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# Stereoselective synthesis of thiaerythrinanes via Parham cyclisation.

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**Abstract—** Parham cyclisation – intermolecular α-amidoalkylation sequence constitute a route to *trans* thiazolo[4,3-*a*]isoquinolinones. These thiazolidindiones, that incorporate allyl groups at C-1 and C-10b, are efficient precursors of thiaerythrinanes by ring-closing methathesis 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 compared with nucleophilic addition to carbonyl groups to allow aromatic metalation and subsequent intramolecular cyclisation reactions, which are known as Parham cyclisations. [1]

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 cyclization.[2] Since the so-obtained fused isoquinolones posses a α–hydroxylactam function, they represent immediate precursors of bicyclic *N*-acyliminium ions, which can be transformed into a variety of derivatives via intermolecular α–amidoalkylation with different nucleophiles. This has been illustrated in the synthesis of the isoindolo[1,2-a]isoquinoline skeleton of nuevamine-type alkaloids.[3]

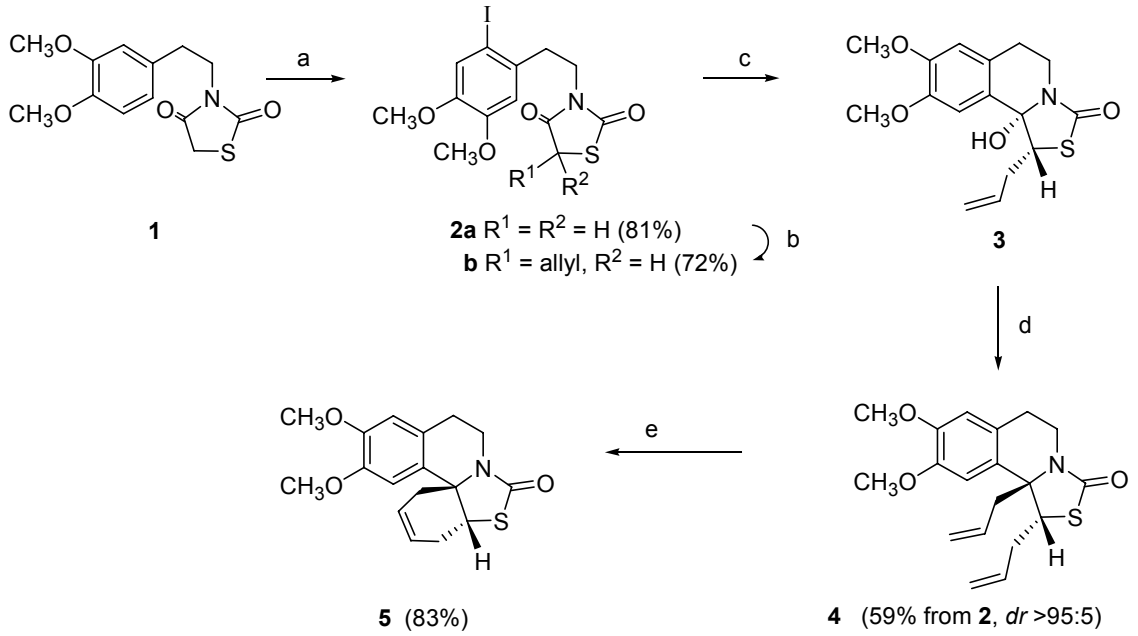
In this context, we have achieved 7-thiaerythrinanes **1** by a strategy that involves Parham cyclisation–intermolecular α-amidoalkylation sequence of thiazolidindiones **4** to afford thiazoloisoquinolines **2**, that incorporate two allyl groups on C-1 and C-10b. Finally, ring A could be assembled through ring-closing metathesis (RCM).

## 2. Results and Discussion

To begin our study, were prepared the thiazolidine-2,4-dione as depicted in Scheme 1. Thus, iodination of thiazolidinedione **1**[4] was achieved with ICl subsequent monoalkylation products was obtained LDA and allyl iodide at -78 ºC.

Firstly, we decided to study the Parham cyclisation on thiazolidine **2**. Iodine—lithium exchange was carried out with *t*-BuLi at —78ºC in THF and, after workup, 10b-hydroxythiazoloisoquinoline **3** was obtained. Iodine-lithium exchange was faster than C-5 deprotonation on C-5 monosustituted thiazolidine **2**, and cyclization took place efficiently with complete regio and stereoselectivity to afford 10b-hydroxy thiazoloisoquinoline **3.** However**,** this product was highly unstable, and partially decomposed upon purification to the corresponding enamide.

As these bicyclic α–hydroxylactams **3** are immediate precursors of *N*-acyliminium ions, intermolecular α-amidoalkylation was undertaken using $TiCl_4$ at -78 ºC and allyltrimethylsilane as nucleophile to introduce an allyl substituent on C-10b. Attack of the organolithium intermediate occurred from the less hindered face of amide group, affording the 1,10b-*trans* thiazoloisoquinoline **4** with complete regio- and stereoselectivity.




**Scheme 1.** Reagents: (a) ICl, AcOH, 5 h. (b) LDA, allyl iodide, -78 °C. (c) *t*-BuLi, THF, —78 °C, 2-21h. (d) $TiCl_4$, allyltrimethylsilane, $CH_2Cl_2$, —78 °C. (e) 2nd generation Grubbs catalyst (10 mol%), $CH_2Cl_2$, reflux, 12h.

We next turned our attention to the synthesis of thiaerythrinanes **5**. Firstly, we studied the ring-closing metathesis reaction of thiazoloisoquinoline **4.**[5] Thus, thiazoloisoquinoline **4** were treated with 10 mol% of the second generation Grubbs' catalyst to afford the corresponding thiaerythrinane derivative **5** in good yield. The relative stereochemistry of the centres at C-5 and C-6 of the thiaerythrinane **5** was confirmed by 2D NOESY and COSY experiments.

## 3. Conclusion

We have shown that the Parham cyclisation–intermolecular α-amidoalkylation sequence constitute a route to 1,10b-*trans* 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 **4**. 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 derivatives shows the synthetic potential of the methodologies developed for the preparation of thiazolo[4,3-*a*]isoquinolinones.

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## 4. Experimental Section

**5-allyl-3-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]thiazolidine-2,4-dione (2b).**
A solution of iodinated thiazolidine-2,4-dione **2a** (0.55 mmol) in dry THF (20 mL) was added dropwise over a solution of LDA (0.62 mmol), [prepared from *i*-$Pr_2NH$ (0.62 mmol) and *n*-BuLi (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 (0.6 mmol) was added and the resulting solution was stirred for 1 h 30 min at –78 °C. The reaction was quenched by addition of 1M HCl solution (10 mL), and was allowed to reach room temperature. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic extracts were dried ($Na_2SO_4$), and the solvent was evaporated under vacuum.

**(1*RS*,10b*SR*)-1,10b-diallyl-8,9-dimethoxy-1,5,6,10b-tetrahydrothiazolo[4,3-*a*]isoquinolin-3-one (4).**
To a solution of iodinated imides **2** (1 mmol) in dry THF (20 mL) at –78 $^{o}$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 x 15 mL) and the organic extracts were dried ($Na_2SO_4$), filtered, and concentrated under vacuum to obtain thiazoloisoquinolines **3**.

To a solution of crude **3** (0.27 mmol), obtained from Parham cyclization, in dry $CH_2Cl_2$ (15 mL), $TiCl_4$ (0.55 mmol) was added at –78 $^{o}$C. After 1 h allyltrimethylsilane (1.1 mmol) was added, 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 x 10 mL). The combined organic extracts were dried ($Na_2SO_4$), and concentrated in vacuum.

**(5*SR*, 6*RS*)-15,16-dimethoxy-8-oxo-7-thiaerythrinan-2-ene (5).**
To a solution of **4** (50 mg, 0.14 mmol) in dry $CH_2Cl_2$ (20 mL), 2$^{nd}$ 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.

## 5. References

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