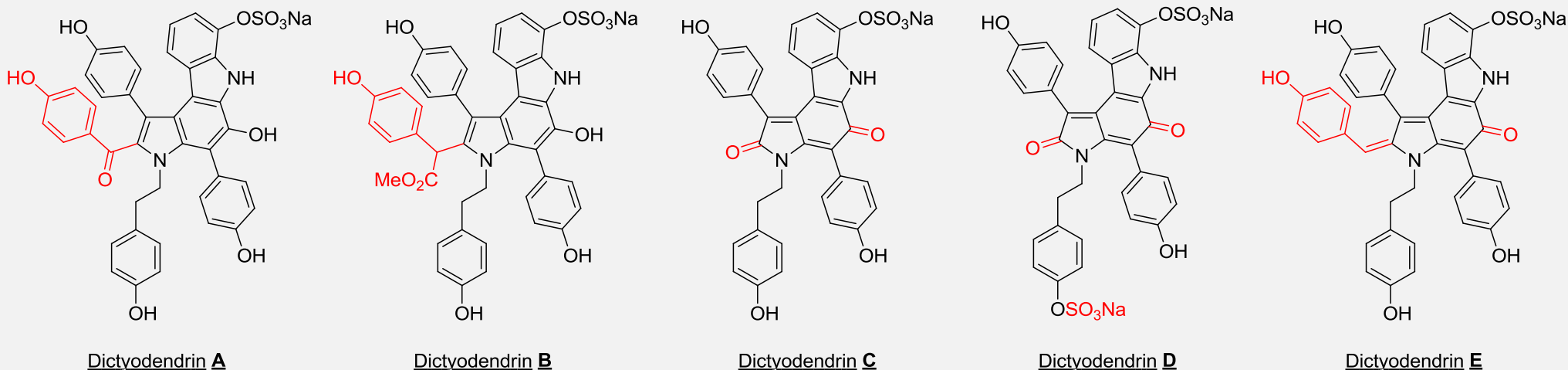


Total synthesis of Dictyodendrin B based on sequential C-H functionalization

Proposed by Amélie CHABRIER, 1st year PhD student, CoSMIT.

According to Matthew J. Gaunt *et al.* synthesis (*Angew. Chem. Int. Ed.* **2015**, *54*, 1-6)

Dictyodendrins (**A** to **E**) are isolated from the marine sponge *Dictyodendrilla verongiformis* collected in southern Japan by Fusetani *et al.* in 2003. These alkaloids were claimed to be the first marine natural products with telomerase inhibitory properties (100% inhibition at 50 $\mu\text{g/mL}$ concentration) and have received significant interest within the scientific community owing to their potential as chemotherapy agents and neurodegenerative probes.

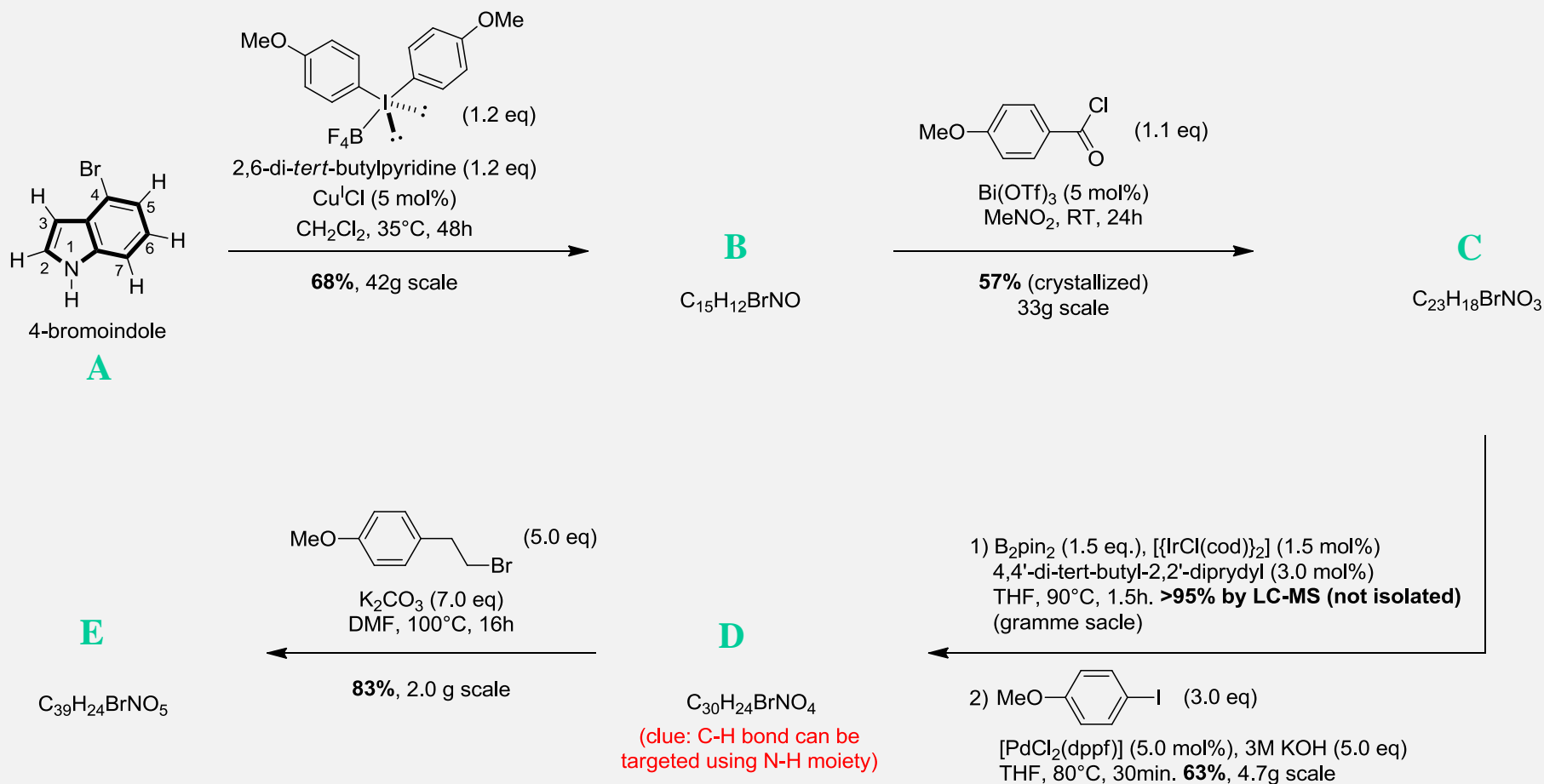


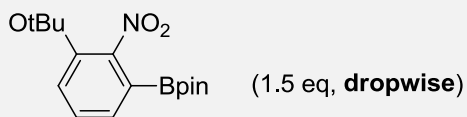
Their complex poly(hetero)aromatic architecture has inspired a number of elegant total syntheses from the groups of Fürstner (*J. Am. Chem. Soc.* **2006**, *128*, 8087-8094), Iwoa and Ishibashi (*Tetrahedron Lett.* **2010**, *51*, 533-536), Tokuyama (*Angew. Chem. Int. Ed.* **2010**, *49*, 5925-5929), and Jia (*Eur. J. Org. Chem.* **2014**, *26*, 5735-5748).

The last total synthesis is the purpose of the present exercise. M. J. Gaunt *et al.* exploited selective reactions based on direct transformation of C-H bonds into useful functional groups and enabled the gram-scale synthesis of the Dictyodendrin **B**.

Questions:

- 1) Find structures of **B**, **C**, **D**, **E**, **F**, **G**, and **H**.
- 2) Propose a catalytic cycle for the Cu^I-catalyzed C₃ C-H arylation (first step of the total synthesis).





[PdCl₂(dppf) (5.0 mol%)
K₂CO₃ (aq) (5.0 eq.)
Dioxane, 90°C, 20h

E

C₃₉H₃₄BrNO₅

93%, 1.5 g scale

F

C₄₉H₄₆BrN₂O₈

1) NBS (1.15 eq),
DMF, RT, 24h
>95% by LC-MS (not isolated).

2) NaOMe (30.0 eq.),
Cu^I (3.0 eq.), DMF, 80°C, 18.5h.
81%, 1.5g scale

C₅₀H₄₈BrN₂O₉

(exclusive selective reaction at
the C₆ position of the indole)

G

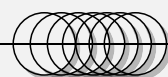
1) Pd(OH)₂ (10 mol%)
10 bar H₂, MeCN, 24h
2) AcOH (30 eq), tBuONO (1.5 eq)
TMSN₃ (1.2 eq), RT, 20 min

95%, 1.3 g scale

H

C₅₀H₄₈BrN₄O₇

Dioxane, 180°C, 30 min



62%, 1.5 g scale

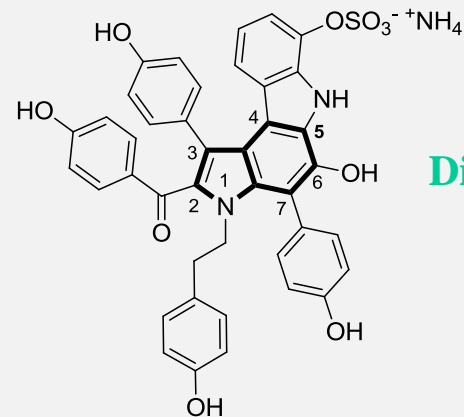
Continuous flow
no chromatography

I

1) BCl₃ (2.5 eq.), C₆HMe₅ (3 eq.)
CH₂Cl₂, -78°C, 25 min, **92%**
2) Cl₃CCH₂OSO₂Cl (2 eq.), DABCO (3 eq.)
CH₂Cl₂, RT, 2h, **93%**

3) BCl₃ (24 eq.), nBu₄Ni (24 eq.)
CH₂Cl₂, 0°C to RT, 1.5h, **67 %**
4) Zn dust (4 eq.), HCO₂NH₄ (6 eq.)
MeOH, RT, 2h, **98%**

(Tokuyama *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 5925 –5929)



Dictyodendrin B