Total Synthesis of (±)-Distomadines A and B

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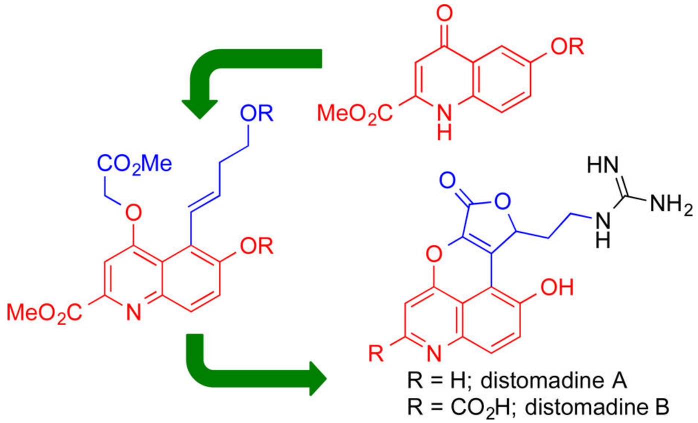


R = H; distomadine A

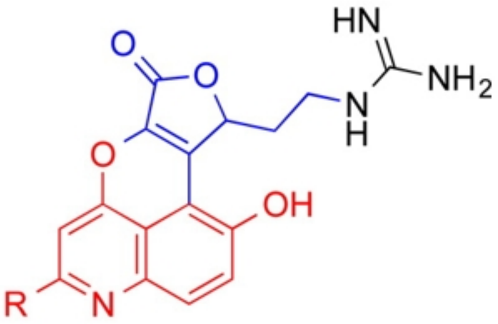
R = CO_2H; distomadine B

Feng Zhang

Wipf Group Current Literature

Feb. 15, 2014

Introduction



1 R = H; distomadine A

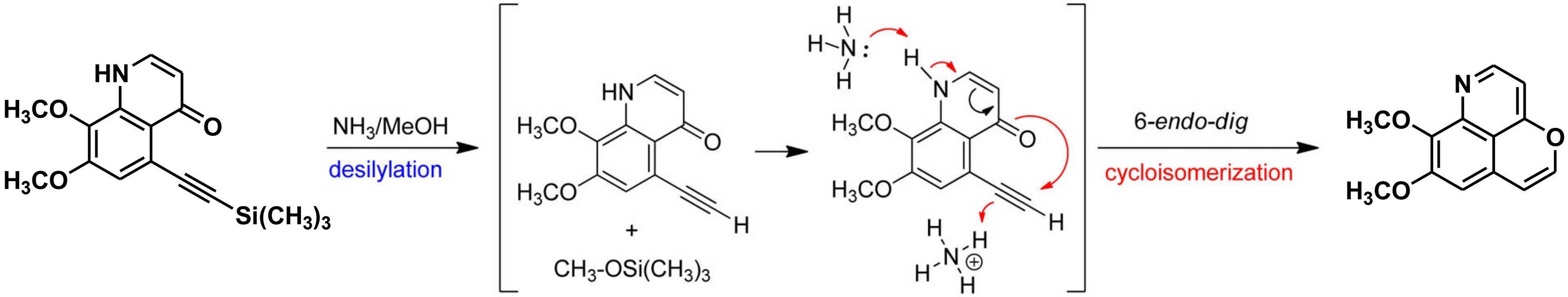
2 R = CO_2H; distomadine B

Distomadines A and B were isolated from the New Zealand ascidian Pseudodistoma aureum by Copp and coworkers in 2003.

Distomadine A exhibited mild antifungal activity but failed to exhibit any biological activity in a range of antitumour, cytotoxicity, anti-inflammatory, and antimycobacterial tests.

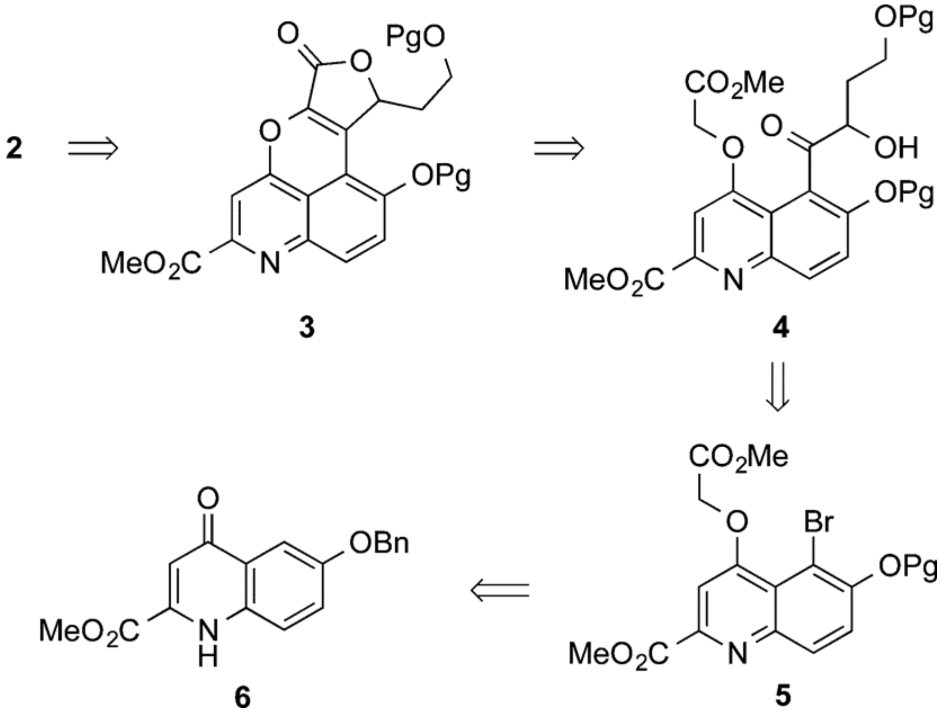
These unusual structures possess a unique tetracyclic core that comprises a pyrano[2,3,4-de] quinoline fused to a butenolide provoked our interest.

Until now, only one compound has been reported which possesses a similar pyranoquinoline core, a synthetic compound related to the aptamine alkaloids.

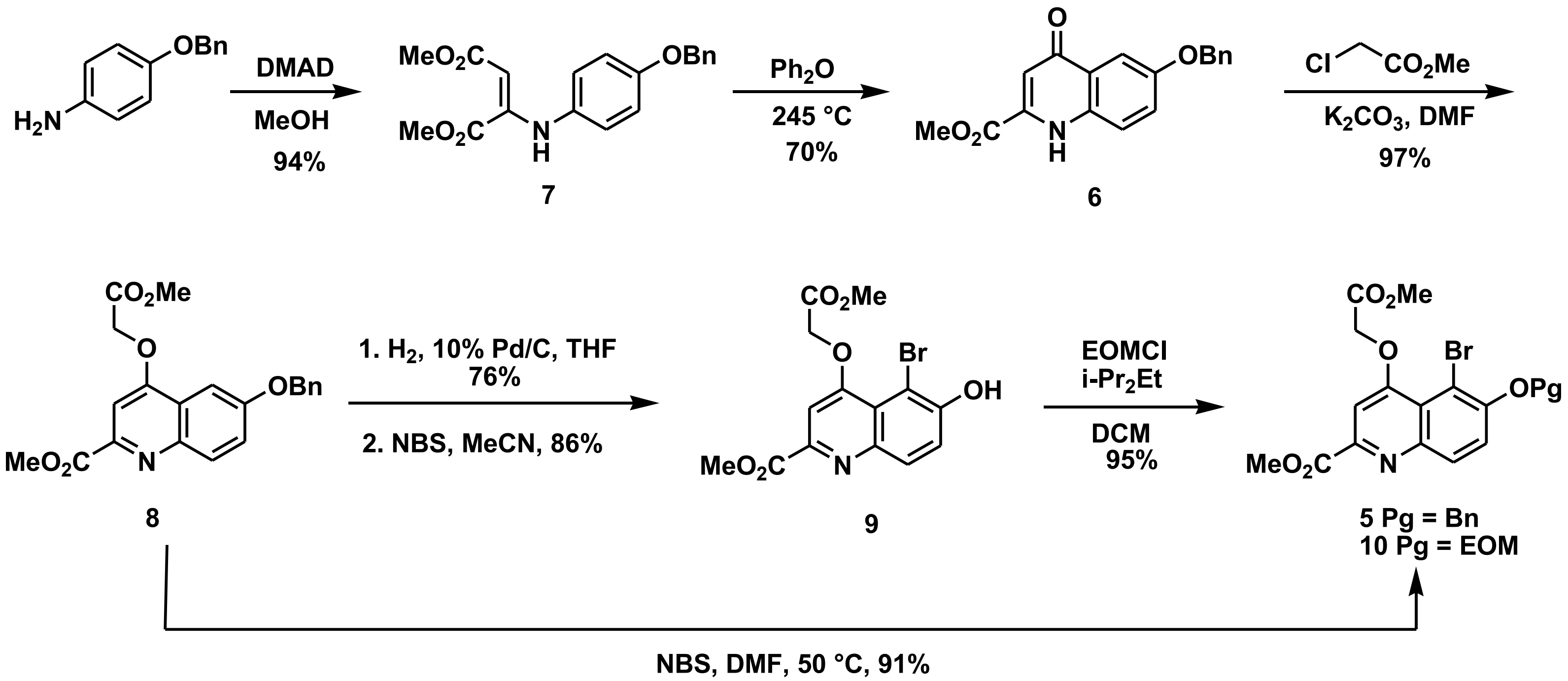


J. Org. Chem. 2012, 77, 10461-10467.

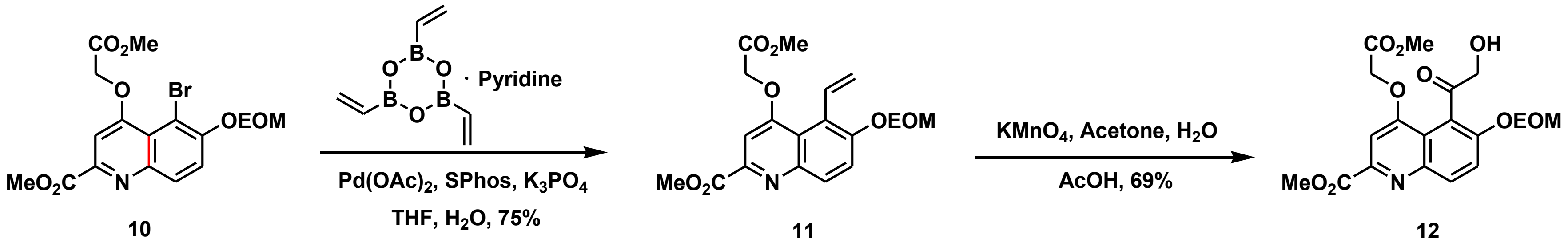
Retrosynthesis Analysis of Distomadine B (Pg = Protecting Group).

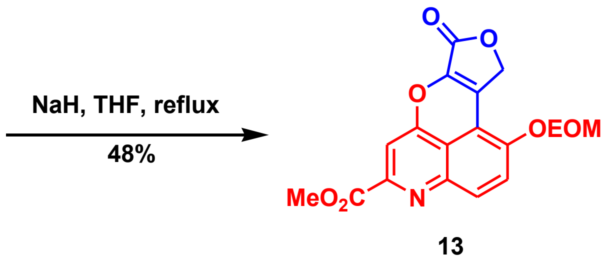


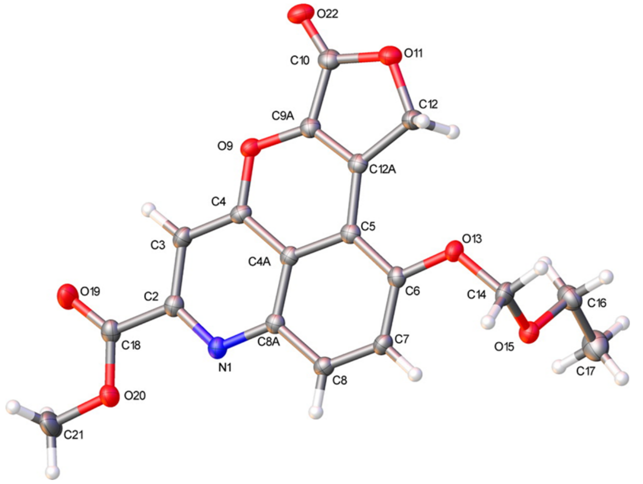
Synthesis of 5-Bromoquinolines 5 and 10



Synthesis of the Model Tetracyclic Core of Distomadine B

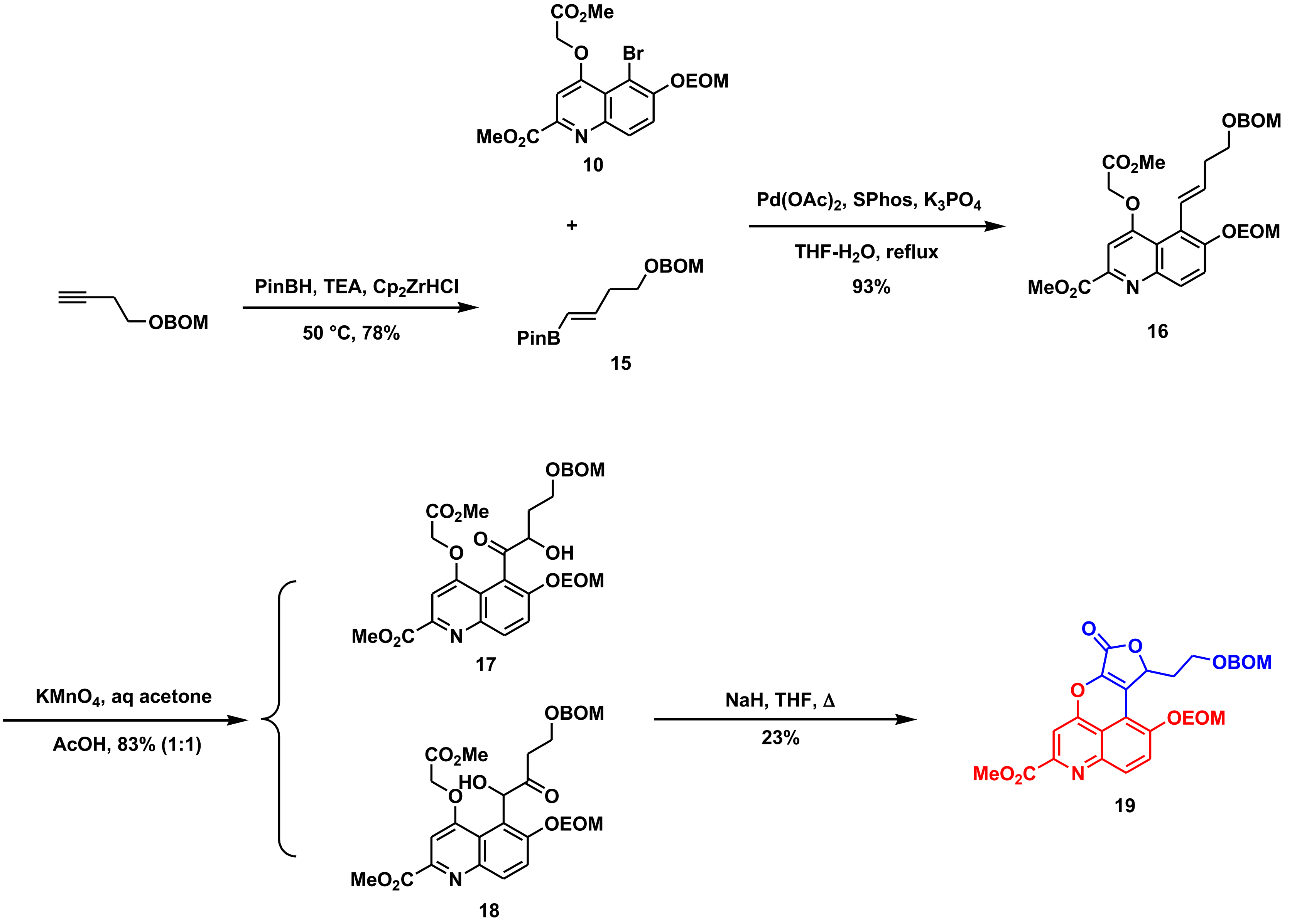




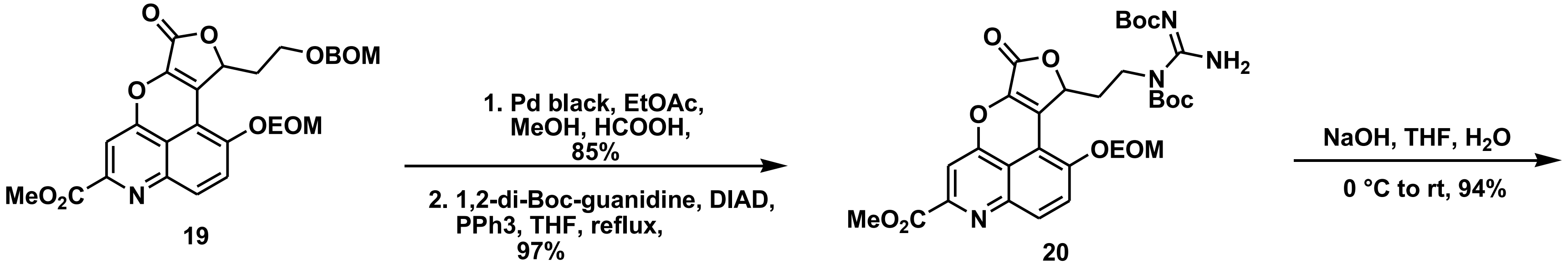


X-ray crystal structure of 13

Synthesis of γ-Butenolide 19 Core of Distomadine B



Completion of Synthesis of Distomadine B



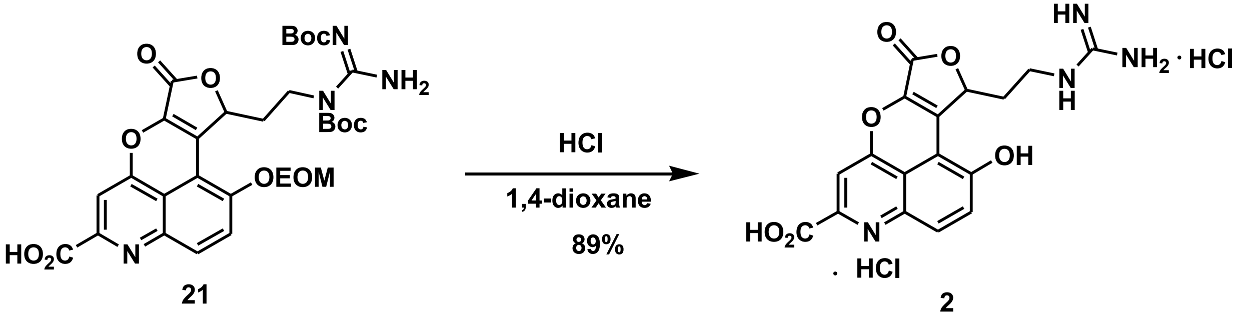
19

1. Pd black, EtOAc, MeOH, HCOOH, 85%
2. 1,2-di-Boc-guanidine, DIAD, PPh3, THF, reflux, 97%

20

NaOH, THF, H_2O

0 °C to rt, 94%



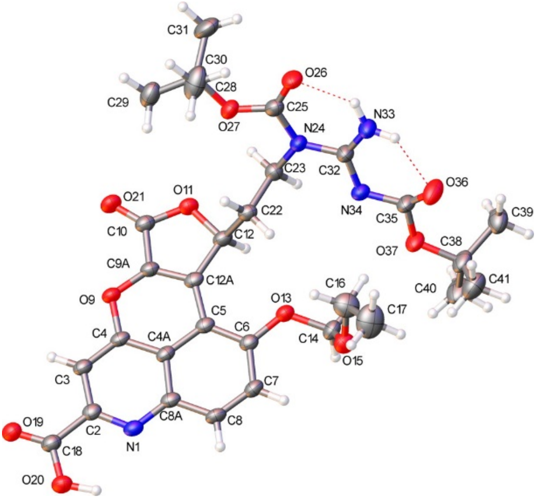
21

HCl

1,4-dioxane

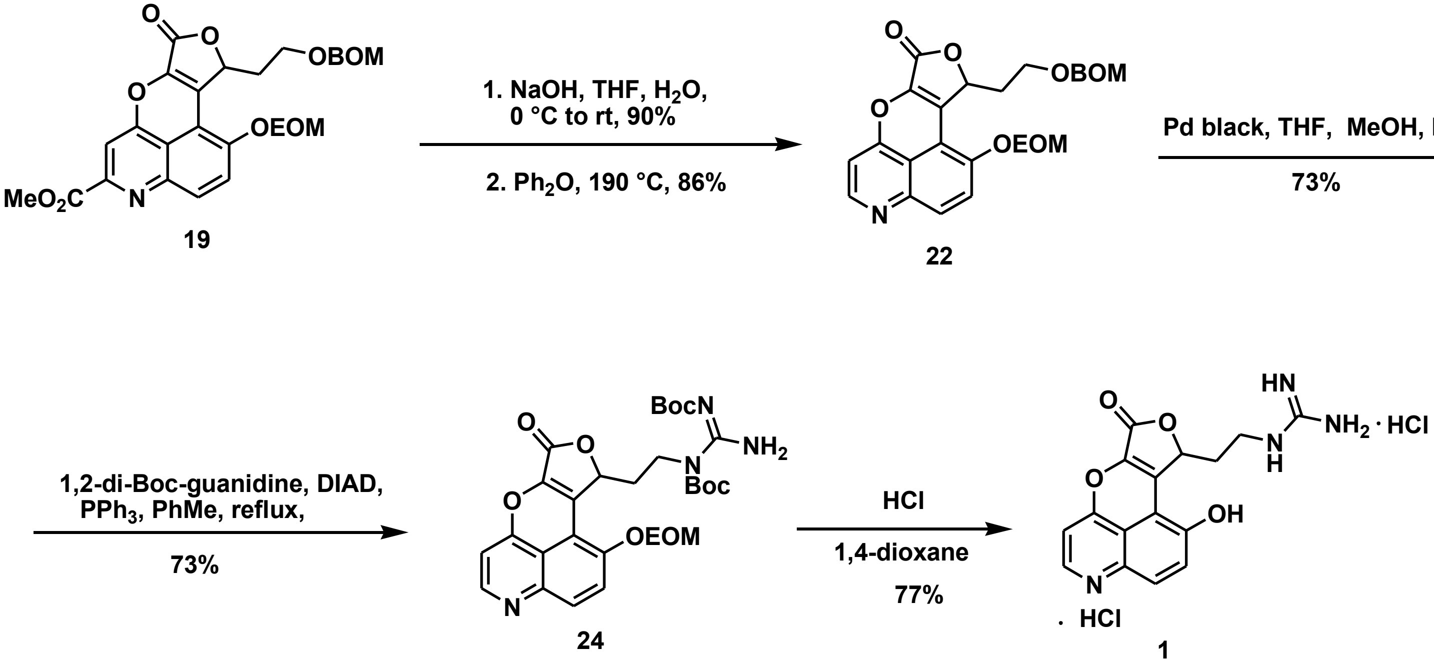
89%

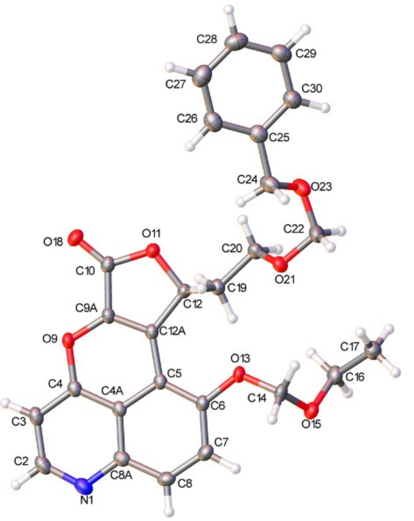
2



X-ray crystal structure of 21

Completion of the Synthesis of Distomadine A





X-ray crystal structure of 22

Conclusions

- We have achieved the first total syntheses of distomadines A and B in 14 steps (3.5% yield) and 13 steps (5.6% yield), respectively
- The key intermediate structures were confirmed by X-ray crystallography.
- Highlight of this synthesis routes were:

  the construction of the butenolide by Suzuki cross-coupling
  oxidation of the resulting alkene
  the intramolecular aldol lactonization sequence

Thanks!