M^+, 33%), 172 (4), 157 (41) and 133 (100).

4.3.2. 9b-Methyl-3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole 6b. The title compound was obtained as a light yellow solid (64%). Mp 145.4–147.6 °C (from ethyl ether). δ_H 2.00 (3H, s), 5.88 (1H, d, *J*=0.7 Hz), 6.03 (1H, d, *J*=0.7 Hz), 7.60–7.65 (2H, m, Ar-H), 7.71–7.76 (1H, m, Ar-H), 7.95–8.00 (1H, Ar-H); *m/z* 216 (MH^+, 3%), 198 (2), 188 (19) and 171 (100); δ_C 32.2, 73.8, 108.0, 122.6, 125.3, 129.0, 130.2, 134.0, 135.8, 148.0, 167.0, 192.3.

4.4. General procedure for the flash vacuum pyrolysis of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids 2a and 2b

Pyrolysis of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids **2a**or **2b** (1.5 mmol) at 600 °C/3×10^{-2}–4×10^{-2} mbar onto a surface cooled at −196 °C over a period of 2 h gave a yellowish pyrolysate [The rate of volatilisation of the starting material was controlled by the use of a Kugelrohr oven which heated the sample at 200 °C]. After cooling to room temperature the pyrolysate was removed from the cold finger with dichloromethane. The solvent was removed in vacuo and the residue purified by flash chromatography [SiO_2, ethyl-acetate–hexane (1:2)] for **7a** and [SiO_2, ethyl-acetate–hexane (1:3)] for **7b**.

4.4.1. (9b*S*)-5-Oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole 7a. The title compound was obtained as a white solid (29%). Mp 99.6–100.3 °C (from ethyl ether/hexane), lit.[9] 97–100 °C. δ_H 3.35–3.44 (3H, m), 4.44–4.45 (1H, m), 5.88 (1H, s), 7.49–7.56 (2H, m, Ar-H), 7.57–7.60 (1H, m, Ar-H), 7.80–7.82 (1H, m, Ar-H); δ_C 36.5, 44.5, 66.0, 123.2, 124.3, 129.2, 131.1, 132.6, 145.1, 170.8; *m/z* 191 (M^+, 84%), 163 (12), 145 (100), 117 (39), 90 (28) and 76 (14). $[\alpha]_D^{25}=-341$ (*c*=0.1, CH_2Cl_2).

4.4.2. (9b*S*)-9b-Methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole 7b. The title compound was obtained

as an yellow oil (21%). δ_H 1.92 (3H, s), 3.35–3.50 (3H, m), 4.54–4.61 (1H, m), 7.45–7.51 (2H, m, Ar-H), 7.57–7.63 (1H, m, Ar-H), 7.76–7.79 (1H, m, Ar-H); *m/z* 205 (M^+, 100%), 190 (21), 158 (68) and 146 (66). $[\alpha]_D^{25}=-69$ (c=0.15, CH_2Cl_2).

4.4.3. Methyl 2-(2-hydroxyphenyl)thiazolidine-4-carboxylate 8. L-Cysteine methyl ester hydrochloride (3.45 g, 20 mmol) was dissolved in water (15 mL) and potassium hydrogen carbonate (2.0 g, 20 mmol) was added following the addition of a solution of the salicylaldehyde (2.68 g, 22 mmol) in ethanol (15 mL). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with dichloromethane. The organic phase was dried and the solvent was evaporated off giving the methyl 2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **8** (60%). Mp 66.7–68.0 °C (from ethyl ether). ν (KBr) 3277 and 1736 cm^{-1}; δ_H (two diastereoisomers, ratio 73:27) 3.20–3.25 (1H, m), 3.40–3.47 (1H, m), 3.78 and 3.83 (3H, 2xs), 4.07–4.19 (1H, m), 5.62 and 5.92 (1H, 2xd, J=5.7, 4.3 Hz respectively), 6.79–6.94 (2H, m, Ar-H), 7.16–7.26 (2H, m, Ar-H); *m/z* 239 (M^+, 19%), 224 (10), 193 (21), 180 (36), 163 (71), 146 (13) and 132 (100). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.42; H, 5.72; N, 5.81; S, 13.02%.

4.4.4. Methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate 9. The methyl 2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **8** (3.75 g, 15.7 mmol) was dissolved in dichloromethane (20 mL) and potassium hydrogen carbonate (1.57 g, 15.7 mmol) and a solution of the phosgene in toluene (10 mL, 18.84 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried and the solvent was evaporated off giving the methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **9** as a white solid (67%). Mp 145.2–146.9 °C. ν (KBr) 3285, 1746 and 1698 cm^{-1}. δ_H (two rotamers) ($CDCl_3$/DMSO-d_6) 3.22–3.41 (2H, m), 3.86 and 3.89 (3H, 2xs), 4.83 and 5.07 (1H, dd, J=6.4, 9.4 Hz and approx. t, J=6.4 Hz, respectively), 6.49 and 6.56 (1H, 2xs), 6.83–6.90 (2H, m, Ar-H), 7.10–7.18 (1H, m, Ar-H), 7.79–7.86 (1H, m, Ar-H); δ_C (two rotamers): major: ($CDCl_3$/DMSO-d_6) 31.7, 52.7, 63.8, 66.1, 115.0, 119.1, 125.6, 126.4, 128.7, 147.7, 153.3, 168.8; minor: 32.4, 52.9, 64.2, 66.8, 115.3, 119.2, 124.2, 126.0, 128.9, 147.7, 153.7, 169.5. *m/z* 265 [(M^+−HCl), 4%], 264 (6), 206 (15) and 179 (100). Anal. Calcd for $C_{12}H_{12}NO_4SCl$: C, 47.77; H, 4.01; N, 4.64; S, 10.62. Found: C, 47.89; H, 4.23; N, 4.57; S, 10.93%. $[\alpha]_D^{25}=+197$ (c=0.1, CH_3COCH_3).

4.4.5. Methyl (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1,3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylate 10. The methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate **9** (0.84 g, 2.8 mmol) was dissolved in ethyl acetate (15 mL). DBU (2 mmol) was added and the reaction mixture was heated at 50 °C for 2 h. Water was added (15 mL) and the solution was extracted with ethyl acetate. The organic phase was washed with water and dried. The residue obtained upon removal of the solvent was purified by column chromatography [ethyl acetate–hexane (1:1)] giving compound **10** as a white solid (87.5%). Mp 127.4–129.1 °C (from ethyl acetate–hexane). δ_H 3.44 (1H, dd, J=0.94, 12.7 Hz), 3.63 (1H, dd, J=7.5, 12.7 Hz), 3.74 (3H, s), 4.88 (1H, dd, J=1.1, 7.5 Hz), 6.05 (1H, s), 7.12–7.22 (3H, m, Ar-H), 7.31–7.44 (1H, m, Ar-H); δ_C 34.0, 53.0, 62.1, 63.0, 116.5, 119.2, 125.1, 125.7, 130.2, 148.2, 149.0, 169.0; *m/z* 265 (M^+, 5%), 206 (17) and 179 (100). Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 53.98; H, 4.43; N, 5.14%. $[\alpha]_D^{25}=+98$ (c=0.1, CH_2Cl_2).

4.4.6. (3*R*,10b*R*)-5-Oxo-2,3-dihydro-10b*H*-[1,3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylic acid 11. The methyl (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1.3]thiazolo-[3,2-*c*][1,3]benzoxazine-3-carboxylate **10** (0.235 g, 1 mmol) and LiI (4 mmol) were dissolved in ethyl acetate (1.3 mL). The reaction mixture was protected from light and heated at reflux for 6 h. Water was added (5 mL) and the solution was acidified with HCl 1 M and extracted with ethyl acetate. The organic phase was washed with water and with saturated aqueous solution of NaCl. The organic solvent was evaporated off. To the residue a saturated aqueous solution of $NaHCO_3$ was added and the solution was washed with DCM. The aqueous solution was acidified with concentrated HCl and extracted with ethyl acetate. The residue obtained upon removal of the solvent was purified by column chromatography [ethyl acetate–hexane (1:1)] giving compound **11** light yellow solid (71%). Mp 173.2–175.3 °C (from ethyl ether–hexane). δ_H ($CDCl_3$/DMSO-d_6) 3.46–3.51 (1H, m), 3.64 (1H, dd, J=7.7, 12.7 Hz), 4.81 (1H, dd, J=1.2, 7.6 Hz), 6.07 (1H, s), 7.09–7.21 (3H, m, ArH), 7.33–7.38 (1H, m, ArH); δ_C ($CDCl_3$/DMSO-d_6) 36.6, 64.6, 65.6, 119.0, 122.0, 127.5, 128.4, 132.6, 148.5, 151.7, 172.7; *m/z* [compound **11** treated with CH_2N_2] 264 [(M^+−H), 5%], 206 (14) and 179 (100). Anal. Calcd for $C_{11}H_9NO_4S$: C, 52.58; H, 3.61; N, 5.57; S, 12.76. Found: C, 52.41; H, 3.38; N, 5.58; S, 12.83%. $[\alpha]_D^{25}=+231$ (c=0.1, MeOH).

4.4.7. 5-Acetyl-2-phenyl-2,3-dihydrothiazole 14. A solution of (3*R*,10b*R*)-5-oxo-2,3-dihydro-10b*H*-[1,3]thiazolo[3,2-*c*][1,3]benzoxazine-3-carboxylic acid **11** (0.75 g, 3 mmol) in Ac_2O (5 mL) was heated, in a sealed tube, at 150 °C for 2 h. The reaction was cooled to room temperature and was diluted with dichloromethane (50 mL). The organic phase was washed with saturated aqueous solution of $NaHCO_3$ and with water, dried ($MgSO_4$) and evaporated off. The crude product was purified by flash chromatography [ethyl acetate–hexane (1:3)] giving compound **14** as a white solid (4%). Mp 73.5–74.5 °C (from dichloromethane–hexane). ν (KBr) 1745, 1690 and 1639 cm^{-1}. δ_H 2.40 (1H, s), 4.70 (1H, s), 4.75 (1H, m, NH), 6.73 (1H, s), 7.10–7.22 (3H, m, Ar-H), 7.32–7.39 (2H, m, Ar-H); δ_C 30.6, 56.9, 97.4, 116.3, 120.7, 125.3, 125.4, 130.2, 130.3, 148.5, 194.3; *m/z* (CI–CH_4) 206 [(MH^+), 28%], 137 (5) and 75 (100).

4.5. X-ray structure determination of methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate 1a

Crystal data. $C_{12}H_{11}NO_3S$, M=249.28, tetragonal, space group $P4_12_12$ (#92), $a=b$=9.424(8), c=26.209(12) Å,

V=2390.1(11) Å^3, Z=8, D_c=1.386 g cm^{-3}, F_{000}=1040, μ=2.454 mm^{-1}, T=296 K. Number of independent intensities 2294 from transparent, colourless prism, 0.39×0.20×0.15 mm^3. Ψ-scan absorption correction applied, T_{min}=0.888, T_{max}=0.986. No significant crystal decay detected.

Data collection. X-ray measurements were performed on a Enraf-Nonius MACH3 diffractometer using ω–2θ scans up to θ_{max}=71.51°.

Structure solution and refinement. The structure was solved using methods using SHELXS97. R=0.0344 for 2116 reflections with $I>2\sigma$, R_w=0.0888 for 2294 reflections used in the refinement and 156 variable parameters. H-atoms were placed at calculated positions except those of the methyl group which were determined from a Fourier difference synthesis and refined as riding on their parent atoms using SHELXL97 defaults.

4.6. X-ray structure determination of methyl (2*R*,4*R*)-*N*-chlorocarbonyl-2-(2-hydroxyphenyl)thiazolidine-4-carboxylate 9

Crystal data. $C_{12}H_{12}ClNO_4S$, M=301.74, orthorhombic, space group $P2_12_12_1$ (#19), a=8.7424(16) Å, b=10.1480(7), c=15.857(3) Å, V=1406.8(4) Å^3, Z=4, D_c=1.425 g cm^3, F_{000}=624, μ=0.428 mm^{-1}, T=296 K. Number of independent intensities: 3210 from transparent, colourless prism, 0.37×0.20×0.15 mm^3. ψ-scan absorption correction applied, T_{min}=0.980, T_{max}=0.961. No significant crystal decay detected.

Data collection. X-ray measurements were performed on a Enraf-Nonius CAD-4 diffractometer using ω–2θ scans up to θ_{max}=27.44°.

Structure solution and refinement. The structure was solved using direct methods using SHELXS97. R=0.0409 for 2182 reflections with $I>2$, R_w=0.0952 for 3210 reflections used in the refinement and 175 variable parameters. H-atoms were placed at calculated positions except those of the methyl group which were determined from a Fourier difference synthesis and refined as riding on their parent atoms using SHELXL97 defaults.

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