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Stereoselective synthesis of thiaerythrinanes based on an α-amidoalkylation/RCM approach

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Abstract

Parham cyclisation–intermolecular α-amidoalkylation and nucleophilic addition–intramolecular α-amidoalkylation sequences constitute diastereocomplementary routes to 1,10b-*cis* and *trans* thiazolo[4,3-*a*]isoquinolinones. These thiazolidinediones, that incorporate allyl groups at C-1 and C-10b, are efficient precursors of thiaerythrinanes by ring-closing metathesis reactions.

Keywords: Lithiation; Lithium–halogen exchange; α-Amidoalkylation; Parham cyclisation; Heterocycles; Thiareythrinanes

1. Introduction

The aromatic metalation–cyclisation sequence has become a valuable protocol for the regioselective construction of carbocyclic and heterocyclic systems. However, certain electrophilic groups, such as ketones and imides, do not remain passive during the metalation process and competitive nucleophilic attack by organolithium base may occur. In these cases, one can take advantage of the very fast rate of metal–halogen exchange[1] compared with nucleophilic addition to carbonyl groups to allow aromatic metalation and subsequent intramolecular cyclisation reactions, which are known as Parham cyclisations.[2]

Our work in this field has demonstrated that iodinated *N*-phenethylimides tolerate iodine–lithium exchange, giving rise to the isoquinoline nucleus via a Parham-type cyclisation.[3] Since the so-obtained fused isoquinolones posses a α-hydroxylactam function, they represent immediate precursors of bicyclic *N*-acyliminium ions,[4] which can be transformed into a variety of derivatives via intermolecular α-amidoalkylation with different nucleophiles. This has been illustrated in the synthesis of isoindolo[1,2-*a*]isoquinoline skeleton of nuevamine-type alkaloids.[5] This approach is complementary to the tandem organolithium addition–*N*-acyliminium ion cyclisation sequence with *N*-phenethylimides, which also constitutes an effective route to several types of isoquinoline alkaloids. Although intramolecular α-amidoalkylation reaction[6] has been widely used in the stereocontrolled synthesis of nitrogen heterocycles, relatively minor effort has been dedicated to stereoselective Parham cyclisation. However, its potential as a useful stereoselective cyclisation procedure has proven extremely interesting.[7] Thus, we have demonstrated that both types of cyclisations constitute diastereocomplementary to 1,10b-*cis* and 1,10b-*trans* thiazolo[4,3-*a*]-isoquinoline systems.[8] Besides, we have also achieved the asymmetric synthesis of C-10b substituted pyrrolo[2,1-*a*]isoquinolines in both enantiomeric forms.[9]

In this context, our next challenge was to achieve 7-thiaerythrinanes **1** by a strategy that involves Parham cyclisation–intermolecular α-amidoalkylation or nucleophilic addition–intramolecular α-amidoalkylation sequence of thiazolidinediones **3** or **4** to afford thiazoloisoquinolines **2**, which incorporate two allyl groups on C-1 and C-10b. Finally, ring A could be assembled through ring-closing metathesis (RCM) (Fig. 1). In addition, the stereochemical features of these sequences would be studied using thiazolidinediones **3** or **4** that incorporate substituents of different size at C-5.

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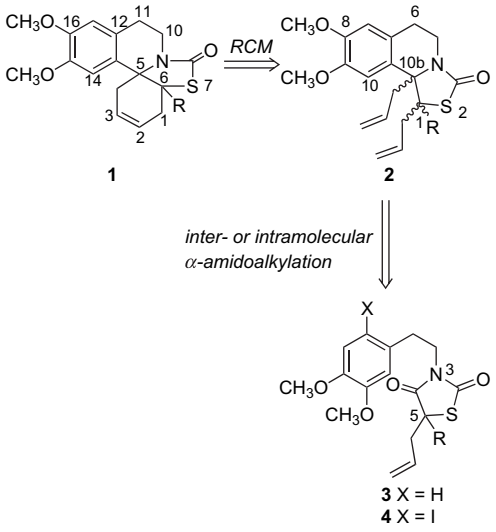
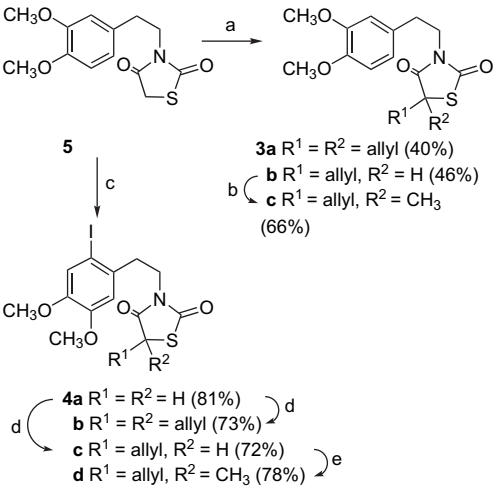


Figure 1.

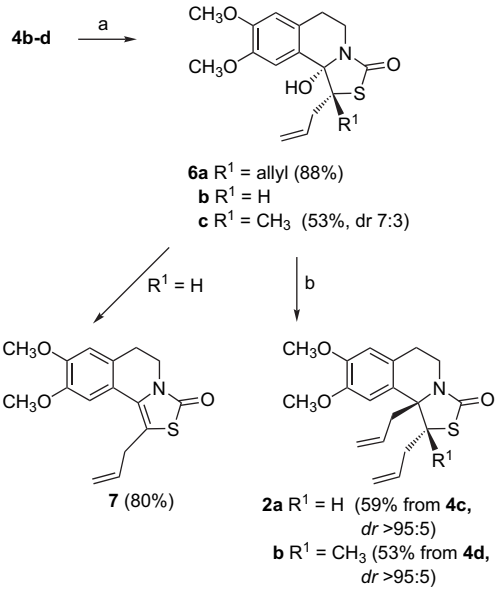
2. Results

To begin our study, a series of thiazolidine-2,4-diones were prepared as depicted in Scheme 1. Thus, dialkylation of thiazolidinedione **5**[8] was achieved with *sec*-BuLi/TMEDA and allyl iodide at −50 °C. However, the best yield of the monoalkylated product **3b** was obtained with LDA at −78 °C. Finally, methylation of **3b** afforded **3c** in moderate yield. The iodinated mono- and dialkylated products were obtained in a similar fashion, from iodinated thiazolidinedione **4a**.[8]

Firstly, we decided to study the Parham cyclisation on thiazolidines **4b–d** (Scheme 2). To test the reaction conditions and the regioselectivity of the cyclisation, the C-5 disubstituted thiazolidine-2,4-dione **4b** was chosen as substrate. Iodine–lithium exchange was carried out with *t*-BuLi at −78 °C in THF and, after work-up, 10b-hydroxy thiazoloisoquinoline **6a** was obtained in high yield. As expected, the addition of the organolithium intermediate proceeded



Scheme 1. Reagents: (a) LDA or *sec*-BuLi/TMEDA, allyl iodide or MeI, −50 °C. (b) *sec*-BuLi/TMEDA, allyl iodide or MeI, −40 °C. (c) ICl, AcOH, 5 h. (d) LDA, allyl iodide, −78 °C. (e) *sec*-BuLi/TMEDA, MeI, −40 °C.



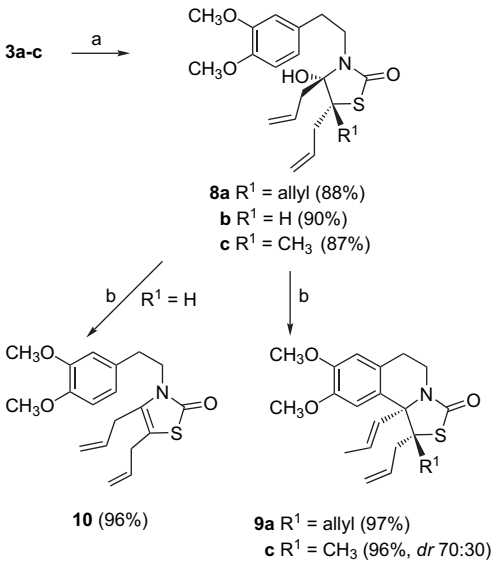
Scheme 2. Reagents: (a) *t*-BuLi, THF, −78 °C, 2–21 h. (b) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, −78 °C.

regioselectively at the more electrophilic amide carbonyl group, in spite of steric hindrance of the substituents at C-5. Under similar conditions, iodine–lithium exchange was faster than C-5 deprotonation on C-5 monosubstituted thiazolidine **4c**, and cyclisation took place efficiently with complete regio and stereoselectivity to afford 10b-hydroxy thiazoloisoquinoline **6b**. However, this product was highly unstable and partially decomposed upon purification to the enamide **7**.

Finally, treatment of **4d** with *t*-BuLi afforded thiazoloisoquinoline **6c**, as a mixture of diastereomers in a 7:3 ratio, which could not be chromatographically separated. The stereoselectivity of this reaction has no relevance in the global process, as a planar *N*-acyliminium ion is going to be generated in the next step.

As these bicyclic α-hydroxylactams **6** are immediate precursors of *N*-acyliminium ions, intermolecular α-amidoalkylation was undertaken using $TiCl_4$ at −78 °C and allyltrimethylsilane as nucleophile to introduce an allyl substituent on C-10b. However, disubstituted hydroxylactam **6a** failed to give the expected α-amidoalkylation product under various conditions, recovering unreacted starting material probably because of steric factors associated with the size of substituents at C-5, which may block the approach of the nucleophile. However, thiazoloisoquinolines **2a**,**b** were obtained as single 1,10b-*trans* diastereomers (Scheme 2).

Our next concern was the intramolecular α-amidoalkylation route to 10b-substituted thiazolo[4,3-*a*]isoquinolines. Thus, addition of allylmagnesium chloride to imides **3a–c** was carried out under standard conditions (THF, −78 °C, 6 h), affording α-hydroxylactams **8a–c** with complete regioselectivity and as single diastereomer. As expected, attack of Grignard reagent took place regioselectively at the more electrophilic carbonyl group. The stereochemistry of these products was not determined, as a planar *N*-acyliminium ion was going to be generated in the subsequent α-amidoalkylation reaction,



Scheme 3. Reagents: (a) allylMgCl, THF, −78 °C, 6 h. (b) TFA, CH_2Cl_2, reflux, 3–4 days.

but attack of the nucleophile presumably occurred from the less hindered side, opposite to the allyl group. The intramolecular α-amidoalkylation was achieved by treatment of hydroxylactams **8a** and **8c** with an excess of TFA in dichloromethane under reflux for 3–4 days. The cyclisation of **8a**,**c** occurred efficiently to afford the thiazoloisoquinoline nucleus, but isomerisation of the allyl group at C-10b was also observed. The formation of a conjugated system in the *N*-acyliminium ion intermediate may be the driving force of this process. *cis*-Thiazoloisoquinoline **9c** was obtained in good yield (96%) but with a poor diastereoselectivity (dr 70:30). The mixture of diastereomers could not be chromatographically separated. However, cyclisation of monosubstituted **8b** failed upon treatment with protic acid (TFA) and different Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$), under different conditions. In all cases, the dehydration reaction to the enamide was faster than intramolecular α-amidoalkylation, obtaining enamide **10** (Scheme 3).

The relative stereochemistry of 1,10b-*trans* and *cis* thiazoloisoquinolines was confirmed by nuclear Overhauser effect difference spectroscopy and $^1H-^1H$ decoupling experiments. Selected examples are represented in Figure 2. For example, the NOE enhancement between H-1 and the methylene group at C-10b and the absence of NOE between the methylene groups at C-1 and C-10b were consistent with the trans disposition of allyl groups in thiazoloisoquinoline **2a**. In the case of thiazoloisoquinoline **9c** the NOE enhancement between methylidene proton at C-10b and methylene group at C-1 and the absence of NOE between methyl group at C-1 and the methylene group at C-10b confirm the cis disposition for these substituents.

The stereochemical outcome in both inter- and intramolecular α-amidoalkylation reaction is controlled by the substituents on the ring. Thus, attack of the nucleophile occurs from the less hindered side of the intermediate *N*-acyliminium ion, opposite to the bulkiest substituent, to afford 1,10b-*cis* or 1,10b-*trans* thiazoloisoquinolines, respectively (Fig. 3).

We next turned our attention to the synthesis of thiaerythrinanes **1**. Firstly, we studied the ring-closing metathesis reaction of thiazoloisoquinolines **2a**,**b**.

Olefin RCM has become a powerful tool in organic synthesis, which is routinely applied to construct cyclic olefins of virtually all ring sizes bearing ether, ester, amide, amine and other functionalities.[10] However, few examples of substrates containing sulfur atoms have been so far reported.[11] Molybdenum[12] and tungsten[13] catalysts were the first known catalysts to display efficiency in metathesis reactions on substrates containing sulfur atoms. More recently, first generation Grubbs' catalyst was shown to perform enyne metathesis of sulfur-containing alkynes and RCM reactions of acyclic sulfones,[14] α-thiophosphonate,[15] sulfamides[16] and phenylthiopyridones.[17] The potential of second generation Grubbs' catalyst (**11**)[18] in RCM reactions involving acyclic diene sulfides, disulfides and dithianes has been also investigated.[19] This catalyst has been successfully employed in the synthesis of more complex

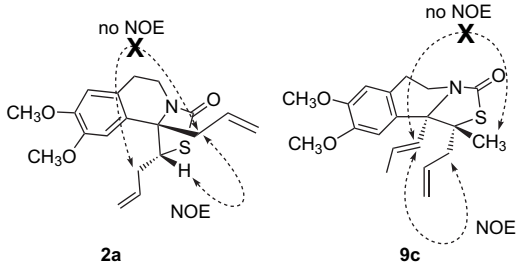


Figure 2.

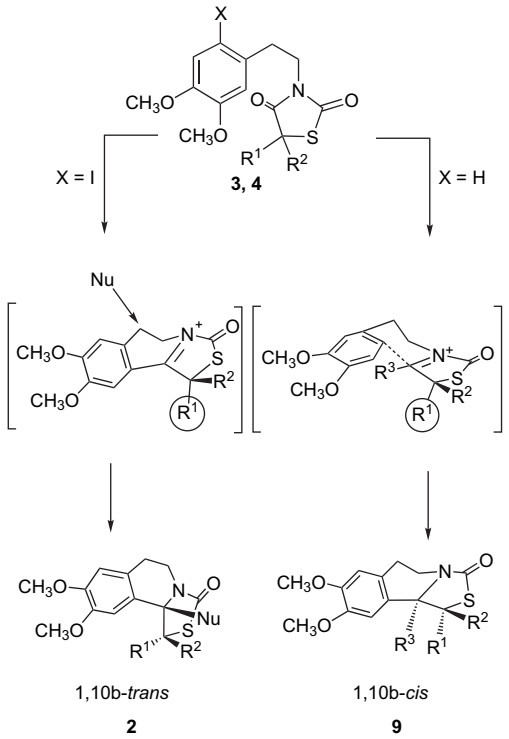
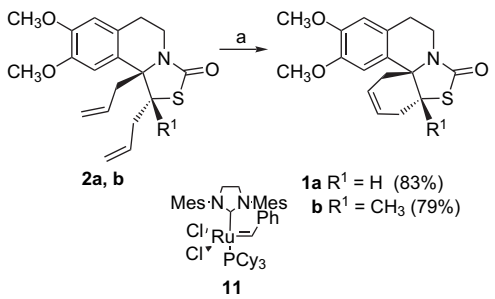


Figure 3. Stereochemical outcome of the α-amidoalkylation reactions.

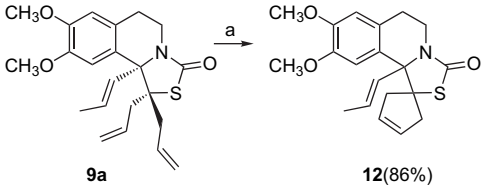


Scheme 4. Reagents: (a) second generation Grubbs' catalyst **11** (10 mol %), CH_2Cl_2, reflux, 12 h.

sulfur-containing heterocycles, such as thienocarbazoles[20] and thiepinpyrones.[21]

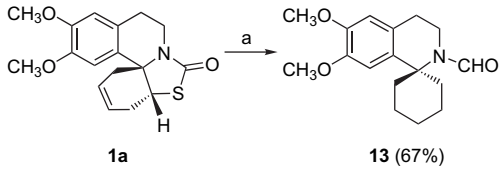
Thus, thiazoloisoquinolines **2a**,**b** were treated with 10 mol % of the second generation Grubbs' catalyst **11** to afford the corresponding thiaerythrinane derivatives **1a**,**b** in good yield (Scheme 4). The relative stereochemistry of the centres at C-5 and C-6 of the thiaerythrinanes **1a**,**b** was confirmed by 2D NOESY and COSY experiments.

Next, we studied the feasibility of performing the ring-closing metathesis reaction on thiazoloisoquinolines **9a** and **9c**. However, metathesis reaction on **9a** using second generation Grubbs' catalyst **10** took place between the two terminal double bonds instead of the internal alkene, to form a five membered ring, affording spiro derivative **12** in good yield. In case of **9c**, the reaction failed and starting material was recovered (Scheme 5).



Scheme 5. Reagents: (a) second generation Grubbs' catalyst **11**, CH_2Cl_2, reflux.

To illustrate the synthetic utility of the procedure, we decided to use a reductive desulfurisation procedure[22] to transform these thiaerythrinanes into the corresponding spiroisoquinoline derivatives, which could posses interesting pharmacological properties.[23] Thus, a Raney nickel slurry was added to a solution of thiazoloisoquinolone **1a** in EtOH, and the solution was heated under reflux for 7 h to obtain spiroisoquinoline **13** in good yield, where reduction of the double bond had also occurred (Scheme 6). This method could effectively compete with other methods for the synthesis of these types of heterocycles.[24]



Scheme 6. Reagents: (a) Raney Ni, EtOH, reflux, 7 h.

3. Conclusion

We have shown that the Parham cyclisation–intermolecular α-amidoalkylation and nucleophilic addition–intramolecular α-amidoalkylation sequences constitute diastereocomplementary routes to 1,10b-*trans* and *cis* thiazolo[4,3-*a*]isoquinolinones. Thus, intermolecular α-amidoalkylation reactions with allyltrimethylsilane allows the stereoselective synthesis of 1,10b-*trans* diallyl substituted thiazolo[4,3-*a*]isoquinolinones **2**. However, the intramolecular α-amidoalkylation reactions of α-hydroxythiazolidinones take place with isomerisation of the 10b-allyl group, thus leading to 1,10b-*cis* 1-allyl-10b-propenylthiazolo[4,3-*a*]isoquinolinones **9**. The synthesis of thiaerythrinanes can be achieved by a strategy that involves Parham cyclisation–intermolecular α-amidoalkylation sequence, followed by ring-closing metathesis (RCM) reaction. This procedure for the synthesis of thiaerythrinane and spiroisoquinoline derivatives shows the synthetic potential of the methodologies developed for the preparation of thiazolo-[4,3-*a*]isoquinolinones.

4. Experimental section

4.1. General

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or neat (oils). NMR spectra were recorded at 20–25 °C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solutions. Assignment of individual ^{13}C resonances is supported by DEPT experiments. $^1H-\{^1H\}$ NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[25] Mass spectra were recorded under electron impact at 70 eV. GC–MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m×0.25 mm×0.25 μm). TLC was carried out with 0.2 mm thick silica gel plates. Visualisation was accomplished by UV light. Flash column chromatography[26] on silica gel was performed with Kiesegel 60 (230–400 mesh). All solvents used in the reactions were anhydrous and purified according to standard procedures.[27] Organolithium reagents were titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

4.2. C-Alkylation of N-phenethylimides

4.2.1. 5,5-Diallyl-3-[2-(3,4-dimethoxyphenyl)-ethyl]thiazolidine-2,4-dione (*3a*)

s-BuLi (0.8 mL of 0.78 M solution, 0.6 mmol) was added to a solution of TMEDA (0.09 mL, 0.6 mmol) in dry THF (5 mL), at −50 °C. The mixture was stirred at −50 °C for 30 min, then a solution of **5** (0.16 g, 0.56 mmol) in dry THF (8 mL) was added slowly and via cannula, and the reaction mixture was stirred for 1 h 30 min. Allyl iodide (0.05 mL, 0.6 mmol) was added dropwise and the mixture was stirred for 1 h 30 min. The reaction was quenched by adding 1 M

HCl solution (5 mL) at −50 °C, allowed to reach room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under vacuum. Flash column chromatography (silica gel 60% hexane/AcOEt) afforded 5,5-diallyl imide **3a** as colourless oil (0.08 g, 40%): IR (neat) 1690, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) 2.53–2.60 (m, 4H), 2.81 (t, *J*=7.7 Hz, 2H), 3.73–3.79 (m, 2H)*, 3.81 (s, 3H)*, 3.84 (s, 3H)*, 5.10–5.15 (m, 4H), 5.51–5.65 (m, 2H), 6.70–6.74 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 32.9, 42.2, 42.5, 55.7, 62.6, 110.9, 111.7, 120.8, 120.9, 129.6, 130, 147.6, 148.7, 170.3, 176; MS (EI) *m/z* (rel intensity) 361 (M^+, 14), 165 (15), 164 (100), 151 (28), 149 (13), 85 (10), 77 (5). Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.04; H, 6.88; N, 3.88.

*4.2.2. 5-Allyl-3-[2-(3,4-dimethoxyphenyl)ethyl]thiazolidine-2,4-dione (**3b**)*

A solution of **5** (0.19 g, 0.66 mmol), in dry THF (20 mL), was added slowly to a solution of LDA [0.78 mmol, formed from *i*-Pr_2NH (0.11 mL, 0.78 mmol) and *n*-BuLi (0.71 mL of 1.1 M solution, 0.78 mmol)] in dry THF (5 mL) at −78 °C. After 1 h, allyl iodide (0.07 mL, 0.73 mmol) was added and the reaction mixture was stirred at this temperature for 1 h 30 min. HCl (1 M) solution was added (5 mL) and the reaction mixture was allowed to reach room temperature. Then, organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried (Na_2SO_4) and the solvent was evaporated under vacuum. Purification by flash column chromatography (silica gel 60% hexane/AcOEt) afforded **3b** as solid, that was crystallised from pentane: (0.1 g, 46%) mp (pentane) 58–59 °C: IR (neat) 1751, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) 2.40–2.53 (m, 1H), 2.80–2.90 (m, 3H), 3.78–3.82 (m, 2H)*, 3.84 (s, 3H)*, 3.86 (s, 3H)*, 4.15–4.20 (m, 1H), 5.12–5.19 (m, 2H), 5.59–5.75 (m, 1H), 6.71–6.80 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 32.9, 36.6, 42.8, 48.9, 55.8, 111.1, 111.8, 119.7, 120.9, 129.6, 131.8, 147.7, 148.8, 171.1, 173.7; MS (EI) *m/z* (rel intensity) 321 (M^+, 18), 165 (12), 164 (100), 151 (39), 149 (13), 107 (5). Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.79; H, 6.22; N, 4.41.

*4.2.3. 5-Allyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-methylthiazolidine-2,4-dione (**3c**)*

To a cold solution of TMEDA (0.12 mL, 0.77 mmol) in dry THF (3 mL) at −40 °C, *s*-BuLi (0.95 mL of 0.8 M solution, 0.77 mmol) was added. After 20 min, a solution of **3b** (0.234 g, 0.730 mmol) in THF (8 mL) was added and the mixture was stirred at this temperature for 20 min. Then, MeI (0.07 mL, 1.09 mmol) was added and the reaction mixture was stirred at this temperature for 2 h, allowed to reach room temperature, and quenched by adding 1 M HCl solution (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel 60% hexane/AcOEt) to obtain **3c** as colourless oil (0.16 g, 66%): IR (neat) 1746, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) 1.55 (s, 3H), 2.45–2.59 (m, 2H), 2.80–2.86 (t, *J*=7.5 Hz, 2H), 3.76–3.84 (m, 2H)*, 3.81 (s, 3H)*, 3.84 (s, 3H)*, 5.10–5.16 (m, 2H), 5.52–5.68 (m, 1H), 6.69–6.78 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 25.8, 32.8, 42.6, 43.7, 55.8, 58.1, 111.1, 111.9, 120.9, 121.0, 129.6, 130.9, 147.7, 148.8, 170.4, 177.2; MS (EI) *m/z* (rel intensity) 336 (M^++1, 2), 335 (M^+, 11), 164 (100), 151 (29), 149 (11), 77 (2). Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.74; H, 6.29; N, 4.22.

*4.2.4. 5,5-Diallyl-3-[2-(2-iodo-4,5-dimethoxyphenyl)-ethyl]-thiazolidine-2,4-dione (**4b**)*

A solution of iodinated thiazolidine-2,4-dione **4a** (0.3 g, 0.7 mmol) was added dropwise over a solution of LDA (2.04 mmol) [prepared from *i*-Pr_2NH (0.28 mL, 2.04 mmol) and *n*-BuLi (2.04 mL of 1 M solution, 2.04 mmol)] in THF (10 mL) at −78 °C and the resulting solution was stirred for 1 h. Allyl iodide (0.19 mL, 2.1 mmol) was added and the resulting solution was stirred for 1 h 30 min at −78 °C. The reaction was quenched by addition of 1 M HCl solution (10 mL) and was allowed to warm-up to room temperature. Ether was added, the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under vacuum. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **4b** as colourless oil (0.25 g, 73%): IR (neat) 1682, 1747 cm^{-1}; ^1H NMR ($CDCl_3$) 2.51–2.69 (m, 4H), 2.90–2.96 (m, 2H), 3.78–3.90 (m, 2H)*, 3.84 (s, 3H), 3.85 (s, 3H)*, 5.14–5.20 (m, 4H), 5.55–5.73 (m, 2H), 6.71 (s, 1H), 7.2 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 37.9, 41.2, 42.4, 55.9, 56.0, 62.8, 88.0, 112.5, 121.2, 121.7, 130.6, 132.4, 148.3, 149.3, 170.6, 176.0; MS (EI) *m/z* (rel intensity) 488 (14), 487 (M^+, 61), 277 (17), 164 (14), 150 (6), 120 (6), 85 (20), 77 (6). Anal. Calcd for $C_{19}H_{22}INO_4S$: C, 46.83; H, 4.55; N, 2.87. Found: C, 47.01; H, 4.58; N, 2.88.

*4.2.5. 5-Allyl-3-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]-thiazolidine-2,4-dione (**4c**)*

A solution of iodinated thiazolidine-2,4-dione **4a** (0.22 g, 0.55 mmol) in dry THF (20 mL) was added dropwise over a solution of LDA (0.62 mmol), [prepared from *i*-Pr_2NH (0.09 mL, 0.62 mmol) and *n*-BuLi (0.41 mL of 1.5 M solution, 0.62 mmol)] in dry THF (10 mL) at −78 °C and the resulting solution was stirred for 1 h. Allyl iodide (0.05 mL, 0.6 mmol) was added and the resulting solution was stirred for 1 h 30 min at −78 °C. The reaction was quenched by addition of 1 M HCl solution (10 mL) and was allowed to reach room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under vacuum. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **4c** as solid, that was crystallised from Et_2O: (0.18 g, 72%) mp (Et_2O) 95–96 °C: IR (neat) 1749, 1681 cm^{-1}; ^1H NMR ($CDCl_3$)

2.42–2.54 (m, 1H), 2.83–2.90 (m, 1H)*, 2.93–2.99 (m, 2H)*, 3.80–3.87 (m, 2H)*, 3.82 (s, 3H)*, 3.83 (s, 3H)*, 4.15–4.20 (m, 1H), 5.13–5.19 (m, 2H), 5.60–5.77 (m, 1H), 6.66 (s, 1H), 7.18 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 36.6, 37.6, 41.4, 49, 55.9, 56, 88.0, 112.5, 119.8, 121.6, 131.9, 132.4, 148.3, 149.2, 171, 173.6; MS (EI) *m/z* (rel intensity) 448 (M^++1, 14), 447 (M^+, 69), 291 (11), 290 (100), 277 (37). Anal. Calcd for $C_{16}H_{18}INO_4S$: C, 42.97; H, 4.07; N, 3.13. Found: C, 43.02; H, 4.18; N, 3.28.

*4.2.6. 5-Allyl-3-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]-5-methylthiazolidine-2,4-dione (**4d**)*

To a cold solution of TMEDA (0.03 mL, 0.21 mmol) in THF (3 mL) at −40 °C, *s*-BuLi (0.26 mL of 0.8 M solution, 0.21 mmol) was added and after 20 min, thiazolidinedione **4c** (90 mg, 0.2 mmol) in THF (8 mL) was added. The mixture was stirred at this temperature for 20 min, MeI (0.02 mL, 0.4 mmol) was added and stirred for 2 h at −40 °C. The reaction mixture was allowed to reach room temperature and quenched by adding 1 M HCl solution (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the organic extracts were dried (Na_2SO_4), and concentrated under vacuum. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **4d** as colourless oil (70 mg, 78%): IR (neat) 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.57 (s, 3H), 2.45–2.62 (m, 2H), 2.97 (t, *J*=7.1 Hz, 2H), 3.82 (s, 3H)*, 3.83 (s, 3H)*, 3.82–3.87 (m, 2H)*, 5.13–5.19 (m, 2H), 5.59–5.7 (m, 1H), 6.67 (s, 1H), 7.19 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 25.9, 37.7, 41.2, 43.8, 55.9, 56.0, 58.3, 88.0, 112.6, 121.2, 121.6, 130.9, 132.4, 148.3, 149.2, 170.5, 177.2; MS (EI) *m/z* (rel intensity) 461 (M^+, 12), 290 (100), 277 (31), 77 (13), 59 (46). Anal. Calcd for $C_{17}H_{20}INO_4S$: C, 44.26; H, 4.37; N, 3.04. Found: C, 44.02; H, 4.28; N, 3.08.

4.3. Parham cyclisation of iodinated N-phenethylimides: general procedure

To a solution of iodinated imides **4** (1 mmol) in dry THF (20 mL) at −78 °C, *t*-BuLi was added, the reaction mixture was stirred at this temperature for 2–24 h, quenched by addition of saturated NH_4Cl (5 mL), and allowed to reach room temperature. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to obtain thiazoloisoquinolines **6**.

*4.3.1. 1-Diallyl-10b-hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydrothiazolo[4,3-a]isoquinolin-3-one (**6a**)*

According to the general procedure, *t*-BuLi (0.13 mL of 1 M solution, 0.13 mmol) was added at −78 °C to a solution of iodinated imide **4b** (0.04 g, 0.08 mmol), in dry THF (20 mL) and the resulting solution was stirred at this temperature for 2 h. After work-up, flash column chromatography (silica gel 60% hexane/AcOEt) afforded the hydroxythiazoloisoquinoline **6a** as colourless oil (0.03 g, 88%): IR (neat) 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.40–2.50 (dd, *J*=13.5, 9.1 Hz, 1H), 2.58–2.61 (m, 2H), 2.66–2.68 (m, 1H), 2.71–2.89 (m, 2H), 3.33–3.45 (m, 1H), 3.45 (s, 1H), 3.85 (s, 3H), 3.90 (s, 3H), 4.27–4.35 (m, 1H), 4.99–5.14 (m, 2H), 5.29–5.52 (m, 2H), 5.52–5.68 (m, 1H), 5.68–5.83 (m, 1H), 6.53 (s, 1H), 6.90 (s, 1H); ^{13}C NMR ($CDCl_3$) 28.2, 37.2, 43.4, 44.0, 55.9, 56, 62, 90.8, 108.4, 110.5, 119.8, 121.5, 124.3, 129.4, 132.3, 134.5, 148.3, 149.3, 171.9; MS (EI) *m/z* (rel intensity) 344 (M^+−17, 100), 303 (59), 207 (23), 192 (37), 85 (59), 77 (29).

*4.3.2. 1-Allyl-8,9-dimethoxy-5,6-dihydrothiazolo[4,3-a]-isoquinolin-3-one (**7**)*

According to general procedure, *t*-BuLi (0.7 mL of 1.17 M solution, 0.78 mmol) was added at −78 °C to a solution of imide **4c** (0.14 g, 0.3 mmol) in dry THF (20 mL) and the resulting solution was stirred at this temperature for 2 h. Flash column chromatography (silica gel 60% hexane/AcOEt) afforded the hydroxythiazoloisoquinoline **7** as colourless oil (0.09 g, 80%): IR (neat) 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.89 (t, *J*=6.1 Hz, 2H), 3.52–3.55 (m, 2H), 3.87 (s, 3H)*, 3.90 (s, 3H)*, 3.84–3.91 (m, 2H)*, 5.23–5.30 (m, 2H), 5.97–6.08 (m, 1H), 6.75 (s, 1H), 7.03 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 29.4, 32.0, 40.5, 55.9, 56.0, 109.2, 109.6, 110.9, 117.4, 120.0, 127.6, 127.7, 134.5, 147.9, 149.0, 170.0; MS (EI) *m/z* (rel intensity) 304 (M^++1, 19), 303 (M^+, 100), 276 (10), 272 (6), 242 (10), 228 (5). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.54; H, 5.78; N, 4.41.

*4.3.3. 1-Allyl-10b-hydroxy-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydrothiazolo[4,3-a]isoquinolin-3-one (**6c**)*

According to the general procedure, *t*-BuLi (0.2 mL of 0.8 M solution, 0.14 mmol) was added at −78 °C to a solution of iodinated imide **4d** (0.05 g, 0.10 mmol), in dry THF (20 mL) and the resulting solution was stirred at this temperature for 3 h. After work-up, flash column chromatography (silica gel 60% hexane/AcOEt) afforded the hydroxythiazoloisoquinoline **6c** as a 7:3 mixture of diastereomers. Data of the mixture are given (0.02 g, 53%). IR (neat) 3444, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.54 (s, 3H, minor diast), 1.71 (s, 3H, major diast), 2.35–2.50 (m, 1H, both diast), 2.61–2.68 (m, 1H, both diast), 2.8–2.91 (m, 1H, both diast), 3.35–3.45 (m, 1H, both diast), 3.65 (s, 1H, both diast), 3.84 (s, 3H, minor diast), 3.85 (s, 3H, major diast), 3.88 (s, 3H, major diast), 3.89 (s, 3H, minor diast), 4.25–4.33 (dd, *J*=12.9, 5.9 Hz, 1H, both diast), 4.93–5.09 (m, 1H, both diast), 5.26–5.47 (m, 1H, both diast), 5.50–5.61 (m, 1H, major diast), 5.85–5.94 (m, 1H, minor diast), 6.52 (s, 1H, minor diast), 6.54 (s, 1H, major diast), 6.88 (s, 1H, minor diast), 6.92 (s, 1H, major diast); ^{13}C NMR ($CDCl_3$) 27.3 (one diast), 28.3 (one diast), 27.9 (both diast), 37.1 (one diast), 37.1 (both diast.), 37.2 (one diast), 55.9 (one diast), 56 (one diast), 57.5 (one diast), 57.8 (one diast), 58.5 (both diast), 90.4 (one diast), 91.8 (one diast), 108.2 (one diast), 108.3 (one diast), 110.5 (one diast), 110.7 (one diast), 119.5 (one diast), 121.3 (one diast), 124.1 (one diast), 124.4 (one diast), 129.5 (one diast), 130 (one diast), 132.6 (one diast), 134.7 (one diast), 148.4, 149.4 (both diast), 173 (one diast), 173.8 (one diast).

4.4. Intermolecular α-amidoalkylation reactions

4.4.1. (1RS,10bSR)-1,10b-Diallyl-8,9-dimethoxy-1,5,6,10b-tetrahydrothiazolo[4,3-a]isoquinolin-3-one (**2a**)

To a solution of crude **6b** (88 mg, 0.27 mmol), obtained from Parham cyclisation, in dry CH_2Cl_2 (15 mL), $TiCl_4$ (0.06 mL, 0.55 mmol) was added at −78 °C. After 1 h allyltrimethylsilane (0.18 mL, 1.1 mmol) was added, and the mixture was stirred at this temperature for 18 h and at room temperature for 16 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuum. Flash column chromatography (silica gel, 60% AcOEt/hexane) afforded **2a** as a colourless oil (59 mg, 59%): IR (neat) 1678 cm^{-1}; ^1H NMR ($CDCl_3$) 1.79–2.04 (m, 2H), 2.62–2.87 (m, 3H), 3.14–3.26 (m, 2H), 3.52–3.58 (dd, *J*=3.57, 11.1 Hz, 1H), 3.88 (s, 3H), 3.93 (s, 3H), 4.29–4.36 (dd, *J*=5.74, 11.7 Hz, 1H), 4.86–5.15 (m, 4H), 5.57–5.74 (m, 2H), 6.58 (s, 1H), 6.62 (s, 1H); ^{13}C NMR ($CDCl_3$) 29.9, 37.0, 39.0, 45.0, 54.6, 55.8, 56.3, 68.3, 108.9, 111.6, 118.3, 119.6, 126.6, 127.0, 133.0, 134.0, 148, 148.2, 169.2; MS (EI) *m/z* (rel intensity) 345 (M^+, <1), 320 (4), 304 (15), 289 (42), 276 (21), 263 (20), 165 (14), 164 (100), 151 (27). HRMS Calcd for $C_{19}H_{23}NO_3S$: 345.1415. Found: 345.1408.

4.4.2. (1RS,10bSR)-1,10b-Diallyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydrothiazolo[4,3-a]isoquinolin-3-one (**2b**)

To a solution of crude **6c** (51 mg, 0.14 mmol), obtained from Parham cyclisation, in dry CH_2Cl_2 (15 mL), $TiCl_4$ (0.03 mL, 0.28 mmol) was added at −78 °C. After 1 h allyltrimethylsilane (0.1 mL, 0.56 mmol) was added, the mixture was stirred at this temperature for 5 h. The mixture was allowed to reach room temperature and stirred for another 22 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuum. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **2b** as a colourless oil (15 mg, 30%): IR (neat) 1666.5 cm^{-1}; ^1H NMR ($CDCl_3$) 1.50–1.60 (m, 1H), 1.56 (s, 3H), 2.18–2.22 (dd, *J*=13.8, 5.4 Hz, 1H), 2.62–2.66 (m, 1H), 2.80–2.90 (m, 2H), 3.14 (td, *J*=12.9, 3.4 Hz, 1H), 3.28–3.33 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.38–4.41 (m, 1H), 4.87–5.12 (m, 4H), 5.53–5.63 (m, 1H), 5.72–5.79 (m, 1H), 6.63 (s, 1H), 6.71 (s, 1H); ^{13}C NMR ($CDCl_3$) 19.3, 29.8, 40.0, 41.5, 42.5, 55.8, 56.2, 62.8, 70.1, 108.5, 111.9, 119.4, 126.5, 128.7, 133.1, 133.4, 148.0, 148.2, 168.9; MS (EI) *m/z* (rel intensity) 318 (67), 278 (19), 277 (100), 207 (37), 85 (19), 83 (17), 77 (11), 69 (11), 60 (12), 55 (6). HRMS Calcd for $C_{20}H_{25}NO_3S$: 359.1572. Found: 359.1561.

4.5. Nucleophilic addition of allylmagnesium chloride to imides. Synthesis of hydroxylactams **8**: general procedure

To a solution of imide **3a–c** (1 mmol) in dry THF (20 mL), allylmagnesium chloride (2.5 mmol) was added at −78 °C and the reaction mixture was stirred at this temperature for 6 h. Water (5 mL) was added and the mixture was allowed to reach room temperature. Diethyl ether (5 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum to obtain the corresponding α-hydroxylactams **8a–c**.

4.5.1. 4,5,5-Triallyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxythiazolidine-2-one (**8a**)

According to the general procedure, a solution of **3a** (0.18 g, 0.5 mmol) in (20 mL) dry THF was treated with allylmagnesium chloride (0.63 mL of 2 M solution, 1.25 mmol), at −78 °C. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded α-hydroxylactam **8a** as colourless oil (0.18 g, 88%): IR (neat) 3414, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) 2.41–2.74 (m, 6H), 2.77–2.86 (m, 2H), 3.25–3.39 (m, 1H)*, 3.39 (s, 1H)*, 3.50–3.62 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 5.11–5.27 (m, 6H), 5.63–5.90 (m, 2H), 5.92–6.0 (m, 1H), 6.70–6.74 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 34.7, 39.4, 39.6, 43.9, 44.2, 55.9, 62.7, 94.4, 111.3, 112.1, 119.2, 119.6, 120.8, 131, 132.1, 133.0, 133.9, 147.7, 149.0, 168.8; MS (EI) *m/z* (rel intensity) 403 (M^+, <1%), 362 (2), 361 (5), 164 (100), 91 (6), 77 (4).

4.5.2. 4,5-Diallyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxythiazolidine-2-one (**8b**)

According to general procedure, a solution of **3b** (0.1 g, 0.3 mmol), in (20 mL) dry THF was treated with allylmagnesium chloride (0.4 mL of 2 M solution, 0.8 mmol) at −78 °C. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded α-hydroxylactam **8b** as colourless oil (0.11 g, 90%): IR (neat) 3340, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 2.24–2.39 (m, 1H), 2.55–2.58 (m, 3H), 2.79–2.93 (m, 2H), 3.33–3.39 (m, 1H), 3.49–3.59 (m, 1H), 3.73–3.83 (m, 1H)*, 3.79 (s, 3H)*, 3.80 (s, 3H)*, 3.83 (s, 1H)*, 5.0–5.18 (m, 4H), 5.57–5.76 (m, 2H), 6.7 (s, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 34.0, 34.4, 41.5, 43.9, 49.7, 55.6, 92.0, 111.1, 111.9, 117.9, 120, 120.5, 131.2, 134.3, 147.4, 148.6, 170.9; MS (EI) *m/z* (rel intensity) 363 (M^+, 3), 165 (10), 164 (100), 151 (20), 149 (10), 107 (6), 91 (7), 87 (6), 85 (10), 83 (10), 71 (8), 69 (9), 57 (11), 56 (5), 55 (12).

4.5.3. 4,5-Diallyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-5-methylthiazolidine-2-one (**8c**)

According to the general procedure, a solution of **3c** (0.23 g, 0.7 mmol) in dry THF (20 mL) was treated with allylMgCl (0.88 mL, 1.74 mmol) at −78 °C. Flash column chromatography (silica gel, 60% AcOEt/hexane) afforded α-hydroxylactam **8c** as colourless oil (0.23 g, 87%): IR (neat) 3350, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) 1.42 (s, 3H), 2.36–2.62 (m, 2H), 2.62–2.85 (m, 4H), 3.17 (s, 1H), 3.42–3.47 (m, 1H), 3.57–3.6 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 5.1–5.2 (m, 4H), 5.8–5.82 (m, 1H), 5.92–6.1 (m, 1H), 6.73–6.8 (m, 3H); ^{13}C NMR ($CDCl_3$) 23.1, 34.8, 39.6, 41.7, 44.1, 55.8, 60.6, 94.3, 111.2, 112.1, 119.2, 119.5, 120.8, 131.3, 132.3,

133.9, 147.6, 149, 169; MS (EI) *m/z* (rel intensity) 377 (M^+, <1%), 336 (2), 335 (9), 164 (100), 151 (37), 91 (5), 77 (3).

4.6. Intramolecular α-amidoalkylation reactions: general procedure

To a solution of α-hydroxylactams **8** (1 mmol) in dry dichloromethane (12 mL), TFA was added, and the reaction mixture was heated under reflux for 3–4 days. After cyclisation was completed, the reaction mixture was allowed to reach room temperature, and quenched by addition of water and a saturated solution of $NaHCO_3$. The two layers were separated, the aqueous layer was extracted with dichloromethane (3×10 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum to obtain the thiazoloisoquinolines **9**.

*4.6.1. (1RS,10bRS)-1,1-Diallyl-8,9-dimethoxy-10b-propenyl-1,5,6,10b-tetrahydrothiazolo[4,3-a]isoquinolin-3-one (**9a**)*

According to the general procedure, to a solution of α-hydroxylactam **8a** (0.18 g, 0.45 mmol) in dry dichloromethane (12 mL), TFA (2.33 mL, 30 mmol) was added. The reaction mixture was refluxed for 4 days. After work-up, flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **9a** as colourless oil (0.17 g, 97%): IR (neat) 1679 cm^{-1}; ^1H NMR ($CDCl_3$) 1.50 (d, *J*=7.1 Hz, 3H), 2.38–2.47 (m, 2H), 2.48–2.56 (m, 2H), 3.04–3.19 (m, 1H), 3.39 (dd, *J*=15.9, 5.2 Hz, 1H), 3.82 (s, 3H)*, 3.85 (s, 3H)*, 3.77–3.90 (m, 1H)*, 4.25–4.34 (m, 2H), 4.48 (d, *J*=6.3 Hz, 1H), 4.92–4.99 (m, 2H), 5.09–5.16 (m, 2H), 5.27–5.41 (m, 1H), 5.67–5.81 (m, 1H), 6.60 (s, 1H), 6.67 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 31.4, 34.7, 43.7, 45.2, 47.4, 55.9, 56.1, 60.2, 108.1, 111.7, 114.8, 119.1, 119.5, 127.8, 132.3, 132.7, 135.2, 144.6, 146.6, 147.9, 170.8; MS (EI) *m/z* (rel intensity) 386 (M^++1, 3), 385 (M^+, 12), 193 (20), 192 (100), 177 (14), 91 (11), 77 (4). Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.44; H, 7.15; N, 4.85.

*4.6.2. 4,5-Diallyl-3-[2-(4,5-dimethoxyphenyl)ethyl]-3H-thiazol-2-one (**10**)*

According to the general procedure, to a solution of **8b** (0.1 g, 0.26 mmol) in dry dichloromethane (10 mL) was added TFA (1.4 mL, 17.5 mmol) at room temperature, and the mixture was refluxed for 4 days. After work-up, flash column chromatography (silica gel, 60% AcOEt/hexane) afforded **10** as colourless oil (0.09 g, 96%): IR (neat) 1658 cm^{-1}; ^1H NMR ($CDCl_3$) 2.80–2.88 (m, 4H), 3.09–3.12 (d, *J*=6.3 Hz, 2H), 3.74–3.85 (m, 2H)*, 3.79 (s, 3H)*, 3.82 (s, 3H)*, 4.89–5.10 (m, 4H), 5.61–5.80 (m, 2H), 6.58–6.77 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 28.9, 30.8, 34.2, 45.2, 55.6, 55.7, 110.9, 111.2, 111.9, 116.7, 117, 120.6, 128.7, 130.6, 133, 134.7, 147.6, 148.8, 171.5; MS (EI) *m/z* (rel intensity) 345 (M^+, 14), 165 (15), 164 (100), 149 (7). Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.64; H, 6.40; N, 4.05.

*4.6.3. (1RS,10bRS)-1-Allyl-8,9-dimethoxy-1-methyl-10b-propenyl-1,5,6,10b-tetrahydrothiazolo[4,3-a]isoquinolin-3-one (**9c**)*

According to the general procedure, to a solution of **8c** (0.14 g, 0.39 mmol) in dry dichloromethane (12 mL), TFA (2 mL, 26 mmol) was added. The reaction mixture was stirred under reflux for 4 days. After work-up, flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **9c** as a mixture of diastereomers in a 70:30 ratio. Data of the mixture are given (0.13 g, 96%): IR (neat) 1672 cm^{-1}; ^1H NMR ($CDCl_3$) 1.37 (s, 3H, CH_3–C_1, major diast), 1.47–1.54 (m, 6H, CH_3–CH=, both diast, CH_3–C_1, minor diast), 2.36 (d, *J*=6.7 Hz, 2H, CH_2–CH=CH_2, minor diast), 2.42 (d, *J*=6.7 Hz, 2H, CH_2–CH=CH_2, major diast), 3.10–3.20 (m, 1H, H_{6ax}, both diast), 3.32–3.40 (m, 1H, H_{6eq}, both diast), 3.75–4.17 (m, 1H, H_{5ax}, both diast)*, 3.81 (s, 3H, OCH_3, both diast)*, 3.82 (s, 3H, OCH_3, both diast)*, 4.20–4.30 (m, 2H, H_{5eq}, CH=C*H*–CH_3, both diast), 4.5–4.6 (m, 1H, CH=C*H*–C_{10b}, both diast), 4.91–4.97 (m, 2H, CH_2=$CHCH_2$–, minor diast), 5.07–5.13 (m, 2H, CH_2=CH–CH_2, major diast), 6.6 (s, 1H, H_7, both diast), 6.67 (s, 1H, H_{10}, major diast), 6.68 (s, 1H, H_{10}, minor diast); ^{13}C NMR ($CDCl_3$) 26.0 (CH_3, minor diast), 31.0 (CH_3, major diast), 31.1 (CH_3, major diast), 31.3 (CH_3, minor diast), 34.5 (C_6, major diast), 35.0 (C_6, minor diast), 45.1 (*C*H_2–CH=CH_2, major diast), 45.4 (*C*H_2–CH=CH_2, minor diast), 49.2 (C_5, both diast), 55.8 (OCH_3, both diast), 56 (OCH_3, both diast), 56 (C_{10b}, both diast), 56.7 (C_1, both diast), 110.9 (C_{10}, minor diast), 111 (C_{10}, major diast), 114.6 (–CH=*C*H–CH_3, both diast), 119.2 (CH_2CH=*C*H_2, minor diast), 119.3 (CH_2CH=*C*H_2, major diast), 127.7 (*C*H=CH–CH_3, major diast), 128 (*C*H=CH–CH_3, minor diast), 132.5 (CH_2=*C*H–CH_2, major diast), 132.7 (CH_2=*C*H–CH_2, minor diast), 135 (C_{7a}, major diast), 135.1 (C_{7a}, minor diast), 146.5 (C_{10a}, both diast), 146.6 (C_9, both diast), 147.6 (C_8, minor diast), 147.8 (C_8, major diast), 170.5 (C_3, minor diast), 170.7 (C_3, major diast); MS (EI) *m/z* (rel intensity) 360 (M^++1, 4), 359 (M^+, 18), 192 (100), 191 (15), 177 (15), 77 (4).

4.7. Ring-closing metathesis reactions: general procedure

To a solution of **2** or **9a** (1 mmol) in dry CH_2Cl_2 (200 mL), second generation Grubbs' catalyst (10 mol %) was added at room temperature. The mixture was heated under reflux, for 4 h, another portion of the catalyst was added, and the reaction mixture was heated for another 8 h. The reaction mixture was allowed to reach room temperature and the solvent was removed under reduced pressure. Flash column chromatography afforded **1** or **12**.

*4.7.1. (5SR,6RS)-15,16-Dimethoxy-8-oxo-7-thiaerythrinan-2-ene (**1a**)*

According to the general procedure, a solution of **2a** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (20 mL) was treated with second generation Grubbs' catalyst (10 mol %). After work-up, flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **1a** as colourless oil (38 mg, 83%): IR

(neat) 1666 cm^{-1}; ^1H NMR ($CDCl_3$) 2.44–2.51 (m, 1H), 2.66–2.98 (m, 4H), 3.18–3.41 (m, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 4.09–4.20 (m, 2H), 5.88–5.93 (m, 1H), 6.06–6.10 (m, 1H), 6.56 (s, 1H), 6.99 (s, 1H); ^{13}C NMR ($CDCl_3$) 25.9, 27.2, 38.7, 40.2, 49.4, 55.6, 55.7, 64.4, 110.2, 112.3, 126.5, 127.4, 128.4, 129.1, 146.6, 148.1, 175.1; MS (EI) *m/z* (rel intensity) 318 (M^++1, 27), 317 (M^+, 44), 263 (84), 207 (100), 83 (55). HRMS Calcd for $C_{17}H_{21}NO_3S$: 317.1102. Found: 317.1094.

*4.7.2. (5SR,6RS)-15,16-Dimethoxy-6-methyl-8-oxo-7-thiaerythrinan-2-ene (**1b**)*

According to the general procedure, a solution of **2b** (43 mg, 0.12 mmol) in dry CH_2Cl_2 (20 mL) was treated with second generation Grubbs' catalyst (10 mol %). After work-up, flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **1a** as colourless oil (31 mg, 79%): IR (neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 1.66 (s, 3H), 1.65–1.79 (m, 1H), 2.30–2.40 (m, 1H), 2.57–2.65 (m, 1H), 2.80–2.88 (m, 1H), 3.02–3.10 (m, 2H), 3.43–3.52 (m, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.39–4.43 (m, 1H), 5.88–5.98 (m, 1H), 6.17–6.22 (m, 1H), 6.64 (s, 1H), 6.83 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 18.7, 29.7, 40.1, 40.7, 41.6, 55.8, 56.2, 59.5, 62.3, 110.3, 112.0, 126.1, 127.4, 128.5, 128.9, 148.0, 148.2, 174.3; MS (EI) *m/z* (rel intensity) 331 (M^+, <1), 277 (33), 117 (100), 115 (62), 91 (23), 68 (16). HRMS Calcd for $C_{18}H_{21}NO_3S$: 331.1254. Found: 331.1243.

*4.7.3. 8,9-Dimethoxy-10b-propenyl (1-thia-3-aza-spiro[1.1]non-7-en-2-one)[4,3-a]isoquinoline (**12**)*

According to the general procedure, a solution of **9a** (60 mg, 0.156 mmol) in dry CH_2Cl_2 (20 mL) was treated with second generation Grubbs' catalyst (10 mol %). After work-up, flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **12** as colourless oil (48 mg, 86%): IR (neat) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) 1.47 (d, J=6.3 Hz, 3H), 2.70–2.76 (m, 2H), 2.90–2.94 (s, 2H), 3.08–3.23 (m, 1H), 3.36–3.43 (m, 1H), 3.83 (s, 3H)*, 3.86 (s, 3H)*, 3.83–3.98 (m, 1H)*, 4.26–4.36 (m, 2H), 4.63 (d, J=6.3 Hz, 1H), 5.67 (br s, 2H), 6.61 (s, 1H), 6.68 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 31.2, 35.0, 45.4, 47.6, 51.9, 55.8, 56.0, 60.0, 107.9, 109.7, 114.7, 127.8, 128.5, 129.0, 135.2, 146.5, 147.3, 147.8, 172.0; MS (EI) *m/z* (rel intensity) 358 (M^++1, 19), 357 (M^+, 100), 342 (63), 316 (11), 191 (59), 175 (39), 160 (39), 77 (53). HRMS Calcd for $C_{20}H_{23}NO_3$: 357.1415. Found357.1408.

*4.8. 6,7-Dimethoxy-1,2,3,4-tetrahydro-1-spiro-isoquinoline-2-carbaldehyde (**13**)*

To a solution of **1a** (40 mg, 0.130 mmol) in EtOH (30 mL), nickel Raney slurry (0.90 g) was added and the solution was heated under reflux for 7 h. The mixture was cooled, filtered over Celite, and the filtrate concentrated in vacuum. Flash column chromatography (silica gel, 50% hexane/AcOEt) afforded the spiroisoquinoline **13** (25 mg, 67%): IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) 1.40–1.49 (m, 1H), 1.55–1.60 (m, 1H), 1.71–1.79 (m, 1H), 1.81–1.87 (m, 1H), 1.95 (t, J=3.7 Hz, 2H), 2.27–2.33 (m, 2H), 2.82 (t, J=6.29 Hz, 2H), 3.84 (s, 3H)*, 3.88 (s, 3H)*, 3.83–3.88 (m, 4H)*, 6.55 (s, 1H), 6.75 (s, 1H), 8.55 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 21.9, 25.6, 28.0, 34.4, 36.2, 55.8, 56.3, 59.9, 108.1, 111.9, 126.8, 135.2, 147.2, 147.8, 161.3; MS (EI) *m/z* (rel intensity) 290 (M^++1, 6), 289 (M^+, 60), 288 (62), 246 (88), 245 (67), 218 (67), 217 (69), 205 (100), 204 (70), 189 (67), 173 (65), 90 (59). HRMS Calcd for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1674.

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