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The First Chemical Synthesis of Wortmannin by Starting from Hydrocortisone

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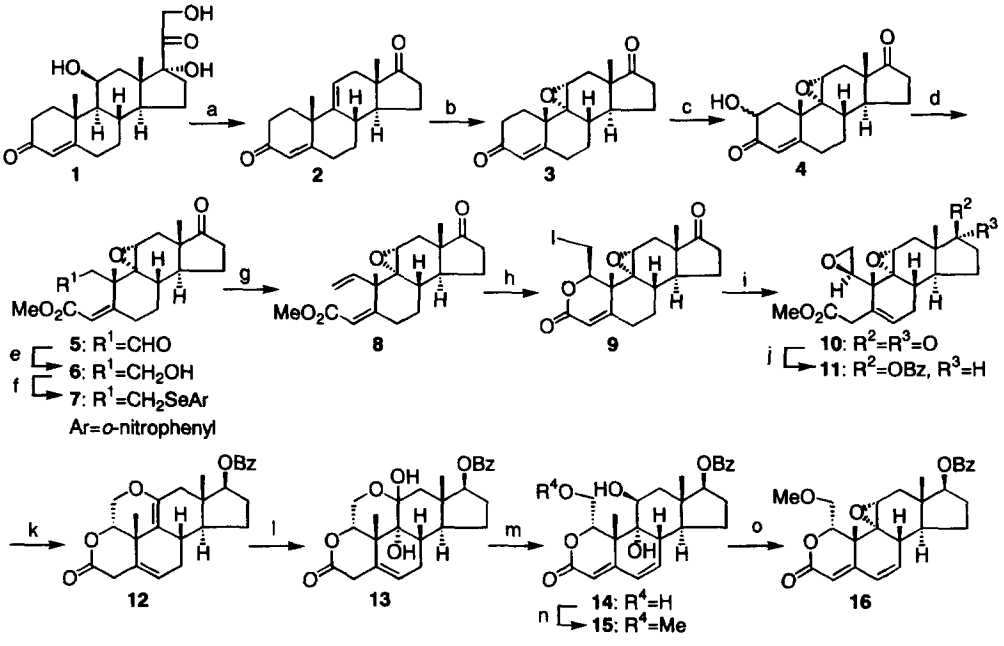
Abstract: The first chemical synthesis of wortmannin, a potent and specific inhibitor of PI 3-kinases, was achieved by starting from commercially available and optically pure hydrocortisone.

Wortmannin (**25**) is an antifungal and anti-inflammatory antibiotic isolated from culture filtrates of several *Penicillium* and *Myrothecium* species.[1,2] Quite recently, wortmannin (**25**) has been found to be a potent and specific inhibitor of PI 3-kinases (IC_{50} = 5 nM) that is believed to bind to the enzymes in an irreversible, presumably covalent manner.[3] We previously reported the synthesis of 17β-hydroxy-16α-[^{125}I]-iodowortmannin as a sensitive labeling agent for PI 3-kinases.[4] As an extension of this research, we undertook synthetic studies on wortmannin (**25**). We report here the first chemical synthesis of wortmannin (**25**) by starting from hydrocortisone (**1**). The structure of **25** is similar to that of steroids and includes a strained and highly reactive furanocyclohexadienone-lactone moiety.

Commercially available and optically pure hydrocortisone (**1**) was selected as a reasonable starting material based on a retrosynthetic analysis of **25**. Hydrocortisone (**1**) was reduced with $NaBH_4$ and then treated with $NaIO_4$ and TsOH to give **2** (90%).[5] Compound **2** was subjected to epoxidation with mCPBA to give **3** (80%),[6] which was chemoselectively converted to an enol silyl ether. Successive treatment of the enol silyl ether with mCPBA and citric acid gave **4** (55% from **3**). Exposure of **4** to $NaIO_4$ followed by reaction with ethereal diazomethane gave **5** (83%), which was further reduced with lithium tri-*tert*-butoxyaluminohydride (LTBA) to give **6** (71%). Treatment of **6** with *o*-nitrophenyl selenocyanate and tributylphosphine gave **7** (89%), which was converted to **8** with 30% H_2O_2 (85%).

With compound **8**, the stage was set for the crucial stereoselective lactonization to construct a lactone ring. First, **8** was treated with iodine and $NaHCO_3$ in CH_2Cl_2 at room temperature for 2 d. Under these conditions, however, only the undesired iodo-lactone **9** was obtained (100%). The stereochemistry of **9** was determined by NOE experiments using **26**.[7] Several reactions using either mCPBA or OsO_4 were also carried out to functionalize the terminal olefin chemoselectively. However, these attempts were unsuccessful owing to the low reactivity at the terminal olefin. Thus, inversion of the newly formed chiral center was required for the successful chemical synthesis of **25**. Iodo-lactone **9** was first treated with NaOMe in MeOH to give **10** (90%). At this stage, the ketone functionality was protected as a benzoate **11** (94%) by reduction with LTBA followed by reaction with benzoyl chloride. Inversion of the configuration was best achieved by

exposure of **11** to dihydroquinone and 10-camphorsulfonic acid in refluxing benzene to give **12** (56%).[8] The stereochemistry of **12** was determined by NOE experiments.[9] Enol ether **12** was subjected to epoxidation with mCPBA and then treated with 2 N HCl to give lactol **13** (61%). Reduction of **13** with $Me_4NBH(OAc)_3$[10] and subsequent oxidation with DDQ gave **14** (68%), which was converted to **15** by treatment with CH_3I and Ag_2O (94%). The stereochemistry of the two newly formed chiral centers was determined based on two results: 1) the efficient conversion of **15** to epoxide **16** by reaction with methanesulfonyl chloride and triethylamine (92%), and 2) the successful transformation of **16** to wortmannin (**25**) itself (Scheme 1).

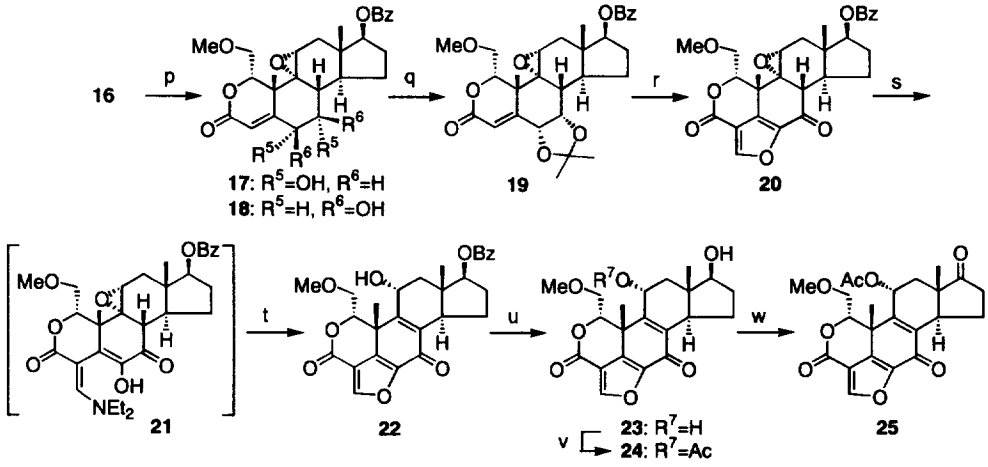


Reagents and conditions: (a) (i) $NaBH_4$, CH_2Cl_2-EtOH (1:1), -10 - -5 °C, 3 h, acetone quench, and then $NaIO_4$, r.t., 1 d; (ii) TsOH, benzene, reflux, 1 d, 90% (2 steps); (b) mCPBA, CH_2Cl_2, -20 → 0 °C, 1 d, 80%; (c) (i) TMSOTf, $^iPr_2NEt$, CH_2Cl_2, -78 °C, 0.5 h; (ii) mCPBA, $KHCO_3$, CH_2Cl_2, -30 °C - -20 °C, 1 h; (iii) citric acid, MeOH, 0 → r.t., 1 h, 55% (3 steps); (d) (i) $NaIO_4$, MeOH-H_2O (1:2), 0 °C, 12 h, r.t., 3 h; (ii) CH_2N_2, $CHCl_3$, r.t., 83% (2 steps); (e) LTBA, THF, -78 → -40 - -35 °C, 4 h, 71%; (f) *o*-nitrophenyl selenocyanate, $^nBu_3P$, THF, 0 → r.t., 1 h, 89%; (g) 30% H_2O_2, THF, 0 → r.t., 18 h, 85%; (h) I_2, $NaHCO_3$, CH_2Cl_2, r.t., 2 d, quant.; (i) NaOMe, MeOH, 0 → r.t., 4 h, 90%; (j) (i) LTBA, THF, 0 °C, 3 h; (ii) BzCl, py, 0 → r.t., 2 h, 94% (2 steps); (k) CSA, dihydroquinone, benzene, reflux, 3 h, 56%; (l) (i) mCPBA, CH_2Cl_2, -30 - -25 °C, 20 h; (ii) 2 N HCl, THF, r.t., 16 h, 61% (2 steps); (m) (i) $Me_4NBH(OAc)_3$, AcOH - CH_3CN (1:1), 0 °C, 2 h; ii) DDQ, dioxane, 80 °C, 4 h, 68%, (2 steps); (n) Ag_2O, MeI - CH_3CN (2:1), r.t., 1 d, 94%; (o) MsCl, Et_3N, CH_2Cl_2, r.t., 92%.

Scheme 1

With epoxide **16** in hand, the construction of a highly reactive furanocyclohexadienone-lactone moiety was then pursued.[11] Toward this end, **16** was subjected to dihydroxylation using OsO_4 and DABCO to give α-diol **17** (47%, 56% based on the recovery of **16**) and β-diol **18** (14%).[12] The α-diol **17**[13] was protected as an acetal (92%).[14] Treatment of **19** with tris(dimethylamino)methane in the presence of DBU and *N,N*-

dimethylformamide dimethyl acetal at 100 °C for 1 h gave the aminomethylene-lactone, which was successively subjected to hydrolysis (2 N HCl) and oxidation (PCC) to give **20**, albeit in low yield (11%).[15] At this stage, we expected that it would be simple to synthesize **22** from **20.** However, this turned out to be the most difficult step in the present synthesis. Compound **20** first had to be transformed into aminomethylene-lactone **21** by exposure to diethylamine in CH_2Cl_2.[16] We were pleased to find that treatment of **21** with DBN in CH_2Cl_2 followed by exposure to 1 N HCl gave **22** [36%, 47% based on the recovery of **20** (22%)]. Again, after opening the furan ring of **22** with diethylamine, a 17-benzoate functionality was deprotected by K_2CO_3 in MeOH and then exposed to 1 N HCl to give **23** (64%). Reaction of **23** with acetic anhydride in pyridine at -20 °C furnished known **24**[17] in 49% yield (72% based on the recovery of **23**), $[\alpha]_D^{28}$ +55 (*c* 0.12, EtOH) [lit.[1], $[\alpha]_D^{20}$ +60 (*c* 0.56, EtOH)]. Finally oxidation of **24** with PCC in CH_2Cl_2 gave wortmannin (**25**) in 73% yield, $[\alpha]_D^{28}$ +88 (*c* 0.17, $CHCl_3$) [lit.[1], $[\alpha]_D^{26}$ +89 (*c* 1.1, $CHCl_3$)], which had spectroscopic properties consistent with the assigned structure and was identical with an authentic sample (Scheme 2).[1]



Reagents and conditions: (p) OsO_4, DABCO, THF, -40 °C, 1 d, 47% (c.y. 56%); (q) PPTS, 2,2-dimethoxypropane, CH_2Cl_2, r.t., 16 h, 92%; (r) (i) DBU, $Me_2NCH(OMe)_2$-$CH(NMe_2)_3$ (1:4), 100 °C, 1 h; (ii) 2 N HCl, THF, r.t., 20 h; (iii) PCC, CH_2Cl_2, r.t., 5 h, 11%, (3 steps); (s) Et_2NH, CH_2Cl_2, r.t., 20 m; (t) (i) DBN, CH_2Cl_2, r.t., 6 h; (ii) 1 N HCl, THF, r.t., 14 h, 36% (c.y. 47%) (3 steps); (u) (i) Et_2NH, CH_2Cl_2, r.t., 10 m; (ii) K_2CO_3, MeOH, r.t., 5 h; (iii) 1 N HCl, THF, r.t., 12 h, 64% (3 steps); (v) Ac_2O, py, -20 °C, 12 h, 49% (c.y. 72%); (w) PCC, CH_2Cl_2, r.t., 2 h, 73%.

Scheme 2

In conclusion, we have achieved the first chemical synthesis of wortmannin (**25**) by starting from optically pure hydrocortisone (**1**). This synthesis still has several drawbacks, such as its low overall yield and its multisteps procedure. However, we believe that the results described here may lead to further progress in this area.

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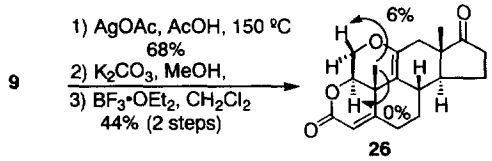
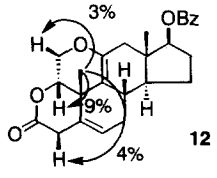
7. The results of the NOE experiments are as follow.



8. Many attempts to invert its configuration without opening an epoxide functionality were unsuccessful.
9. The results of the NOE experiments are as follow.



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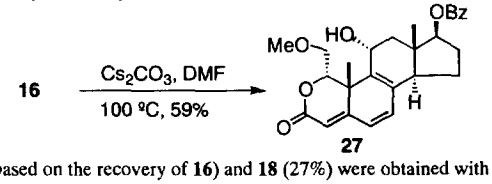
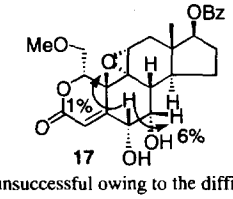
11. The allylic alcohol **27** was readily formed by treatment of **16** with base. However, conversion of **27** to **25** was unsuccessful.



12. Compounds **17** (37%, 46% based on the recovery of **16**) and **18** (27%) were obtained with OsO_4 and pyridine.
13. The stereochemistries of **17** and **18** were determined by NOE experiments.



14. Conversion of **18** to wortmannin (**25**) was unsuccessful owing to the difficulty in forming a furan ring.
15. For a synthetic approach to **25**, see: Broka, C. A.; Ruhland, B. *J. Org. Chem.* **1992**, *57*, 4888 - 4894.
16. Many direct transformations of **20** to **22** were unsuccessful.
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