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A simple and concise route to calothrixin B

Paul H. Bernardo, Christina L. L. Chai* and John A. Elix

Department of Chemistry, Australian National University, Canberra, ACT 0200, Australia

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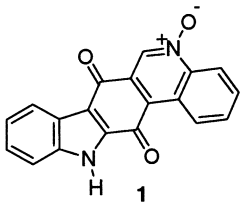
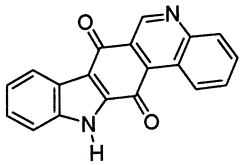
Abstract—A short and concise route to calothrixin B utilising Friedel–Crafts and lithiation reactions of readily available derivatives of quinoline and indole is described.

In 1999, a new class of pentacyclic metabolites with an indolo[3,2-*j*]phenanthridine ring system was isolated from cell extracts of the cyanobacteria *Calothrix*.[1] The metabolites calothrixins A (**1**) and B (**2**) show potent activity against malarial parasites and human cancer cells[1,2] and as such these metabolites constitute interesting targets. To date, calothrixin A and B have been synthesised by Kelly et al.,[3] and herein we describe a shorter, alternative route to calothrixin B.



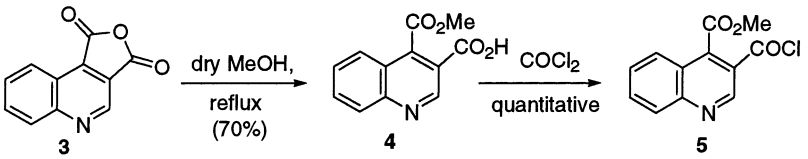
1



2

Our synthesis commenced with the preparation of quinoline-3,4-anhydride (**3**) following modification of literature procedures.[4] Treatment of the anhydride **3** with sodium methoxide in methanol gave a 2:1 mixture of the 4-mono and 3-mono methyl esters. When the anhydride **3** was refluxed in superdry methanol, only the desired 4-mono methyl ester **4** was obtained.[5] This quinoline-3-carboxylic acid 4-methyl ester (**4**) was then converted into the corresponding acid chloride **5** in quantitative yield (Scheme 1).

Our initial attempts to couple *N*-tosyl indole with the acid chloride **5** under Friedel–Crafts conditions in the presence of a number of catalysts proved to be unsuccessful and only starting material was recovered. In the absence of the *N*-tosyl protecting group, successive treatment of indole with $ZnCl_2$ (2 equivalents) and MeMgCl (1 equivalent)[6] followed by the quinoline **5** under Friedel–Crafts conditions gave the desired coupled product **6** in 80% yield (Scheme 2). For ease of handling, the key precursor **6** was protected as the *N*-MOM derivative **7** under standard conditions in excellent yields. Lithiation of **7** with lithium hexamethyldisilazide (LHMDS, 2.2. equivalents) in the presence of tetramethylethylenediamine (TMEDA, 1.1 equivalents) was followed by intramolecular nucleophilic substitution of the ester and the *N*-MOM derivative of calothrixin B (**8**) was obtained in moderate yields (54%). The *N*-MOM derivative **8** displayed identical spectroscopic data to those reported by Kelly et al.[3] Cleavage of the *N*-MOM group was carried out by dissolving the *N*-MOM derivative **8** in DMSO under acidic conditions at 100°C. The physical and spectroscopic data of the synthetic sample so obtained were identical with those of the naturally occurring calothrixin B.[†] The synthesis as described constitutes a



3 **4** **5**

Scheme 1.

Keywords: quinones; lithiation; natural products.

* Corresponding author. Fax: +61-2-6125-0760; e-mail: christina.chai@anu.edu.au

† As reported by Kelly et al.,[3] we also observed small solvent shifts in the ^{13}C NMR spectrum of calothrixin B in DMSO-d_6. In addition, direct TLC comparisons in a number of solvent systems showed that the natural and synthetic compounds are identical.

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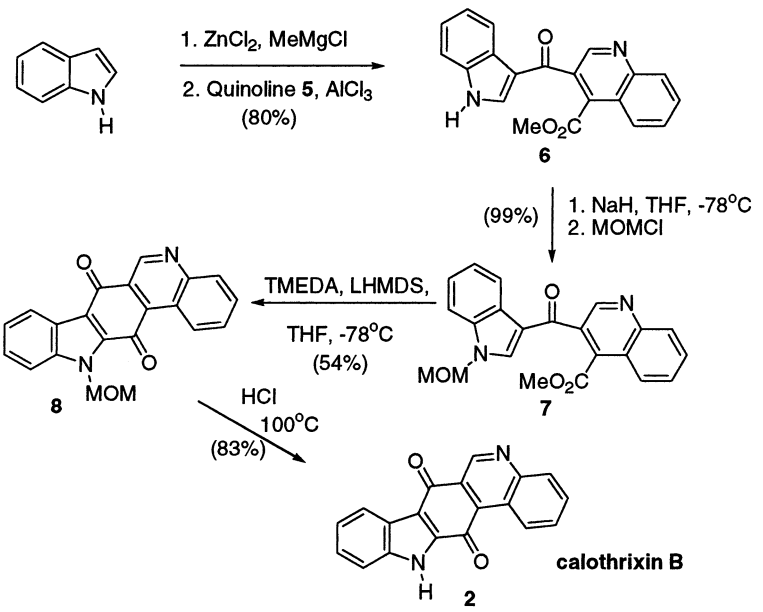

Scheme 2.

short, simple and expedient route to the synthesis of calothrixin B, starting from readily available starting materials.

Acknowledgements

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