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

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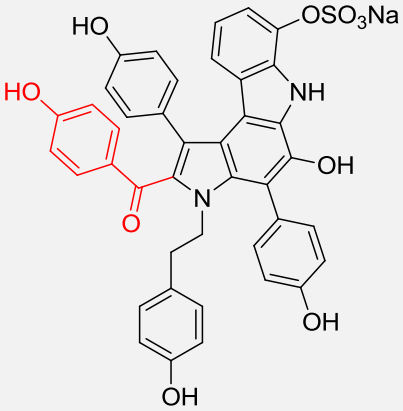
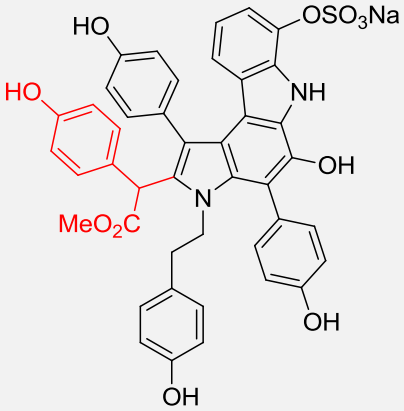
According to Matthew J. Gaunt *et al.* synthesis (*Angew. Chem. Int. Ed.* **2015**, *54*, 1-6)

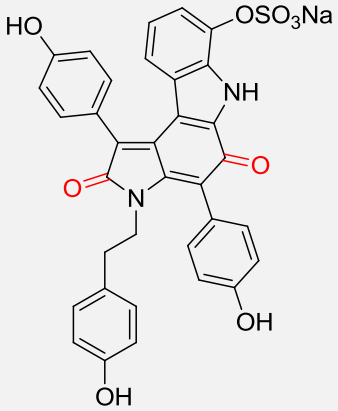
Dictyodendrins (**A** to **E**) are isolated from the marine sponge *Dictyodendrilla verongiformis* collected in southern Japan by Fusetani *et al.* in 2003. These alkaloids were claimed to be the first marine natural products with telomerase inhibitory properties (100% inhibition at 50 íg/mL concentration)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



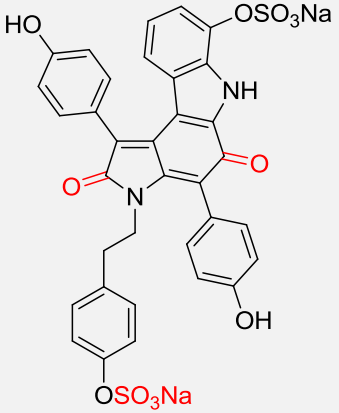
Dictyodendrin **A**



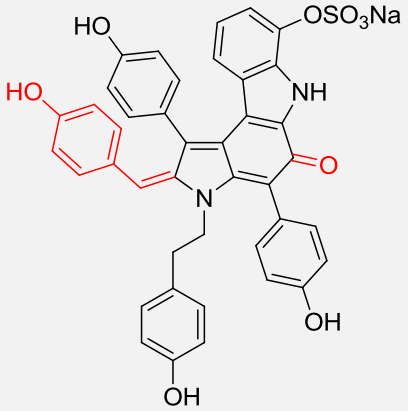
Dictyodendrin **B**



Dictyodendrin **C**



Dictyodendrin **D**



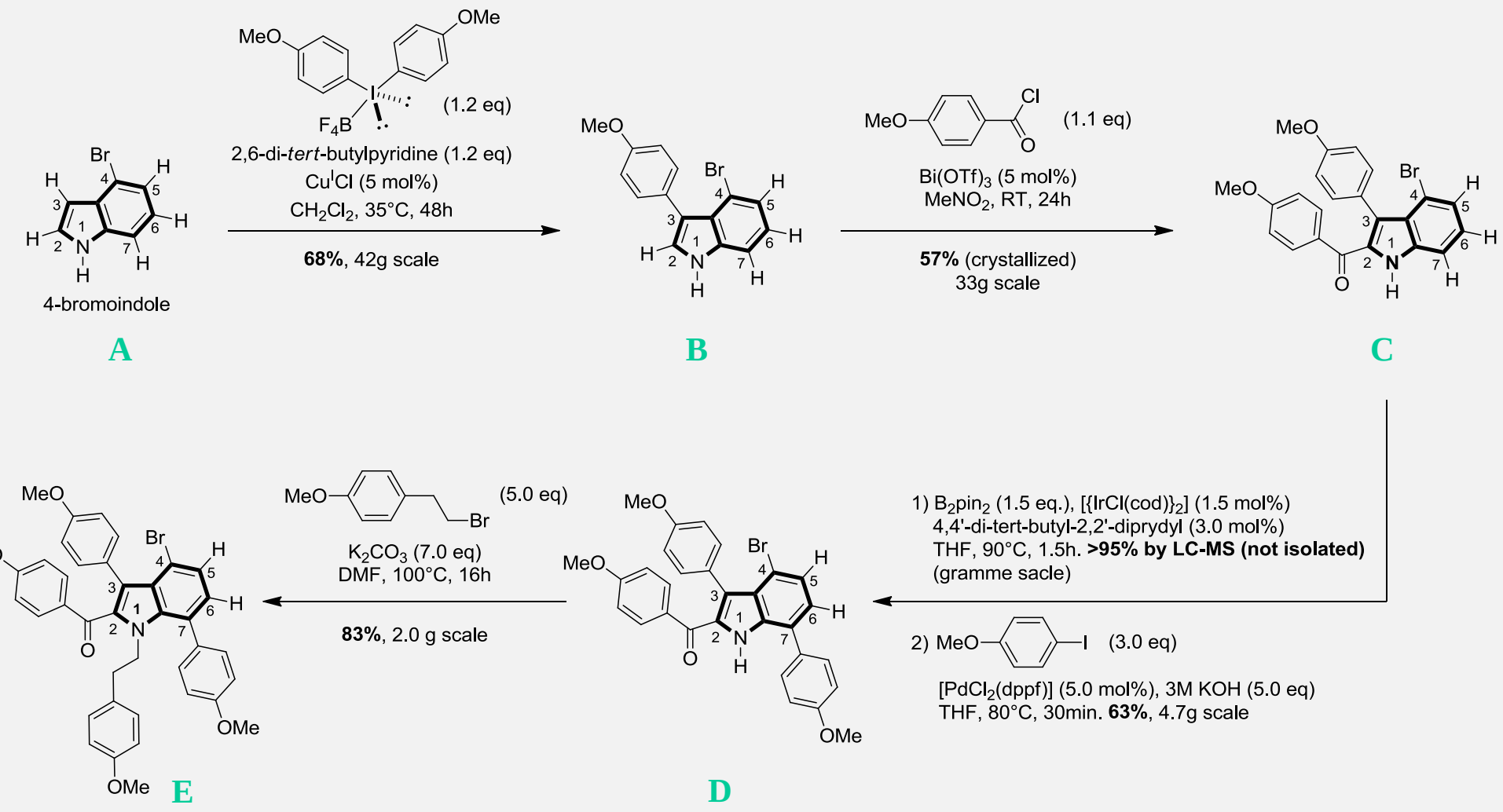
Dictyodendrin **E**

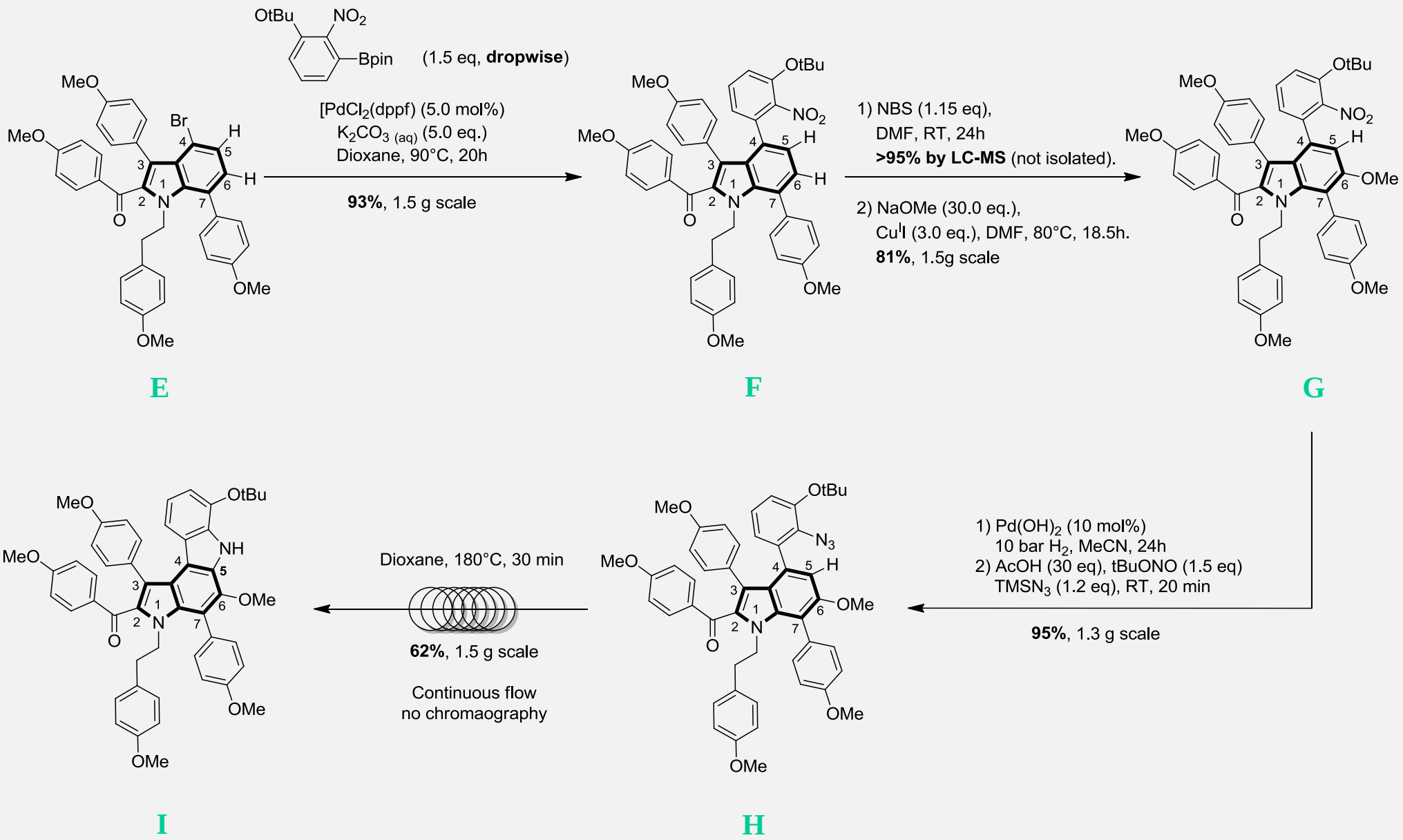
Their complex poly(hetero)aromatic architecture has inspired a number of elegant total syntheses from the groups of Fürstner (*J. Am. Chem. Soc.* **2006**, *128*, 8087-8094), Iwoa and Ishibashi (*Tetrahedron Lett.* **2010**, *51*, 533–536), Tokuyama (*Angew. Chem. Int. Ed.* **2010**, *49*, 5925 –5929),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

Answers:

1) **Structures of B, C, D, E, F, G, and H.**




OtBu
NO2
Bpin
(1.5 eq, dropwise)
[PdCl2(dppf) (5.0 mol%)
K2CO3 (aq) (5.0 eq.)
Dioxane, 90°C, 20h
93%, 1.5 g scale
1) NBS (1.15 eq),
DMF, RT, 24h
>95% by LC-MS (not isolated).
2) NaOMe (30.0 eq.),
CuI (3.0 eq.), DMF, 80°C, 18.5h.
81%, 1.5g scale
E
F
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
Dioxane, 180°C, 30 min
62%, 1.5 g scale
Continuous flow
no chromaography
H
I

2) Catalytic cycle for the Cu^{I}-catalyzed C_3 C-H arylation (first step of the total synthesis).