ACS Group Meeting – Problem Session April 2007

Mahesh M.

Department of Chemistry, Imperial College London, South Kensington Campus, London SW7 2AZ

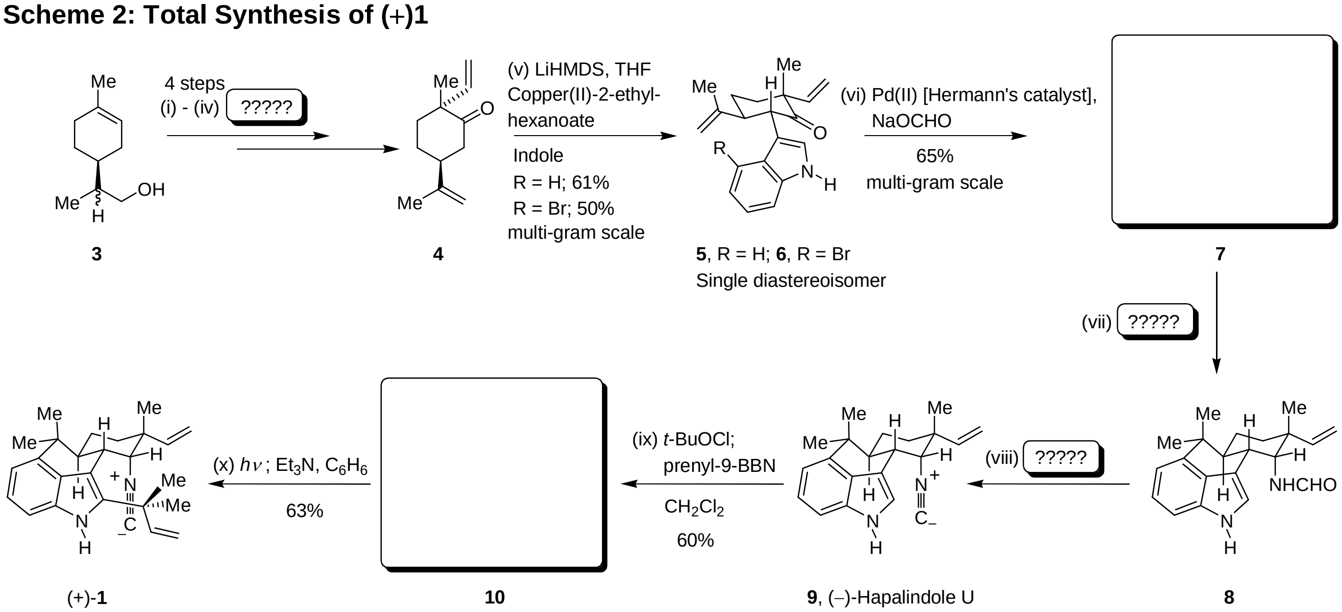
Total Synthesis of Marine Alkaloids without using Protecting Groups

Recently, total synthesis of marine alkaloids **1** and **2** (Scheme 1) has been reported with emphasis on “atom economy” and “step economy”. The hallmark of this synthesis is the fact that protecting groups have not been employed during the course of the total synthesis of the complex alkaloids **1** and **2**. These alkaloids were isolated from Stigonemataceae family of cyanobacteria that produces a class of over 60 biogenetically related, architecturally complex, topologically unique and functionally rich indole natural products. These natural produces posses a broad range of bioactivities including antifungal, antibacterial, antimycotic and anticancer properties, with some members having potencies comparable to clinical agents (streptomycin, puramycin and amphotericin).

Scheme 1

(+) **1** (+) **2**

Scheme 2: Total Synthesis of (+)1



Questions for Discussion (for Scheme 2):

(1) Suggest a route for the synthesis of **4** starting from readily available terpene **3** (the authors achieved the synthesis in four simple steps).

(2) Coupling of the enolate of **4** with simple indole in the presence of Cu(II) catalyst afforded a single diastereoisomer of **5** efficiently. The authors claim that this reaction will not proceed if the *N*-atom of the indole is protected. What will be the mechanism for this Cu-mediated coupling?

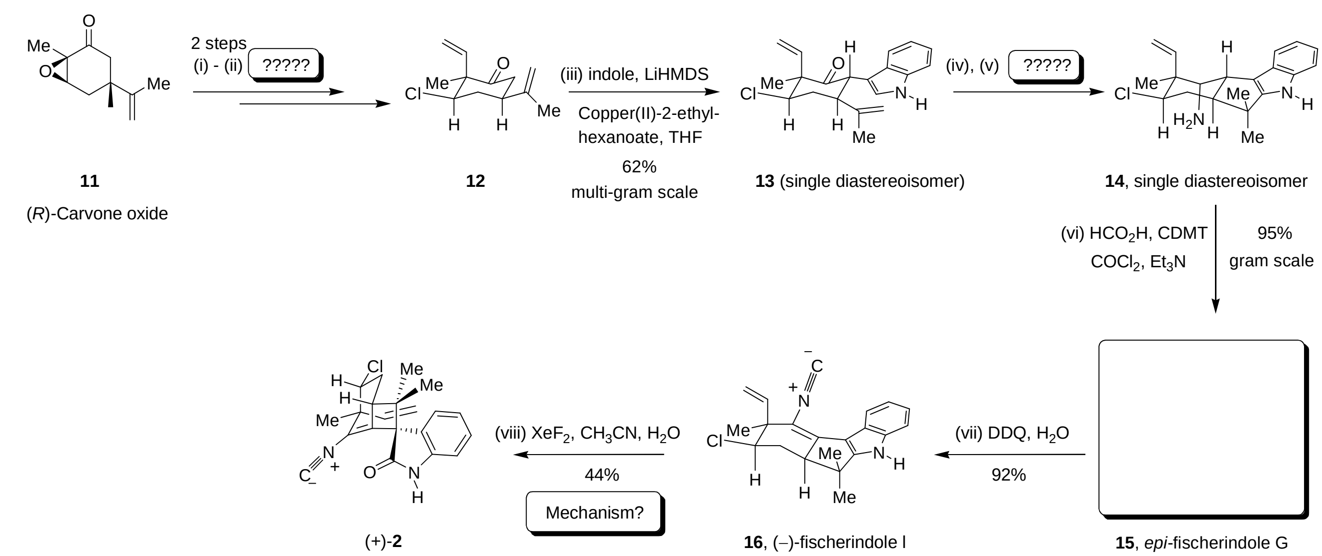
(3) In the subsequent step, the authors struggled to synthesise **7** from **5** by Friedel-Crafts annulation reaction with different acids and hence resorted to carry on palladium-mediated methods with bromo substrate **6**. Compared to reductive Heck methods of Larock and Grigg, Pd(II) [Hermann's catalyst] worked best to afford **7** when it was added slowly to **6**. What is the structure of **7**? What is Pd(II) [Hermann's catalyst]? What other methods will you suggest to synthesise **7** from **6**?

(4) What reagents can be used to synthesise the formamide **8** from **7** and (–)- Hapalindole U **9** from **8**?

(5) Predict the structure of **10** with a suitable mechanism for its formation from **9**. [Hint: Owing to the imcompatibility of the isonitrile with acids and many transition metal catalysts, the authors employed Danishefsky's protocol (*tert*-BuOCl followed by prenyl 9-BBN) for *tert*-prenylation at C-2 position of **9**.]

(6) Finally the authors demonstrated their ingenuity to achieve the natural product (+)-**1** in significant yield by irradiating **10** in the presence of triethylamine. Sketch out the mechanism for the transformation of (+)-**1** from **10** (Clue: NEt_3Cl was formed as the by-product during this reaction).

Scheme 3: Total Synthesis of (+)-2



Questions for Discussion (for Scheme 3):

(7) Propose a two step synthesis of **12** starting from carvone oxide **11**.

(8) What reagents can be used to transform the ketone **13** to the amine **14**?

(9) Predict the structure of *epi*-fischerindole G **15**?

(10) What is the type of reaction involved in the conversion of *epi*-fischerindole G **15** to (–)-fischerindole I **16** using DDQ/H_2O?

(11) Finally, the authors reacted (–)-fischerindole I **16** with XeF_2 to achieve the total synthesis of (+)-**2**. Propose a suitable mechanism for this reaction {Clue: Water is necessary for the reaction and [1,5] sigmatropic rearrangement of one of the key intermediates is involved}.

------------**Thank you**------------

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