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Total Synthesis of (±)-Wortmannin**

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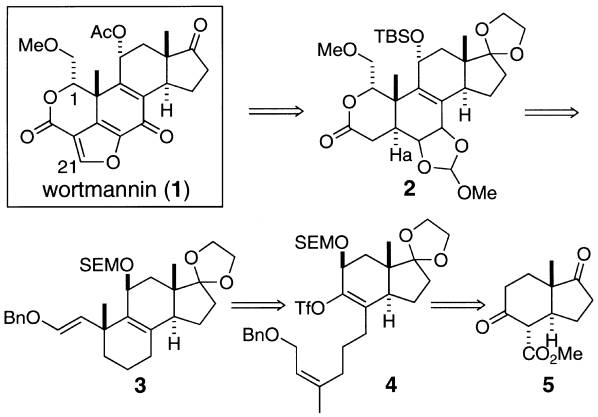
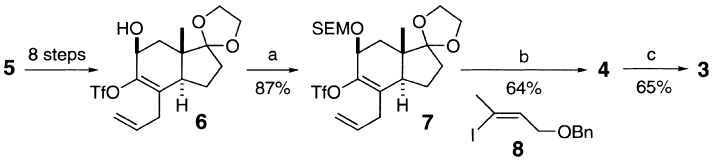
Wortmannin (**1**) is a potent and specific phosphoinositide 3-kinase (PI3K) inhibitor with a low nanomolar IC_{50} value[1] that was originally isolated from *Penicillium Wortmannii* as an anti-inflammatory and antibiotic agent.[2] Wortmannin (**1**) acts by covalently binding Lys802 in the ATP binding pocket of PI3K through nucleophilic attack of the Lys amino group at the C21 position of **1**.[3] PI3K is an important enzyme that functions in signal transduction pathways, and is a potential target for preventing proliferation of cancer cells.[4] Unfortunately, **1** has not yet been applied to medical use because of its high toxicity. Thus, wortmannin derivatives, which possess more potent inhibitory activity against PI3K and have less general toxicity, are necessary for the development of new antitumor drugs. In addition to the medicinal aspect, the challenging structural features of **1**, namely an allylic quaternary carbon center and a furanocyclohexadienone lactone unit, are very attractive from a synthetic point of view. In 1996, we reported the first chemical synthesis of **1** from hydrocortisone.[5] Following this primary achievement, we planned to develop a direct total synthesis of **1**, which would hopefully lead to many more derivatives. Here, we report the first direct total synthesis of (±)-**1** using an intramolecular Heck reaction for stereoselective construction of an allylic quaternary carbon center (Scheme 1)[6] and a diosphenol–Claisen rearrangement (Scheme 3)[7] as key steps.



Scheme 1. Retrosynthesis of (±)-wortmannin. SEM = 2-(trimethylsilyl)-ethoxymethyl; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; Bn = benzyl.

Our synthesis began with alkenyl triflate **6**, which was synthesized from compound **5**, and obtained as a racemate[8] in eight steps and in 27% overall yield (Scheme 2).[6c] After conversion of **6** into the SEM-protected ether **7** (87%), it was chemoselectively coupled with **8** by the Suzuki method to give **4** (64%).[9] An intramolecular Heck reaction of **4** afforded



Scheme 2. Synthesis of enol ether **3**. a) SEMCl, 2,6-lutidine, nBu$_4$NI, CH_2Cl_2, 40°C; b) 9-BBN, THF, RT then **8**, [$PdCl_2$(dppf)], K_3PO_4, THF/DMF, 60°C; c) 10 mol% of $Pd(OAc)_2$, 22 mol% of 1,3-bis(diphenylphosphanyl)propane, 1.0 equiv of nBu$_4$NBr, 2.5 mol equiv of K_2CO_3, toluene, 100°C, 17 h. SEMCl = 2-(trimethylsilyl)ethoxymethyl chloride, 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

enol ether **3** in 65% yield and in excellent diastereoselectivity (β-Me:α-Me = 18:1). It is noteworthy that the stereochemistry of the β-SEM ether in **4** plays a crucial role in the excellent stereoselectivity achieved by the Heck reaction.[6] Unfortunately, the use of the epimer, the α-SEM ether, afforded the undesired (α-Me) isomer as the major product.

Removal of the SEM group, followed by oxidation and reduction, produced α-allylic alcohol **9** (3 steps) together with the β alcohol (Scheme 3). The β-alcohol can be recycled by conventional methods. After protection of **9** as the TBS ether to give **10**, oxidation of the enol ether with 2.5 mol% of OsO_4 and 1.5 equivalents of NMO gave the hydroxyaldehyde, which was then reduced with $LiAlH_4$ to give the desired diol **11**

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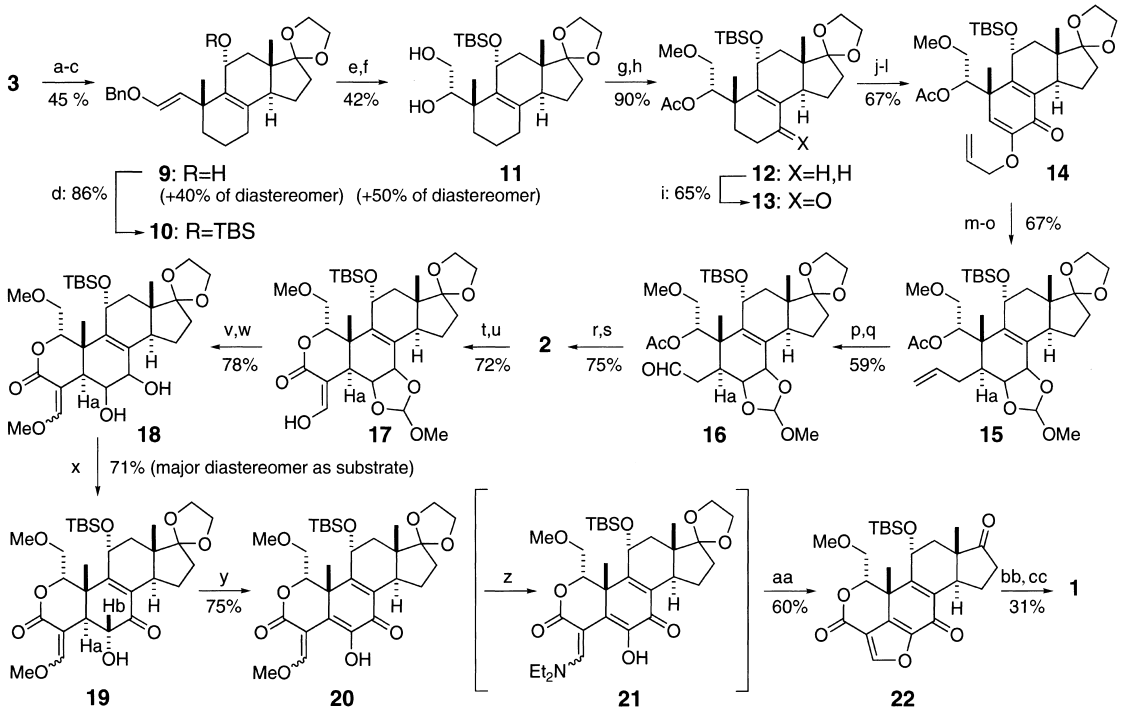

Scheme 3. Total synthesis of **1**. a) CsF, DMF, 130 °C; b) PDC, NaOAc, CH_2Cl_2, RT; c) DIBAL-H, toluene, −78 °C; d) TBSCl, imidazole, DMF, RT; e) OsO_4, NMO, acetone/H_2O, RT; f) $LiAlH_4$, THF, −40 °C; g) MeI, Ag_2O, RT; h) Ac_2O, DMAP, pyridine, CH_2Cl_2, RT; i) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −20 °C; j) 1. TMSOTf, Hünig base, CH_2Cl_2, −78 °C; 2. dimethyldioxirane, acetone, RT; 3. PPTS, MeOH, RT; k) $(COCl)_2$, DMSO, CH_2Cl_2, −40 °C; Et_3N, −40 °C; l) allyl bromide, K_2CO_3, acetone, 40 °C; m) xylene, 200 °C, 50 min; n) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; o) $HC(OMe)_3$, PPTS, RT; p) OsO_4, NMO, CH_3CN/H_2O, RT; q) nBu_4NIO_4, $CHCl_3$, 40 °C; r) K_2CO_3, MeOH, RT; s) TPAP, NMO, 4Å MS, CH_2Cl_2, RT; t) $HC(NMe_2)_3$, DMF, 100 °C; u) phosphate buffer (pH 4–5), THF, RT; v) Me_2SO_4, K_2CO_3, acetone, RT; w) 1N NaOH, THF, RT; x) PDC, NaOAc, CH_2Cl_2, RT; y) $(COCl)_2$, DMSO, CH_2Cl_2, −20 °C; Et_3N, −20 °C; z) Et_2NH, CH_2Cl_2, RT; aa) 1N HCl, THF, RT; bb) 3 HF·Et_3N, THF, 40 °C; cc) Ac_2O, pyridine, RT. PDC = pyridinium dichromate; DIBAL-H = diisobutylaluminum hydride; TBSCl = *tert*-butyldimethylsilyl chloride; DMAP = 4-(dimethylamino)pyridine; TMSOTf = trimethylsilyl trifluoromethanesulfonate; PPTS = pyridinium *p*-toluenesulfonate; NMO = 4-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate.

(2 steps, 42 %) together with the undesired diol (50 %).[10,11] Selective methylation of the primary alcohol of diol **11** and successive protection of the remaining secondary alcohol as an acetyl group gave **12** (2 steps, 90 %). Allylic oxidation of **12** proceeded well with 15 equivalents of CrO_3 and 3,5-dimethylpyrazole at −20 °C to give enone **13**. In the next transformation, we faced a difficult task, that is, introduction of a carbon unit at the sterically crowded neopentyl position for lactone formation. After numerous attempts, a diosphenol–Claisen rearrangement[7] of **14** was found to be effective for introducing a C–C bond at the neopentyl position.[12,13] Thus, enone **13** was converted into **14**, by five successive transformations: enol silyl ether formation, oxidation of enol ether with dimethyldioxirane, removal of the TMS group, oxidation of α-hydroxyketone to a mixture of diosphenol and α-diketone, and allylation with allyl bromide. The Claisen rearrangement of **14** proceeded very well under thermal conditions to give the α-diketone as a single diastereomer.[14,15] The obtained α-diketone was subsequently reduced to the diol, followed by protection to give cyclic orthoester **15** (3 steps) as an inseparable mixture of several diastereomers. The formation of several diastereomers is not a serious problem, because in principle all the isomers can be transformed into **1**. The terminal olefin of cyclic orthoester **15** was oxidatively cleaved (cat. OsO_4 then nBu_4NIO_4[16] in $CHCl_3$ at 40 °C) to give aldehyde **16** (2 steps). Removal of the acetyl group of **16** led to the formation of hemiacetal, which was oxidized by tetrapropylammonium perruthenate (TPAP) to give lactone **2** (2 steps).

After production of **2**, the introduction of a C1 unit at the α position of the lactone and formation of the furan ring remained. Similar to previous reports on synthetic studies[17] and chemical synthesis of **1**,[5] aminomethylenation was effective for the introduction of the C1 unit. As expected, treatment of lactone **2** with $HC(NMe_2)_3$ at 100 °C gave the desired compound in good yield, and the rather unstable product was successively treated with aqueous acid to furnish enol **17** (2 steps). Protection of the enol and conversion of the cyclic orthoester into a formate group occurred simultaneously following treatment of **17** with Me_2SO_4 and K_2CO_3 in acetone, and further treatment with aquous NaOH gave diol **18** (2 steps, ca. 3:1 mixture of diastereomers). Oxidation of the major diastereomer of diol **18** with PDC gave **19**,[14] and then Swern oxidation of **19** afforded diosphenol **20**.[18] Direct construction of the furan ring from **20** was first investigated under acidic conditions. Unexpectedly, however, only decomposition occurred. Several subsequent trials revealed that diosphenol **20** was very reactive toward nucleophiles. Thus, there was clean consumption of **20** to give **21** when it was treated with Et_2NH, and successive treatment of **21** with 1N HCl promoted the desired cyclization and simultaneous deprotection of acetal to afford furan **22** (2 steps). Finally,

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removal of the TBS group proceeded smoothly with excess $3\,HF{\cdot}Et_3N$, and subsequent acetylation of the generated alcohol gave (±)-**1** (2 steps).

In conclusion, we have achieved the first total synthesis of **1**. Although several issues remain to be addressed, such as the low stereoselectivities in several steps, much useful information about the synthesis of wortmannin derivatives has been accumulated. Further optimization of the current scheme and continuing efforts to realize an efficient catalytic asymmetric synthesis are now under intense investigation and the results will be reported in due course.

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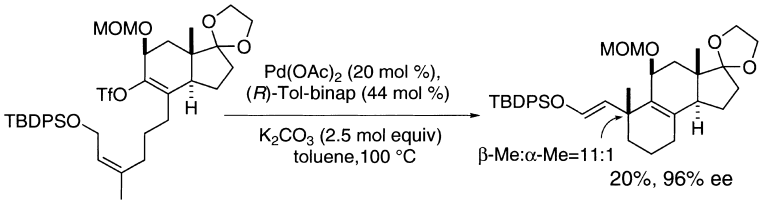

Scheme 4. MOM = methoxymethyl; TBDPS = *tert*-butyldiphenylsilyl; binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

because of the problem of deprotection. Optimization using **4** is currently under investigation, see c) S. Honzawa, T. Mizutani, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 311 – 314.

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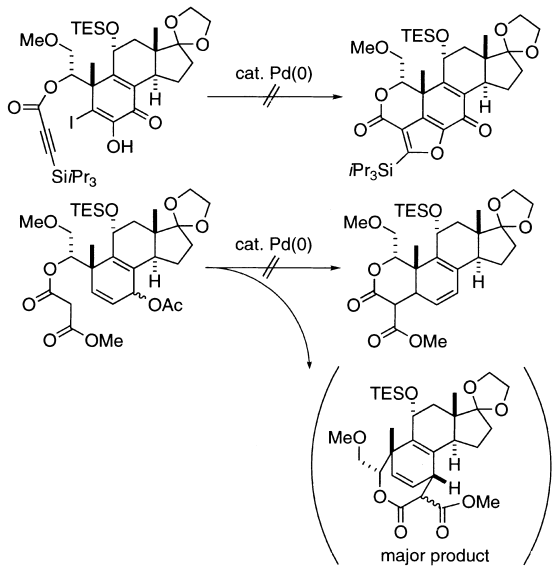
[10] At this stage, the undesired diastereomer of **11** was recrystallized from acetone and an X-ray crystallographic analysis succeeded in confirming the stereochemistry. CCDC-191844 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] The undesired diastereomer could be readily recycled to the desired diastereomer in several ways.

[12] Intermolecular Michael addition of various reagents to the corresponding enone failed.

[13] We tried other several strategies for the construction of wortmannin skeleton from **3** (Scheme 5). These strategies, however, were unsuccessful.



Scheme 5. TES = triethylsilyl.

[14] The stereochemistry of Ha was clearly determined by NOE measurements on **19**, and that of Hb was also determined by the same method.

[15] Longer reaction times (e.g. 3 h) produced the corresponding diosphenol, which could not be converted into **15**.

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[18] When a minor diastereomer was used as a substrate for successive oxidations, only a low yield of **20** was obtained (ca. 10%).

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