Enantioselective Total Synthesis of (+)-Wortmannin


- Belongs to furanosteroid structural class of natural products;
- Potent phosphonoinositide 3-kinase (PI3K) inhibitor;
- 17-β-hydroxywortmannin (24) displayed increased potency against PI3Ks than (+)-Wortmannin (1);
- Two previous syntheses reported by Shibasaki group;
- Synthesis of closely related natural products (+)-Halenaquinone, (+)-Xestoquinone, and (−)-Hibiscone C relied on intramolecular Heck reaction;
- Allowed for optimization of a Pd-catalyzed cascade reaction and Friedel-Crafts alkylation that would ultimately establish 4 of the 5 rings;
- Synthesis completed in 18 steps.
Retrosynthesis

(+) Wortmannin (1) ➔ Oxidation ➔ Oxidation/Lactonization ➔ Friedel-Crafts Alkylation

11 OTBS ➔ 12 ➔ HO-SnBu3 ➔ 10 ➔ 9 Alkylation ➔ 8 Sharpless Epoxidation ➔ Stille Cross-Coupling
Forward Synthesis

13 to 15: Pd-catalyzed decarboxylative alkylation

17 to 9: Nickel boride 1,4-reduction

\[ 8 \text{NaBH}_4 + 4 \text{NiCl}_2 + 18 \text{MeOH} \rightarrow 2 \text{Ni}_2\text{B} + 6 \text{B(OH)}_3 + 8 \text{NaCl} + 25 \text{H}_2 \]
9 to 18: Vinyl triflate formation

9 to 18: Modified Stille Cross-Coupling

**Forward Synthesis**

18 to 8: Sharpless epoxidation

8 to 20: Lewis-acid catalyzed epoxide opening
Forward Synthesis

20 to 6: Alcohol oxidation

(a) TEMPO, Phl(OAc)₂
DCM, rt, 20 h
(b) NaClO₂, NaH₂PO₄ 2H₂O, 
2-methyl-2-butene
/iBuOH:THF:H₂O (3:2:1), rt, 1.5 h
(c) CMPI, Et₃N
DCM, rt, 12 h

20 to 6: Pinnick oxidation

\[ \text{ClO}_2^- + \text{H}_2\text{PO}_4^- \]
Forward Synthesis

20 to 6: Lactone formation

6 to 21: Epoxide formation

21 to 5: Allylic oxidation

(a) TEMPO, PhI(OAc)₂, DCM, rt, 20 h
(b) NaClO₂, NaH₂PO₄ 2H₂O, 2-methyl-2-butene, tBuOH:THF:H₂O (3:2:1), rt, 1.5 h
(c) CMPI, Et₃N, DCM, rt, 12 h

H₂O₂, urea, TFAA, Na₂CO₃
DCM, 0 °C, 1.5 h

NBS, AIBN
CCl₄, reflux, 1.5 h
then AgBF₄, Et₃N
DMSO, rt

MeO
OTBS

MeO
OTBS

MeO
OTBS

MeO
OTBS

MeO
OTBS

MeO
OTBS

20

H₂O₂, urea, TFAA, Na₂CO₃
DCM, 0 °C, 1.5 h

NBS, AIBN
CCl₄, reflux, 1.5 h
then AgBF₄, Et₃N
DMSO, rt

MeO
OTBS

MeO
OTBS

MeO
OTBS

MeO
OTBS

MeO
OTBS

21

21

21

21

21
Forward Synthesis

25 to 26: DMP oxidation
Forward Synthesis

26 to 27: Epoxide opening

[Chemical and reaction mechanisms for the Forward Synthesis are depicted in the image, including reactions with reagents such as Et$_3$N, DMP, and Ac$_2$O.]