

Synthetic Approaches Towards the Synthesis of the α -Carboline Mescengricin

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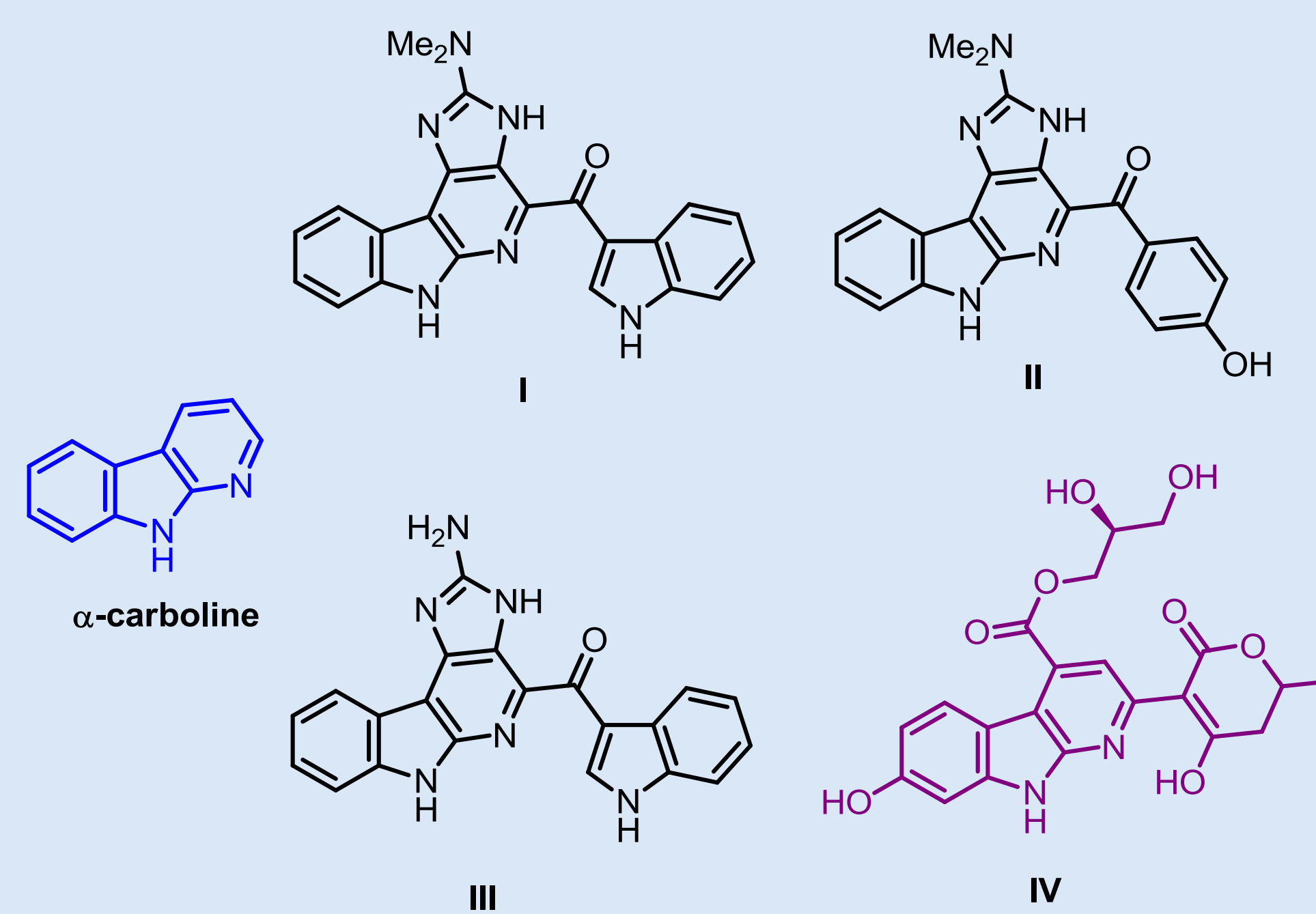
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1. Introduction

The pyrido[2,3-*b*]indole (α -carboline) skeleton is rather rare in Nature, but is exhibited in several natural products with interesting biological properties, for example, the grossularines **I**, **II** and **III**.

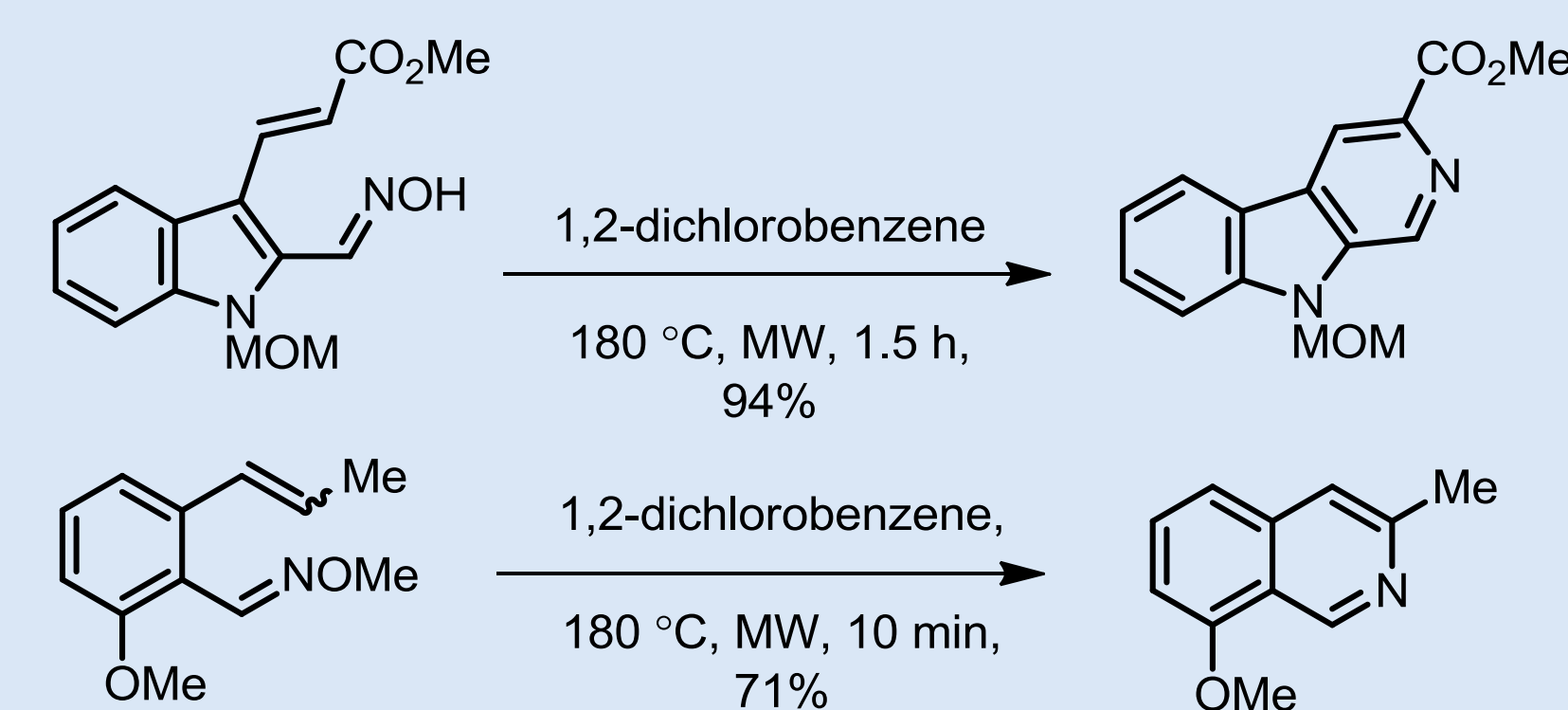
Mescengricin (**IV**) was isolated from *Streptomyces griseoflavus* in 1997 by Seto *et al.* and exhibited protective activity of chick neuronal cells against L-glutamate toxicity with an EC₅₀ of 6 nM.¹

α -Carboline synthesis is most commonly achieved using modified Graebe-Ullmann conditions or palladium cross-couplings to form a biaryl system that can later be cyclised to the α -carboline.



Less has been reported about electrocyclic routes, which have a number of advantages over stepwise formation.²

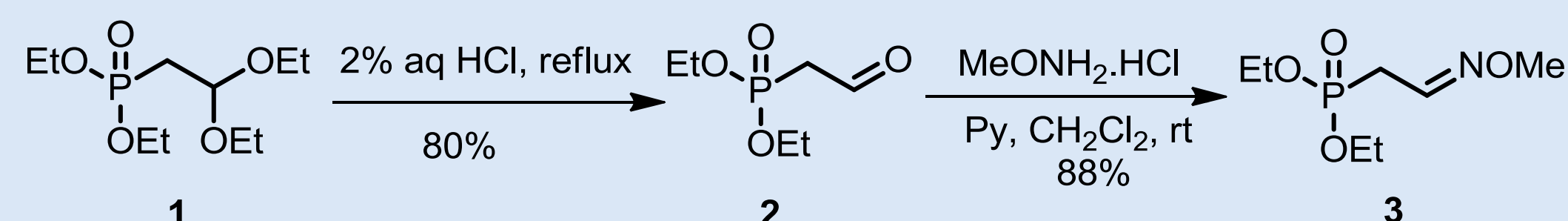
Hibino *et al.*^{3,4} have shown β -carbolines and isoquinolines can be synthesised by a 6 π -electrocyclisation, using oximes:



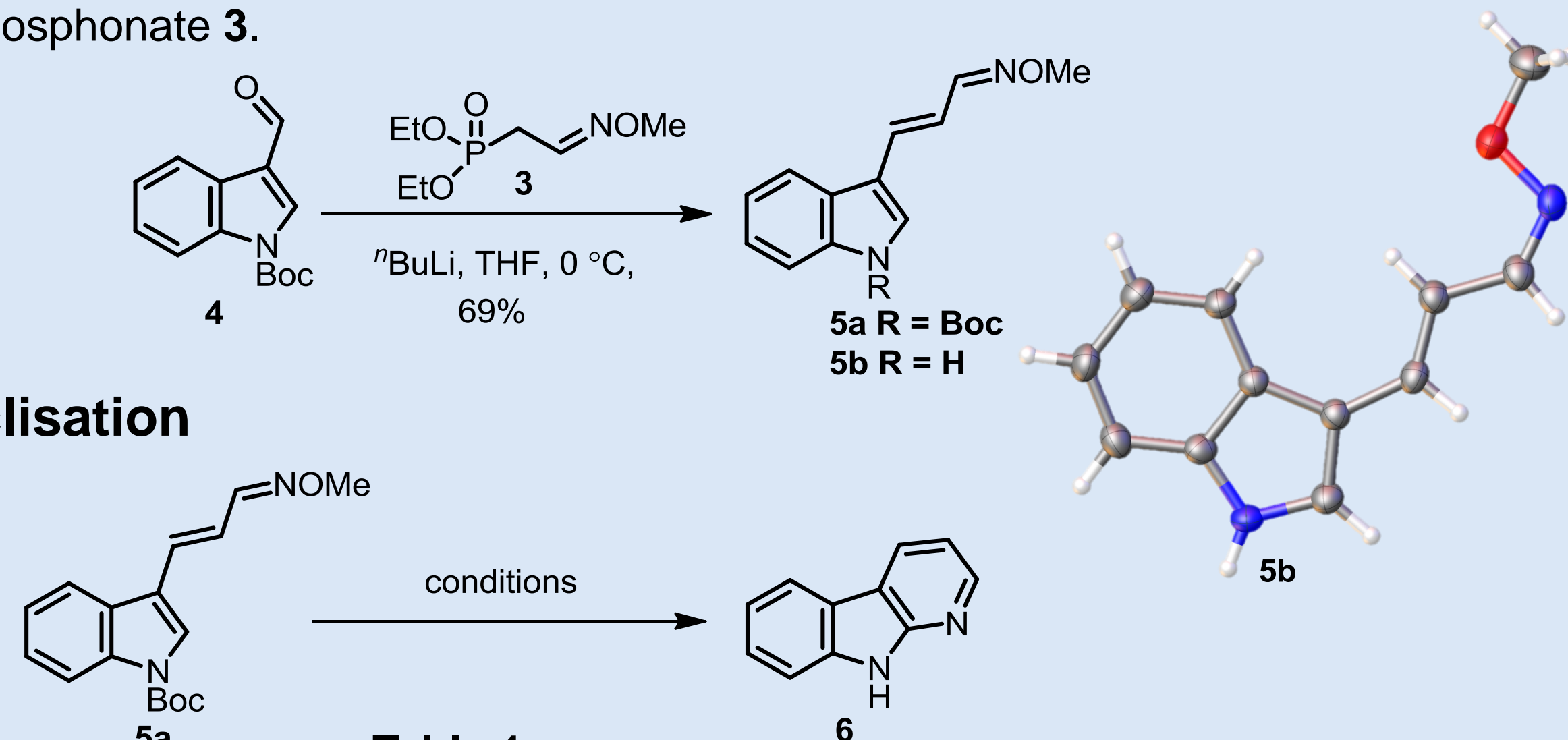
Here we describe a new methodology for α -carbolines, utilising a 6 π -electrocyclisation, show the reaction scope and apply it to the synthesis of mescengricin.

2. Methodology Development

Horner-Wadsworth-Emmons (HWE) reaction:



- Oxime **3** was synthesised from commercially available phosphonate **1** in high yield.
- Simple *N*-Boc protected indole-3-carboxaldehyde **4** was chosen as a model for the HWE reaction.
- Indole **5** was successfully made using 1 equiv. of *n*-butyllithium in THF with a slight excess of phosphonate **3**.



6 π -Electrocyclisation

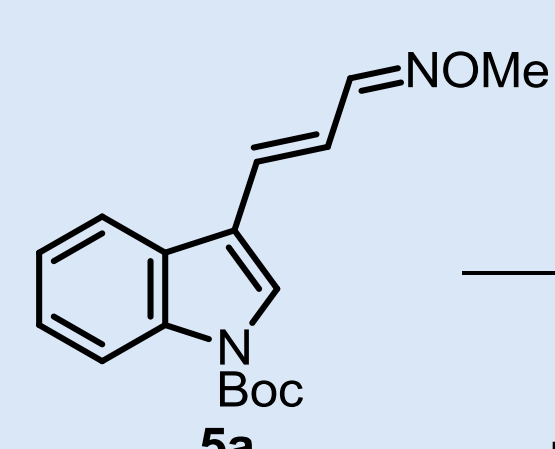


Table 1

Entry	Solvent	T (°C) * = MW	time	Yield (%)
1	toluene	110	16 h	0
2	1,2-dichlorobenzene	180	5 h	12
3	1,2-dichlorobenzene	180*	40 min	-
4	1,2-dichlorobenzene	200*	40 min	-
5	1,2-dichlorobenzene	220*	40 min	-
6	1,2-dichlorobenzene	240*	40 min	53
7	1,2-dichlorobenzene	240*	3 h	75

- A number of conditions were screened for the cyclisation (Table 1).
- The best result was at 240 °C in 1,2-dichlorobenzene in the microwave (Entry 7).

Reaction scope: substituted α -carbolines

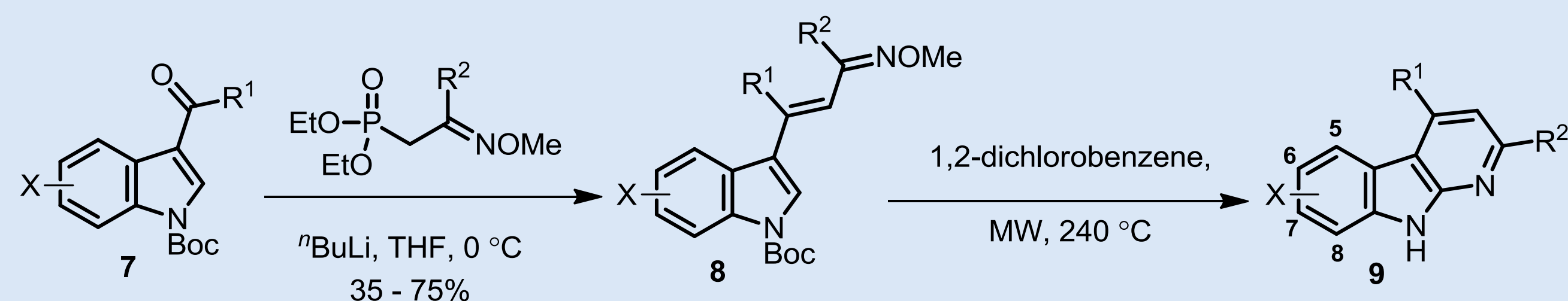
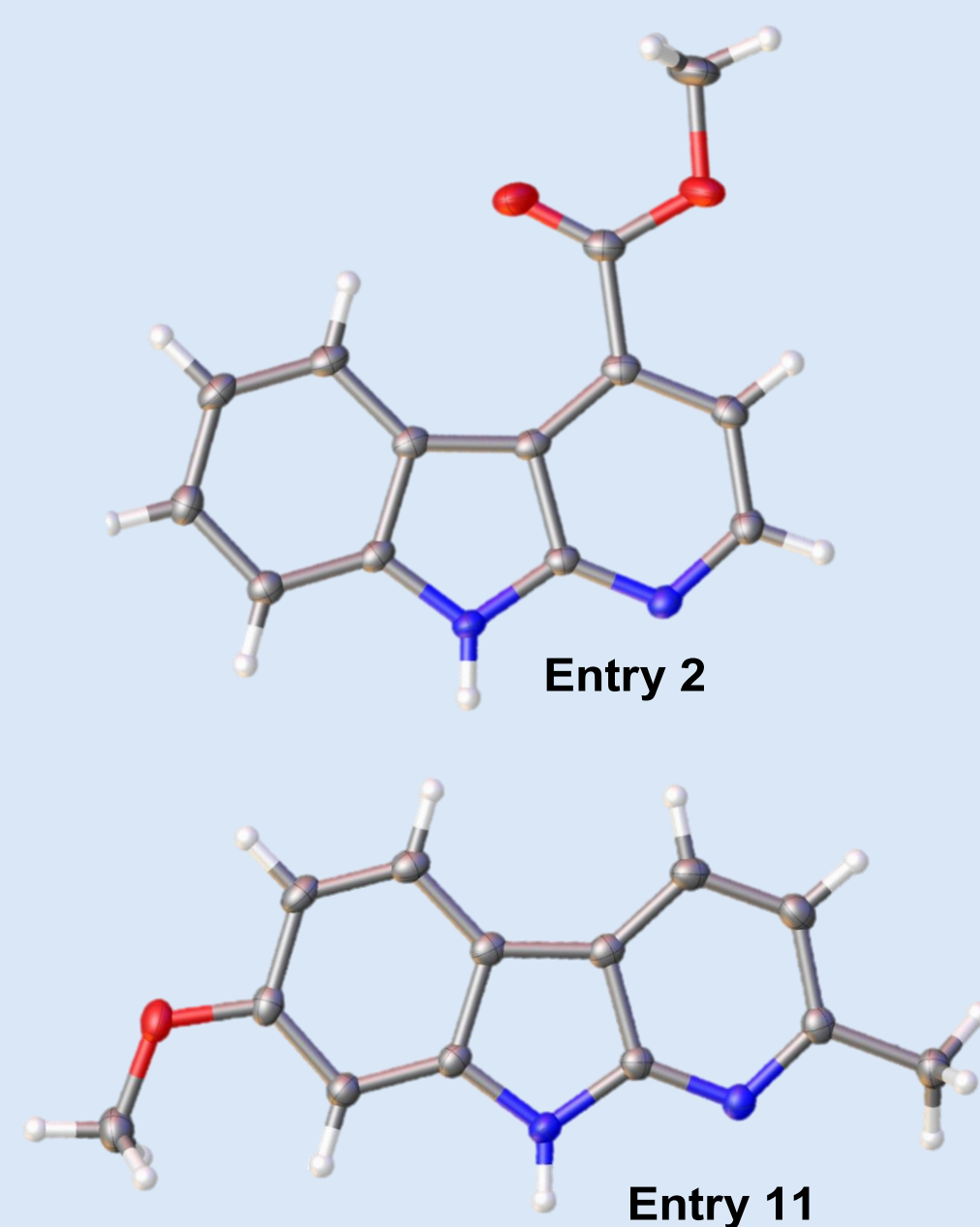


Table 2

Entry	R ¹	R ²	X	Yield (%)
1	H	H	H	73
2	CO ₂ Me	H	H	52
3	Me	H	H	62
4	H	Me	H	90
5	CO ₂ Me	Me	H	51
6	Me	Me	H	65
7	H	H	7-OMe	30
8	H	H	6-Cl	55
9	H	H	8-OBn	62
10	H	H	6-OMe	43
11	H	Me	7-OMe	77

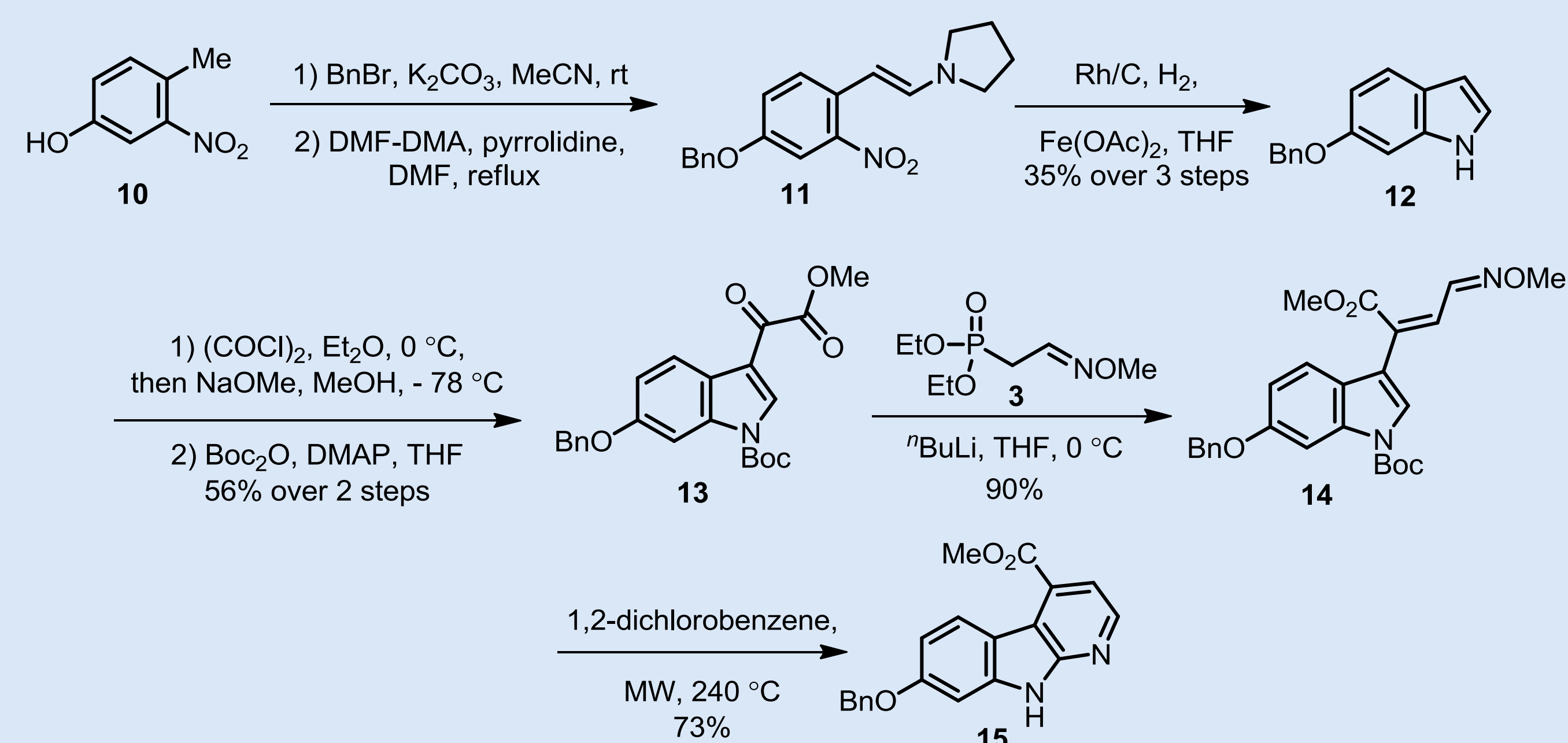


- A number of substituted α -carbolines were synthesised using our new method (Table 2).
- Entries **2** and **5** show we can introduce an ester into the 4-position, which is ideal for the synthesis of mescengricin.
- Entries **7** and **11** show that the 7-position can be functionalised, and successfully carried through, which is also required for mescengricin.

References

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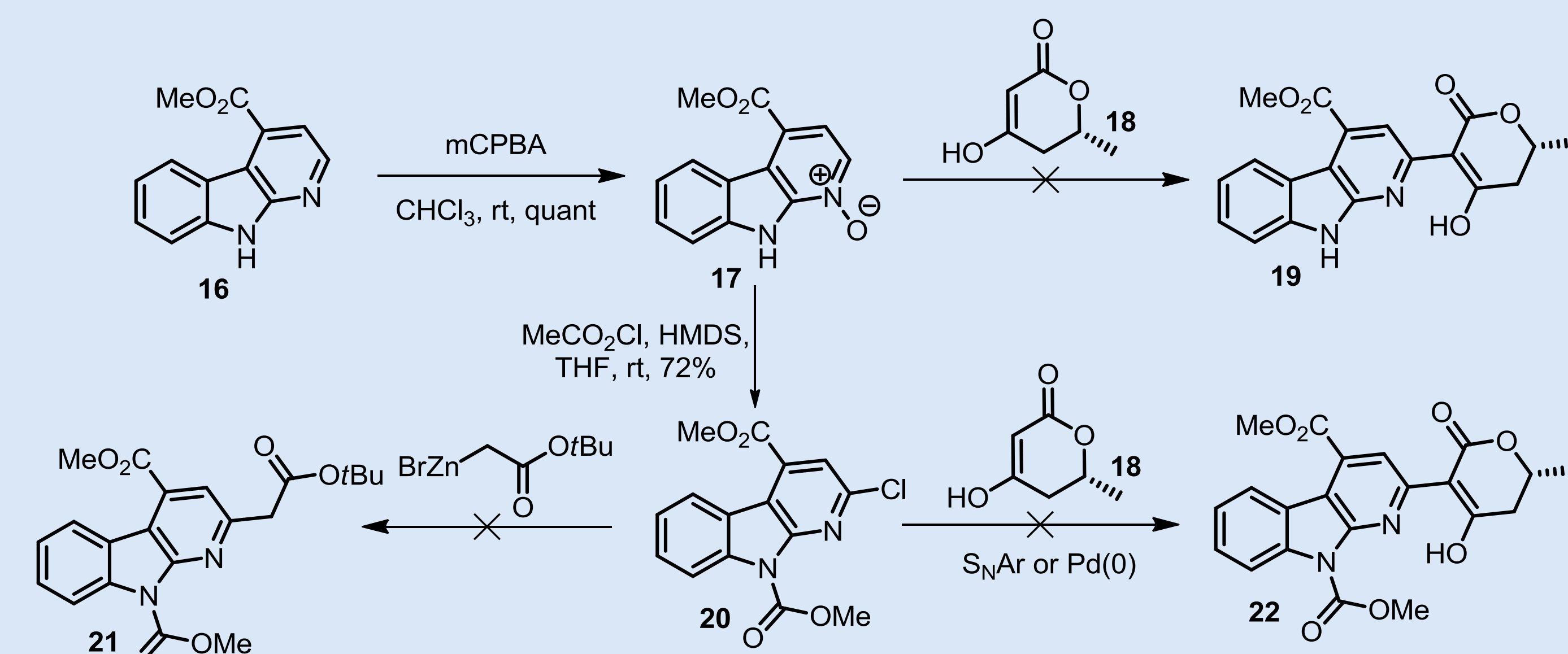
3. Application to the Synthesis of Mescengricin



- 6-Benzyloxyindole **12** was synthesised using the Leimgruber-Batcho synthesis
- Acylation to α -keto-ester **13**, followed by a HWE reaction with phosphonate **3** gave oxime **14**.
- The 6 π -electrocyclisation to α -carboline **15** was successful in 73% yield.

Functionalisation at the 2-position

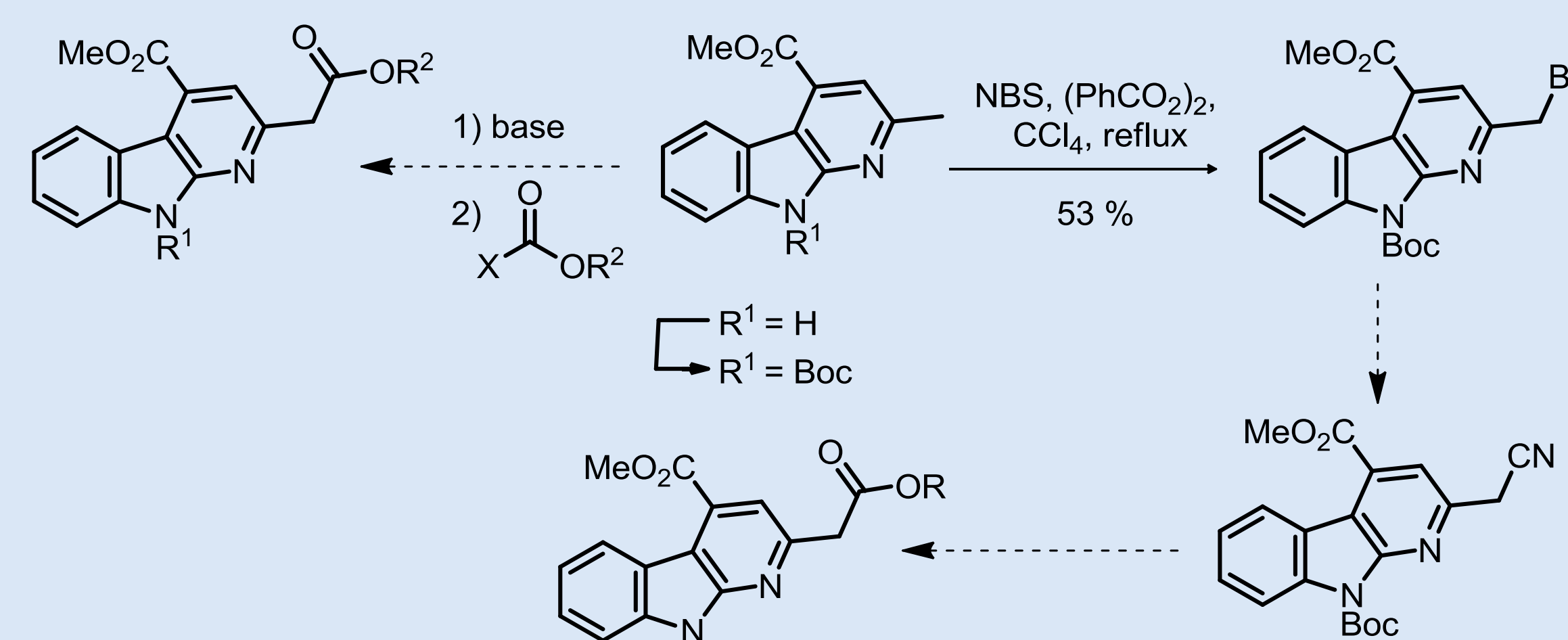
- Model studies were carried out using *N*-oxide **17** in the hope to functionalise the 2-position with lactone **18** or an ester that can later be transformed to the lactone.



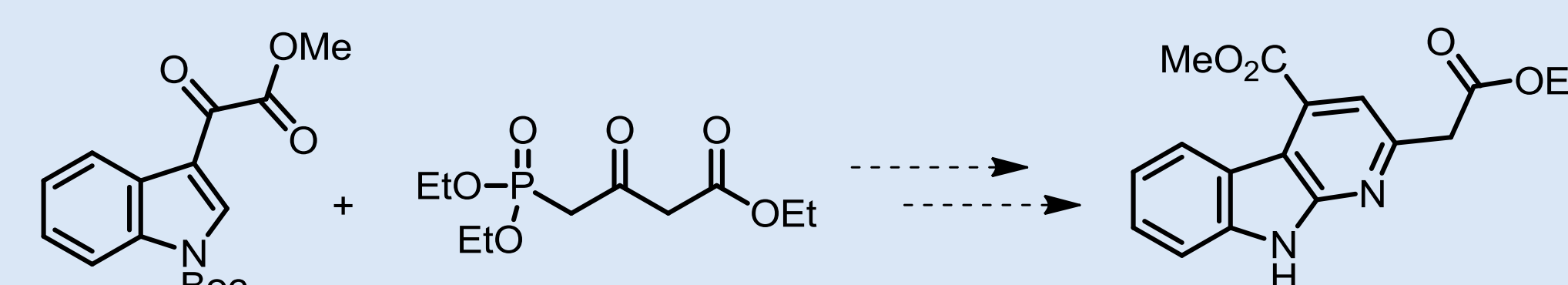
- However, many attempts were unsuccessful starting from α -carboline **16**.

4. Current & Future Work

- Currently working on other ways to install the ester and build up the lactone ring; possible solutions are:



- Build up the lactone from methyl functionality in the 2-position of the α -carboline ring.



- Synthesise β -ketoester phosphonate to install more carbons before cyclisation.

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