Syntheses of Xanthofulvin and Vinaxanthone, Natural Products Enabling Spinal Cord Regeneration

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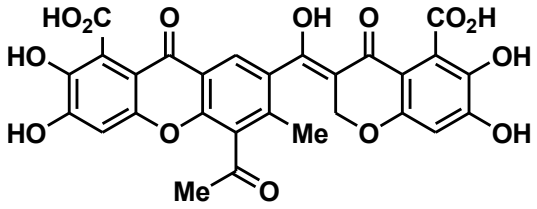
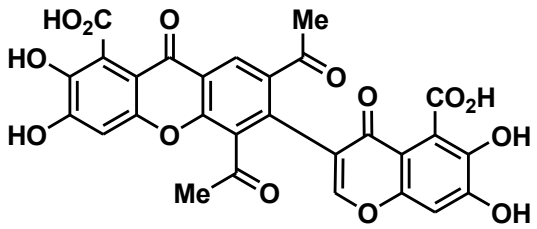


xantofulvin (1)

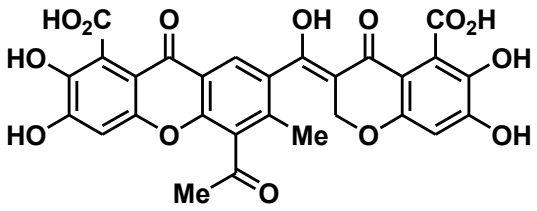


vinaxanthone (2)

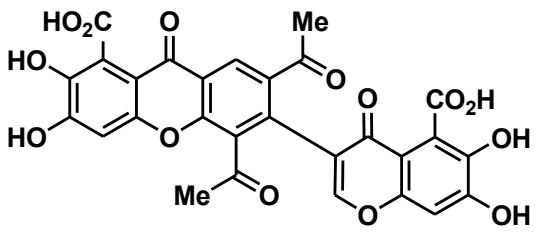
Feng Zhang
Wipf Group Current Literature
April 20, 2013

Introduction

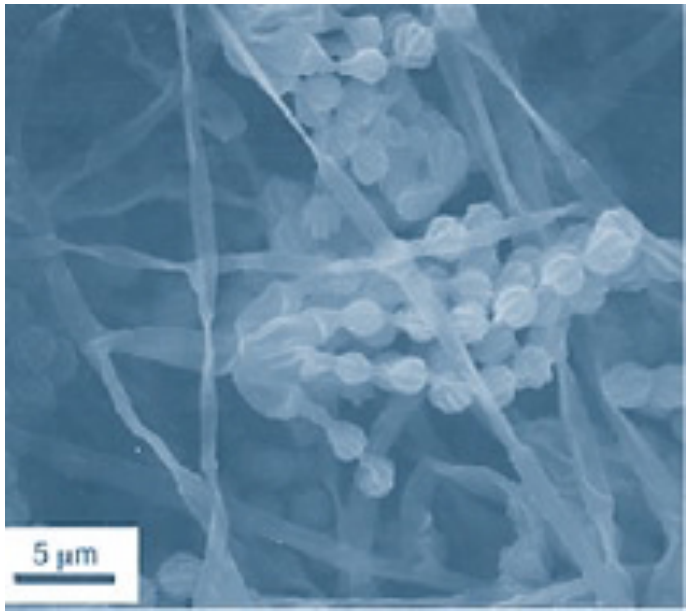
- The failure of neurons in the central nervous system (CNS) to undergo regeneration following injury accounts for the permanent and debilitating effects that accompany spinal cord injury, for which there is no cure.
- Gene therapy, biologics, and stem-cell-based approaches have received considerable attention in promoting CNS regeneration
- The delivery of drugs directly into the spinal cavity through spinal injection can expedite small-molecule-based drug development.
- Moreover, a variety of hydrogels and other polymers for continuous drug delivery, developed specifically for spinal cord therapy, when coupled with a validated small molecule will provide a unique and promising platform for therapeutic development.



xantofulvin (1)



vinaxanthone (2)



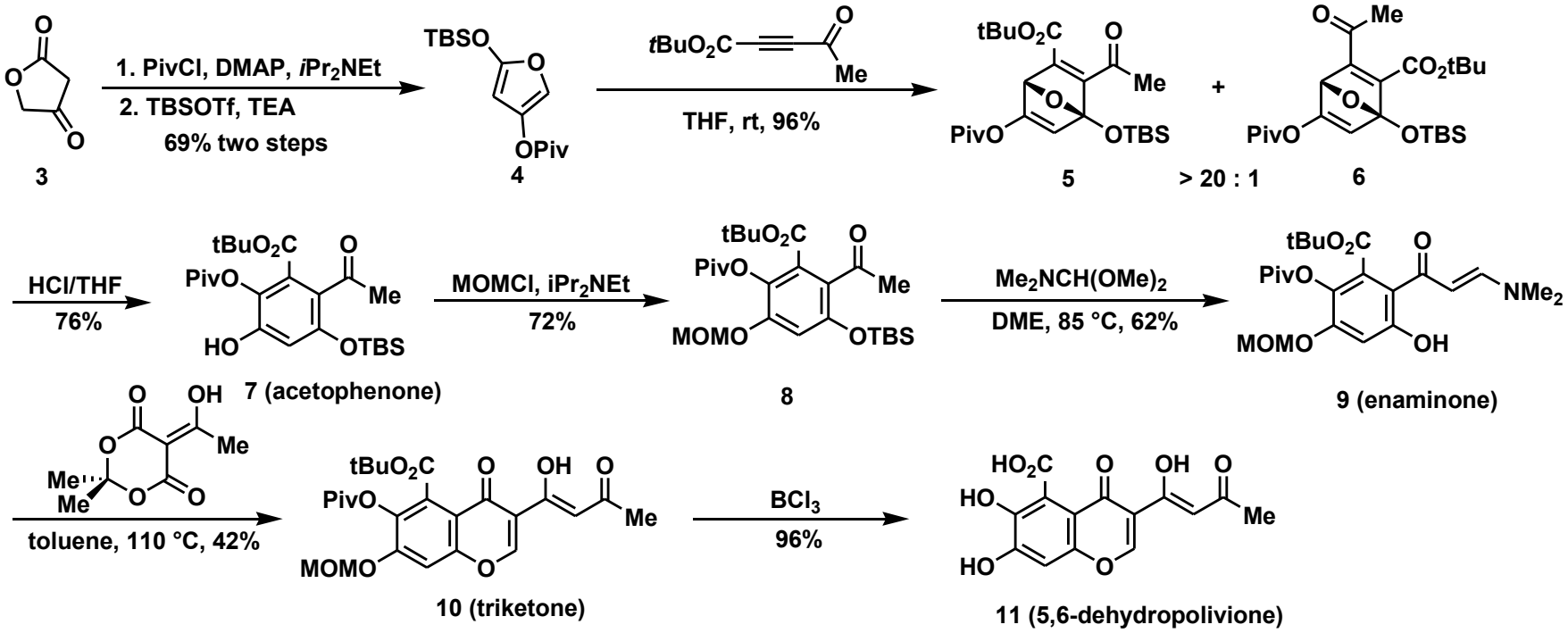
Strongly block the effects of the inhibitor of axonal regeneration semaphorin3A (Sema3A) with no observable cytotoxicity at concentrations above 1000 times the effective dose.

Animal studies of xanthofulvin have demonstrated remarkable effects after complete spinal cord transection.

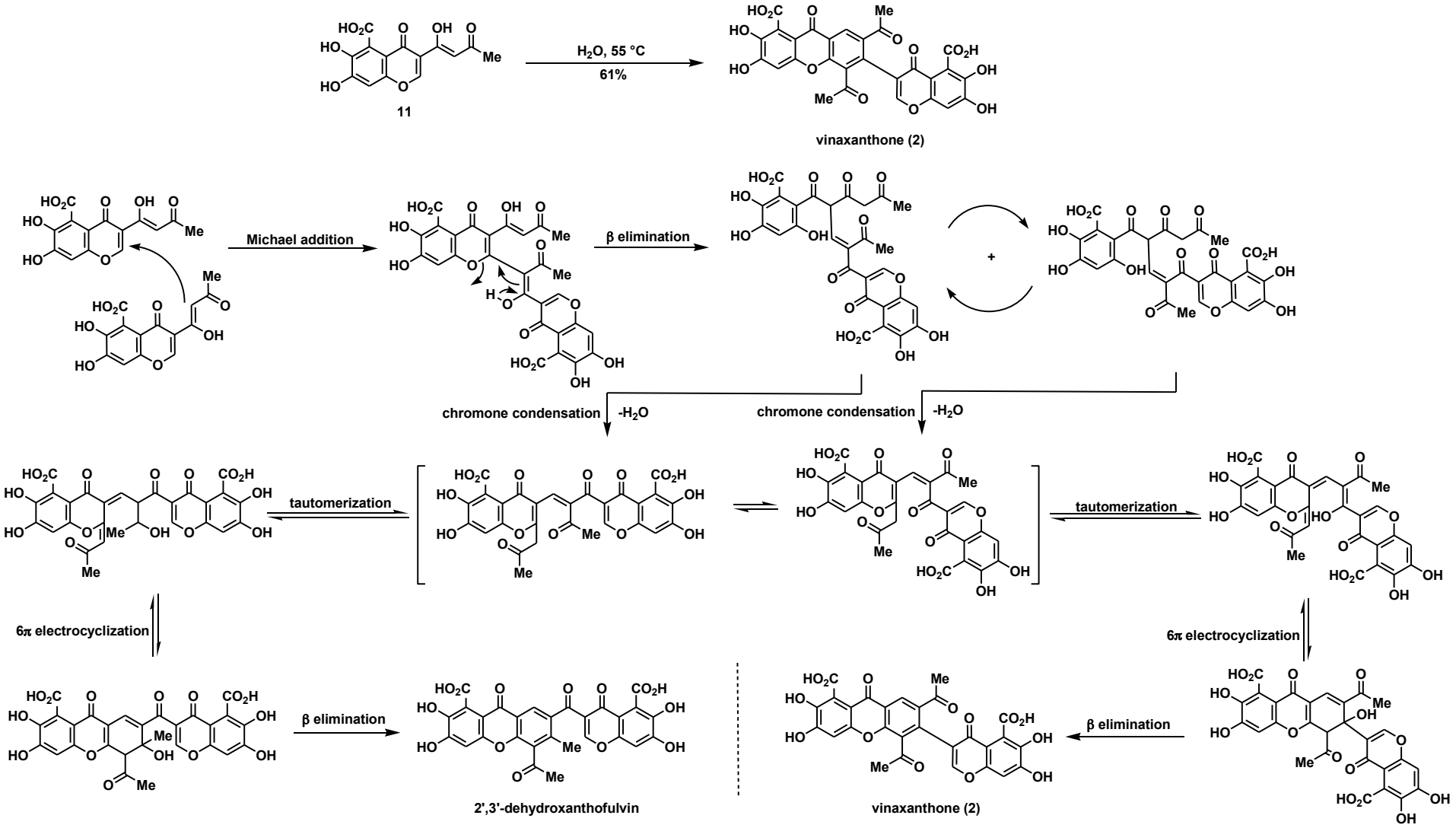
Scanning electron micrograph of *Penicillium* sp. SPF-3059

Tetrahedron Lett. 1991, 32, 4737 – 4740; Antibiot. 2003, 56, 610 – 616.
Sumitomo Kagaku 2005, 1–8; Nat. Med. 2006, 12, 1380 – 1389.

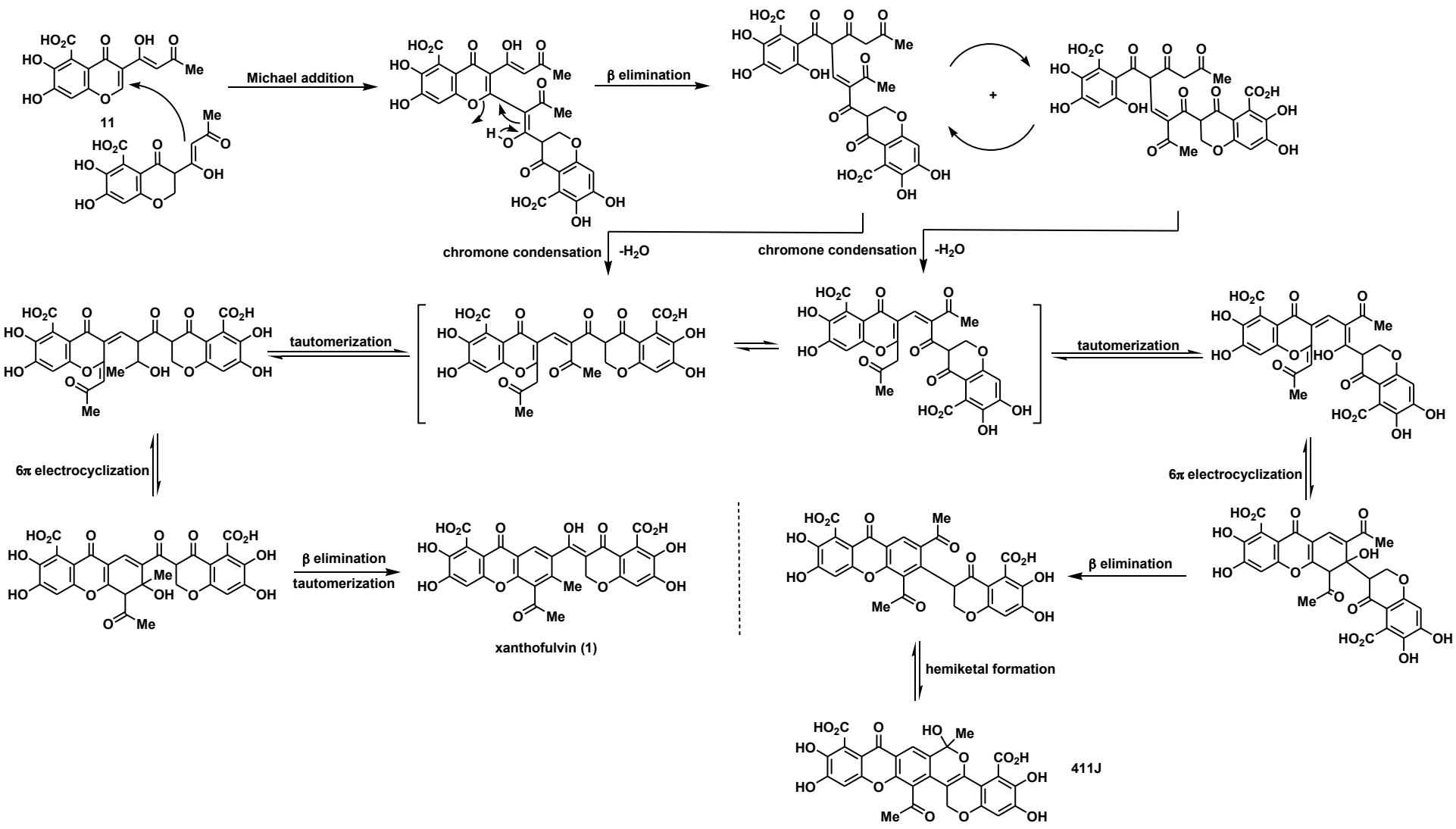
Synthesis of 5,6-dehydropolivione (11)



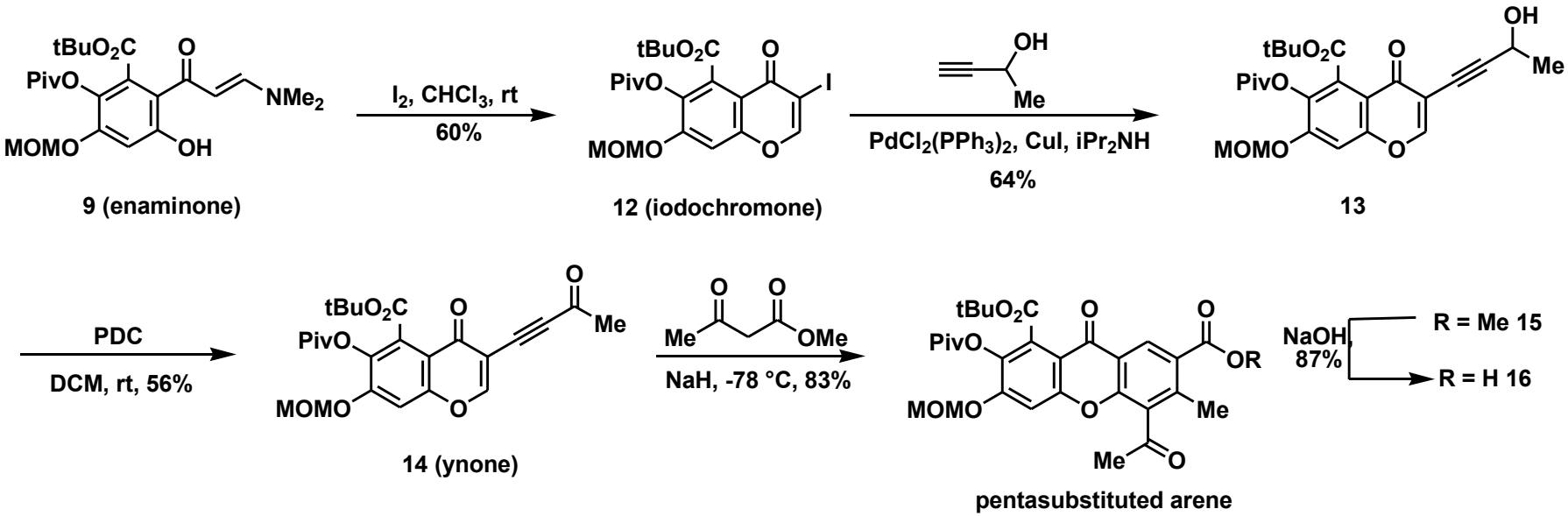
Proposed dimerization of 5,6-dehydropolivione (11) generating vinaxanthone (2)



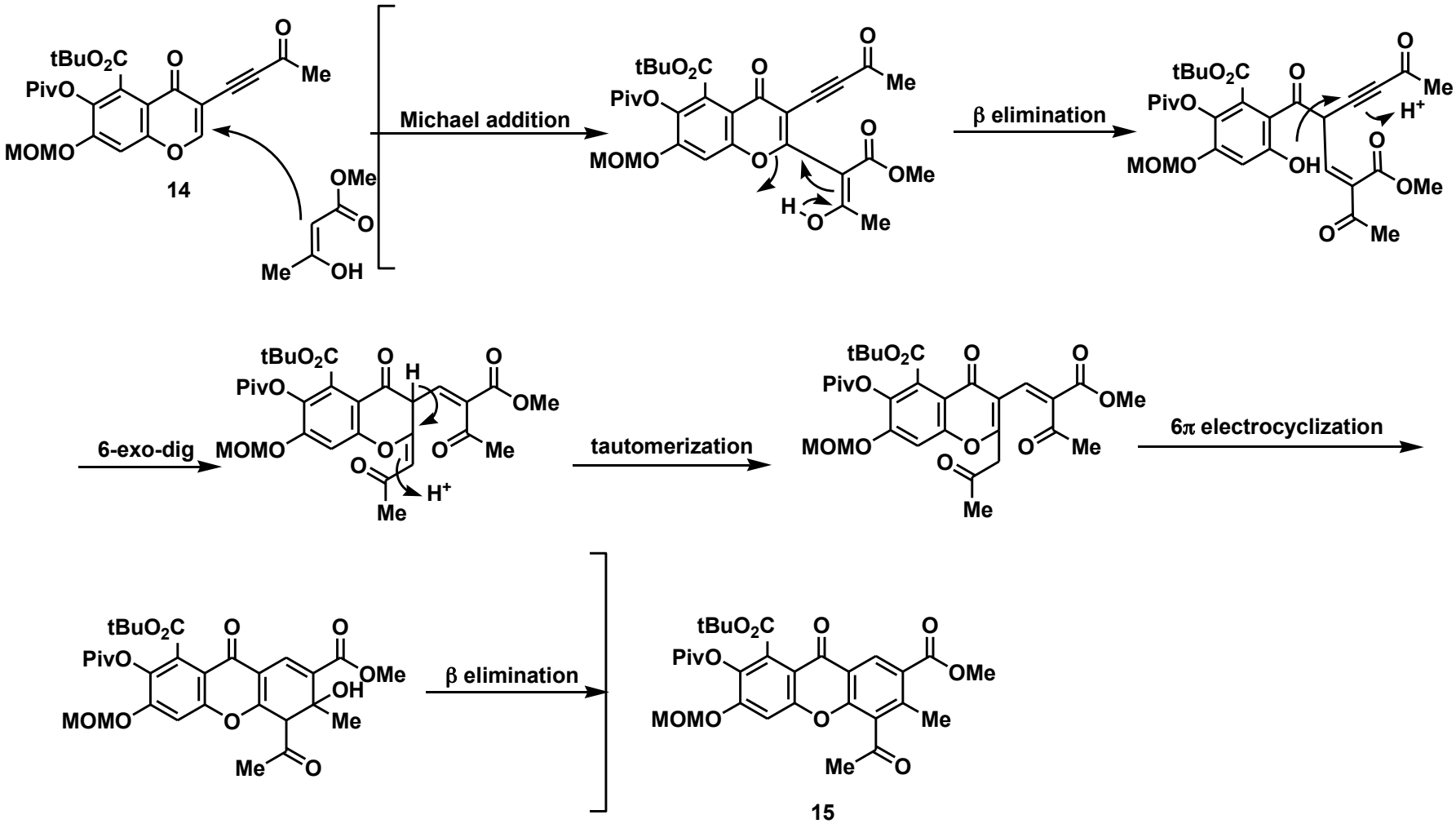
Proposed reaction of Polivione with 5,6-Dehydropolivione



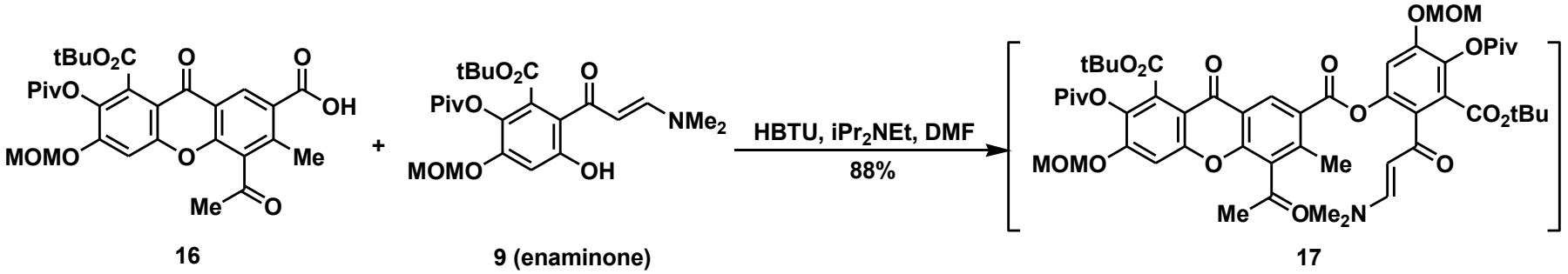
Synthesis of intermediate 15



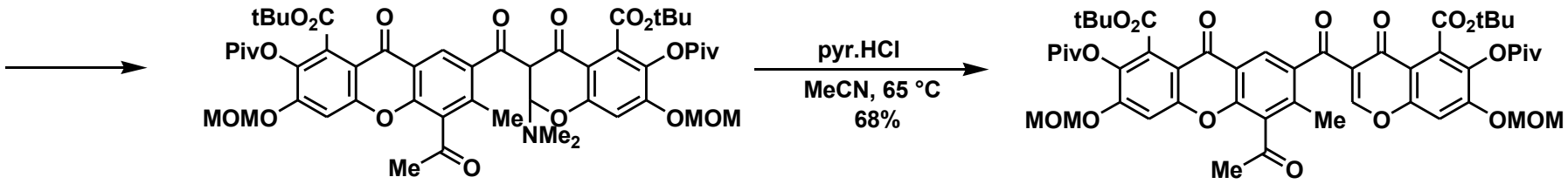
Proposed mechamism of ynone (14) generating intermediate (15)



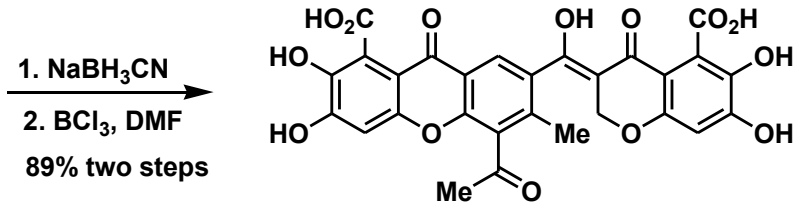
Completion of the synthesis of xanthofulvin (1)



16 + 9 (enaminone) → 17

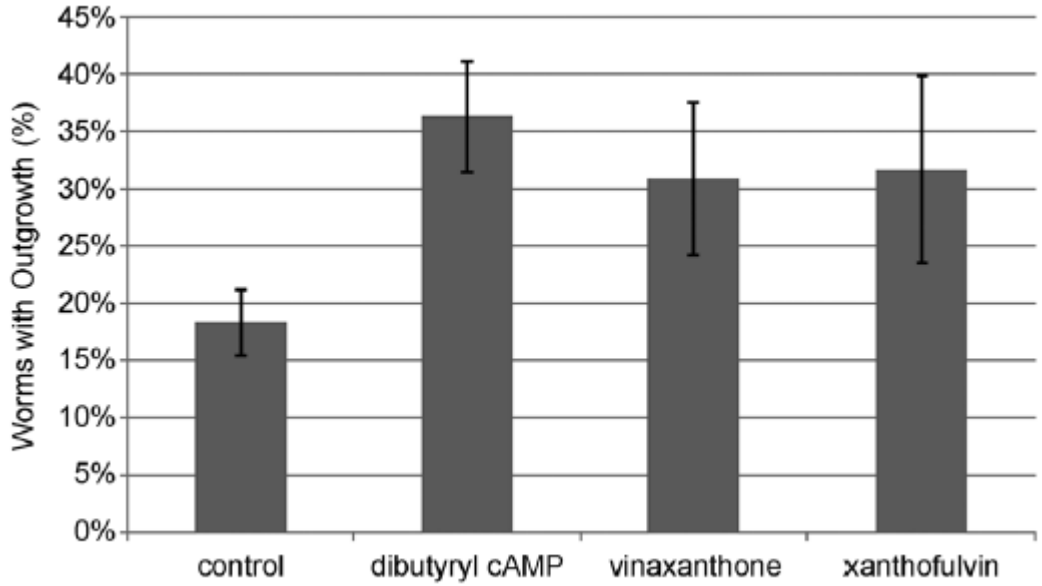


18 (diketone) → 19



xantofulvin (1)

Outgrowth of GFP-labled cholinergic neurons in vivo in C. elegans after treatment with dibutyryl cAMP, xanthofulvin, and vinaxanthone.



Control: 0.2% DMSO in M9 buffer

Conclusions

- The first report of the total synthesis of natural product xanthofulvin.
- The steps for total synthesis of vinaxanthone are shorter than previous medthods
- A highly regioselective Diels–Alder reaction of an ynone ester.
- Tandem reaction sequences for the formation of vinaxanthone from 5,6-dehydropolivione.
- An HBTU-mediated coupling of carboxylic acid derivative and ortho hydroxy enaminone with subsequent O-to-C transfer, bringing two functionalized fragments together

Thanks!