H. W. PAULS* ET AL. (UNIVERSITY HEALTH NETWORK, TORONTO, CANADA AND CELTIC CATALYSTS, DUBLIN, IRELAND)
The Discovery of Polo-Like Kinase 4 Inhibitors: Identification of (1R,2S)-2-(3-((E)-4-((cis)-2,6-Dimethylmorpholino)methyl)styryl)-1H-indazol-6-yl)-5′-methoxyspirocyclopropane-1,3′-indolin-2′-one (CFI-400945) as a Potent, Orally Active Antitumor Agent

Synthesis of Polo-Like Kinase 4 Inhibitor CFI-400945

**Significance:** CFI-400945 is an inhibitor of Polo-like kinase 4 (PLK4) that is a lead for the treatment of various cancers. The synthesis depicted features a diastereoselective one-pot double S_{N}2 displacement reaction (E→H) for the creation of the cyclopropane ring. The authors propose that the stereoselectivity of the cyclopropanation is a consequence of π–π interactions that stabilize conformer G.

**Comment:** Attempted hydrogenolysis of the benzyl protecting groups from a close relative of H was accompanied by partial ring opening of the cyclopropane. However, the benzyl groups were removed cleanly using potassium tert-butoxide in an oxygen-saturated solution in THF and DMSO (R. M. Williams, E. Kwast Tetrahedron Lett. 1989, 30, 451).

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**Synthesis of PLK4 Inhibitor CFI-400945**

- **A** → **B** (1.2 equiv)
  - Pd(PPh_{3})_{4} (0.05 equiv)
  - K_{2}CO_{3} (3.0 equiv)
  - DME–H_{2}O (3:1), 80 °C, 7 h
  - mp not reported
  - 65% (1.05 mol scale)
  - Suzuki–Miyaura reaction

- **B** → **C**
  - (DHQ)_{2}PHAL (0.005 equiv)
  - K_{2}OsO_{4}·2H_{2}O (0.005 equiv)
  - K_{3}Fe(CN)_{6} (3.0 equiv)
  - K_{2}CO_{3} (3.0 equiv)
  - t-BuOH–H_{2}O (1:1), 0 °C, 5 h
  - mp not reported
  - 68% (410 mmol scale)
  - Sharpless asymmetric dihydroxylation

- **C** → **D**
  - MsCl (2.1 equiv)
  - Et_{3}N (2.5 equiv)
  - CH_{2}Cl_{2}, 0 °C, 30 min
  - mp not reported
  - 87% (500 mmol scale)
  - 99% ee

- **D** → **E**
  - NaH (2.1 equiv)
  - THF, 0 °C, 3 h
  - (224 mmol scale)
  - mp not reported
  - >99.9% ee

- **E** → **F** (1.0 equiv)
  - MsO
  - NaO
  - H
  - O
  - mp not reported

- **F** → **G**
  - t-BuOK (20 equiv)
  - CH_{2}Cl_{2}, 0 °C, 30 min
  - mp not reported
  - 87% (500 mmol scale)

- **G** → **H**
  - t-BuOK (20 equiv)
  - DMSO (19 equiv)
  - THF, 0 °C to r.t., o/n
  - mp not reported
  - 95% (820 mmol scale)

- **H** → **I** (1.3 equiv)
  - I_{2}
  - K_{2}CO_{3} (2.0 equiv)
  - DMF–MeOH (2:1), r.t., 6 h
  - mp not reported
  - 95% (820 mmol scale)

- **I** → **J** (1.1 equiv)
  - Na_{2}CO_{3} (2.0 equiv)
  - Pd(PPh_{3})_{4} (0.03 equiv)
  - Dioxane–H_{2}O, 85 °C, 24 h
  - mp not reported
  - 48% (46 mmol scale)

- **J** → **K** (1.1 equiv)
  - Na_{2}CO_{3} (2.0 equiv)
  - Pd(PPh_{3})_{4} (0.03 equiv)
  - dioxane–H_{2}O, 85 °C, 24 h
  - mp not reported
  - 48% (48 mmol scale)

- **K** → **L**
  - mp not reported
  - 95% (820 mmol scale)

- **L** → **M**
  - mp not reported
  - 95% (820 mmol scale)

- **M** → **N**
  - mp not reported
  - 95% (820 mmol scale)

- **N** → **O**
  - mp not reported
  - 95% (820 mmol scale)

- **O** → **P**
  - mp not reported
  - 95% (820 mmol scale)

- **P** → **Q**
  - mp not reported
  - 95% (820 mmol scale)

- **Q** → **R**
  - mp not reported
  - 95% (820 mmol scale)

- **R** → **S**
  - mp not reported
  - 95% (820 mmol scale)

- **S** → **T**
  - mp not reported
  - 95% (820 mmol scale)

- **T** → **U**
  - mp not reported
  - 95% (820 mmol scale)

- **U** → **V**
  - mp not reported
  - 95% (820 mmol scale)

- **V** → **W**
  - mp not reported
  - 95% (820 mmol scale)

- **W** → **X**
  - mp not reported
  - 95% (820 mmol scale)

- **X** → **Y**
  - mp not reported
  - 95% (820 mmol scale)

- **Y** → **Z**
  - mp not reported
  - 95% (820 mmol scale)

- **Z** → **CFI-400945**
  - mp not reported
  - 48% (46 mmol scale)

- **CFI-400945**
  - mp not reported