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Synthetic Studies on (+)-Wortmannin. An Asymmetric Construction of an Allylic Quaternary Carbon Center by a Heck Reaction.

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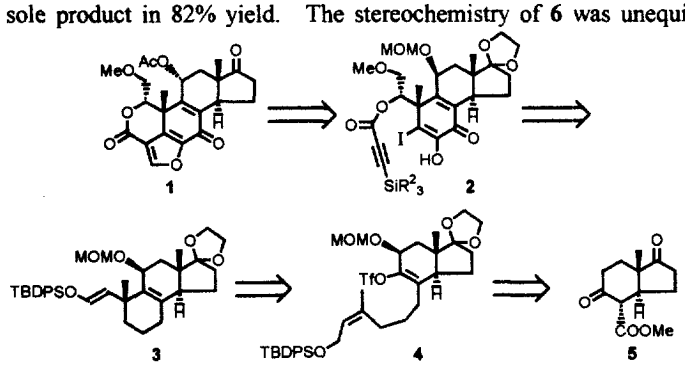
Abstract: Treatment of (±)-**4** with $Pd(OAc)_2$, DPPP, TBAB and K_2CO_3 in toluene gave **16β** in a highly stereoselective manner (17:1, 90%). Moreover, reaction of (±)-**4** with $Pd(OAc)_2$, (*R*)-Tol-BINAP and K_2CO_3 in toluene afforded **16β** in 96% ee and in 20% yield.

Keywords: Intramolecular Heck reaction; Kinetic resolution

Wortmannin (**1**) is an antifungal and anti-inflammatory antibiotic isolated from the culture filtrates of several *Penicillium* and *Myrothecium* species [1],[2]. Recently, wortmannin (**1**) has been found to be a potent and specific inhibitor of PI 3-kinases (IC_{50}=5 nM) by, it is believed, irreversibly binding to enzymes presumably in a covalent manner [3]. In 1996, we reported the first chemical synthesis of wortmannin (**1**) [4]. However, this synthesis (from hydrocortisone) is lengthy, and so we initiated a research program to find a more direct asymmetric synthesis of **1**. Our proposed retrosynthetic analysis is shown in Scheme 1 [5], and we anticipated that one of the most challenging and crucial key steps in this route will be the conversion of **4** → **3**. However, we have found interesting ligand, solvent and additive effects on the stereochemical control of an allylic quaternary carbon center, which have allowed us to develop an efficient kinetic resolution of **3**. All of these results are described in this communication.

Initially, alkenyl triflate **4** was efficiently synthesized as shown in Scheme 2. Treatment of known ester **5** [6] with NaH in THF, followed by addition of allyl acetate, $Pd(OAc)_2$ and triphenylphosphine, gave **6** as the sole product in 82% yield. The stereochemistry of **6** was unequivocally determined by NOE experiments. After selective acetal protection of the 5-membered ring ketone (80% yield), demethoxycarbonylation of **7** proceeded smoothly by treatment of LiCl and H_2O in DMF, to give **8** in near quantitative yield (99% yield). The stereochemistry of **8** was again determined by NOE experiments. The reaction of **8** with KHMDS in THF, followed by TMSCl, produced the enol silyl ether, which was further treated with *m*CPBA and $KHCO_3$,



Scheme 1. A Retrosynthetic Analysis of **1**

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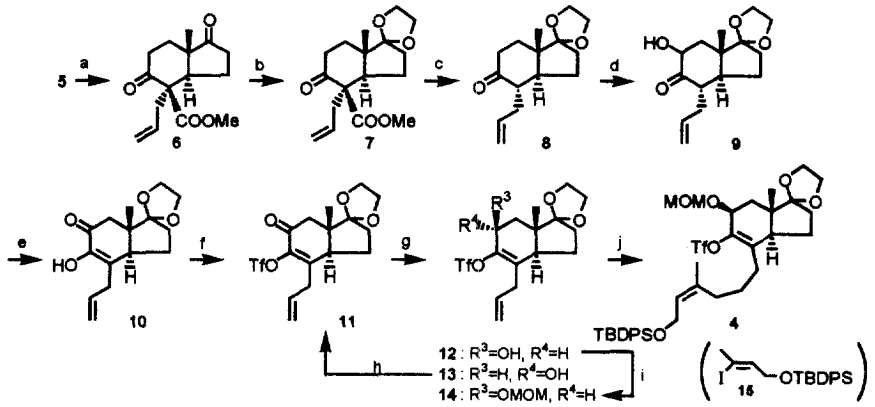


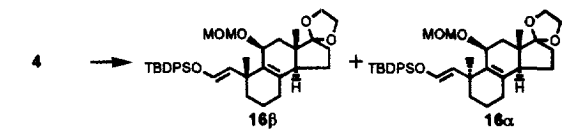
Reagents and Conditions: a) 1) NaH (1.1 equiv), THF, 0 °C → r.t., 45 min, 2) allyl acetate (1.2 equiv), $Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %), 60 °C, 30 min, 82 %. b) $TMSOCH_2CH_2OTMS$ (1.5 equiv), TMSOTf (5 mol %), CH_2CH_2, -78 °C → -40°C, 3 days, 80%. c) LiCl (2 equiv), H_2O (1 equiv), 150 °C, 8 hr, 99%. d) 1) KHMDS (1.3 equiv), THF, -78 °C, 1 hr, 2) TMSCl (1.6 equiv), -78 °C, 30 min,3) *m*CPBA (1.2 equiv), $KHCO_3$ (5 equiv), CH_2Cl_2, -40 °C → -5 °C, overnight, 4) 1N NH_4Faq, MeOH, 0 °C, 30 min, 96% for 4 steps. e) 1) $Cu(OAc)_2 \cdot H_2O$ (1.1equiv), MeOH, 0 °C → r.t., 2) DBU (1.1 equiv), CH_2Cl_2, 0 °C, 10 min, 70% for 2 steps. f) Tf_2O (1.2 equiv), *i*-Pr_2NEt (1.5 equiv), CH_2Cl_2, -78 °C, 20 min, 95%. g) $NaBH_4$ (1.1 molar equiv), $CeCl_3 \cdot 7H_2O$ (1.1 equiv), MeOH, 0 °C, 40 min, 62% for **12**, 33% for **13**. h) PCC (2 equiv), MS4A, CH_2Cl_2, r.t., 1 hr, 95%. i) $(MeO)_2CH_2$, P_2O_5 (excess), $CHCl_3$, r.t., 20 min, 83 %. j) 1) 9-BBN (1.5 equiv), THF, 0 °C → r.t., 90 min, 2) H_2O (2 equiv), 3) $PdCl_2(dppf)$ (5 mol %), K_3PO_4 (2.5 molar equiv), **15** (1.2 equiv), reflux, 3 hr, 85%.

Scheme 2. Synthesis of **4**

and then aqueous NH_4F to give **9** in 96% yield. We were pleased to find that oxidation of **9** with $Cu(OAc)_2 \cdot H_2O$ in MeOH, followed by treatment with DBU in CH_2Cl_2, afforded **10** exclusively in 70% yield. After conversion to the triflate **11** (95%), reduction with $NaBH_4$, and $CeCl_3 \cdot 7H_2O$ in MeOH, gave the desired β-alcohol **12** (62%) and the α-alcohol **13** (33%). The stereochemistry of **12** and **13** was determined by NOE experiments. The undesired α-alcohol **13** was recycled to **11** (95%) by treatment with PCC and MS4A in CH_2Cl_2. After protection as a MOM ether (83%), treatment of **14** with 9-BBN in THF, gave the hydroborated product. After addition of H_2O, the product was treated with the alkenyl iodide **15** [7], $PdCl_2(dppf)$ and K_3PO_4. This gave **4** in 85% yield.

Having obtained **4** in large quantities, we then focused our attention on the intramolecular Heck reaction [8]. This key reaction is interesting because control of the relative stereochemistry at the resulting quaternary carbon center is essential. Firstly, an intramolecular Heck reaction using $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), PPh_3 (20 mol %) and K_2CO_3 (2.5 molar equiv), in DMSO (85 °C, 12 hr), was performed on bicyclic acetal **4**. Tricyclic acetal **16** was isolated in 13% yield (**16β**:**16α** = 1:4), together with a substantial amount of starting material **4** (47%). The stereochemistry of **16β** and **16α** was determined by NOE experiments. However, when tetrabutylammonium bromide [9] (2 equiv) was added to the reaction mixture (entry 2, Table 1), the yield of **16** was improved to 32%, affording **16β**: **16α** = 1:1.2. Next, the use of toluene (a nonpolar solvent) was examined, and this did increase significantly the yield of the desired tricyclic acetal **16β** (entry 3 and 4, Table 1). In an attempt to improve the intramolecular Heck reaction to a synthetically useful level, the use of $Pd(OAc)_2$ as a Pd(0) source was investigated. We were pleased to find that treatment of **4** with $Pd(OAc)_2$ (20 mol %), PPh_3 (80 mol %), K_2CO_3 (2.5 molar equiv) and tetrabutylammonium bromide (2 equiv), in toluene at 100 °C for 5.5 hr, produced the tricyclic acetal in a ratio of **16β**:**16α** = 7.8:1 (97% yield) (entry 6, Table 1). As expected, the use of DMSO under analogous reaction conditions (as in entry 6) gave a less satisfactory result (entry 7, Table 1). At present, solvent effects cannot be explained reasonably. Having found that the conditions in entry 6 (Table 1) give the most promising result so far, we used them to examine the effects that different ligands had

Table 1. An Intramolecular Heck Reaction of **4**



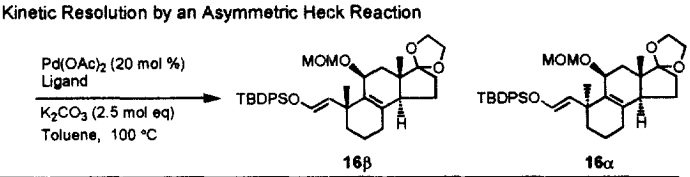
entry	Pd sourse (mol %)	ligand (mol %)	additive (molar equiv)	solvent (temp.)	reaction time (hr)	**16** (%) (**16β**:**16α**)	recovery of **4** (%)
1	$Pd_2(dba)_3$ (5)	PPh_3 (20)	K_2CO_3 (2.5)	DMSO (85)	12	13 (1:4)	47
2	$Pd_2(dba)_3$ (5)	PPh_3 (20)	K_2CO_3 (2.5) TBAB (2)	DMSO (85)	12	32 (1:1.2)	
3	$Pd_2(dba)_3$ (5)	PPh_3 (20)	K_2CO_3 (2.5)	toluene (100)	12	17 (5:1)	82
4	$Pd_2(dba)_3$ (5)	PPh_3 (20)	K_2CO_3 (2.5) TBAB (2)	toluene (100)	12	70 (3.7:1)	30
5	$Pd(OAc)_2$ (20)	PPh_3 (80)	K_2CO_3 (2.5)	toluene (100)	15	46 (5.5:1)	49
6	$Pd(OAc)_2$ (20)	PPh_3 (80)	K_2CO_3 (2.5) TBAB (2)	toluene (100)	5.5	97 (7.8:1)	
7	$Pd(OAc)_2$ (20)	PPh_3 (80)	K_2CO_3 (2.5) TBAB (2)	DMSO (85)	14	58 (2:3)	32
8	$Pd(OAc)_2$ (20)	DPPE (40)	K_2CO_3 (2.5)	toluene (100)	4.5	81 (8.7:1)	
9	$Pd(OAc)_2$ (20)	DPPP (40)	K_2CO_3 (2.5)	toluene (100)	7	90 (17:1)	
10	$Pd(OAc)_2$ (20)	DPPB (40)	K_2CO_3 (2.5)	toluene (100)	2	78 (11:1)	

TBAB : tetrabutylammonium bromide

on the reaction. Consequently, the use of DPPP [1,3-bis(diphenylphosphino)propane] was found to give the best result, providing **16** in 90% yield (**16β**:**16α** = 17:1) as shown in entry 9 (Table 1). Based on the results summarized in Table 1, we can conclude that generally bidentate ligands give **16β** with higher selectivity.

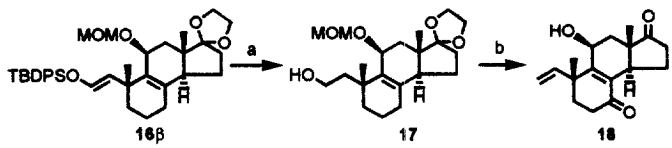
Since entries 8-10 (Table 1) gave the best results, a kinetic resolution was attempted using optically active bidentate ligands. First of all, (*R*,*R*)-CHIRAPHOS was examined, but both the yield and ee of **16β** were low (entry 1, Table 2). The enantiomeric excess of **16β** was determined (by chiral stationary phase HPLC) after conversion to **17** (Scheme 3). In an attempt to improve the enantioselectivity of **16β**, we next examined other chiral ligands and, as shown in entry 3 (Table 2), we found that, when (*R*)-Tol-BINAP was used, **16** was produced in 20% yield (**16β**:**16α** = 11:1) and 96% ee [10]. The enantiomer of **4** that should have led to the enantiomer of **16β**, afforded many by-products [11]. The absolute configuration of **16β** was unequivocally

Table 2. A Kinetic Resolution by an Asymmetric Heck Reaction



ligand (mol %)	reaction time (hr)	products (y. %) (**16β** : **16α**)	ee of **16β** (%)[3]
(*R*,*R*)-CHIRAPHOS (40)[1]	20	14 (6 : 1)	4
(*R*)-BINAP (40)[2]	2	17 (5 : 1)	97
(*R*)-Tol-BINAP (40)[2]	1.5	20 (11 : 1)	96

[1] S.M. was recovered (80%). [2] S.M. could not be recovered. Several by-products appeared. [3] Ee was determined by chiral stationary phase HPLC (DAICEL CHIRALCEL OD, Hexane : ^{i}PrOH, 50 : 1) at the stage of **17** (see Scheme 3).



Reagents and Conditions: a) 1) TBAF (3 equiv), AcOH (5 equiv), THF, r.t., 30 min. 2) $NaBH_4$ (1.1 molar equiv), MeOH, 0 °C, 10 min, 58% for 2 steps. b) 1) *o*-nitrophenyl selenocyanate (1.3 equiv), P^nBu_3 (1.2 equiv), pyridine, 0 °C → r.t., 1 hr. 2) 30% H_2O_2 (2 equiv), $NaHCO_3$ (2 equiv), THF, 0 °C → r.t., 1 hr, 84% for 2 steps. 3) CrO_3 (15 molar equiv), 3,5-dimethylpyrazole (15 equiv), CH_2Cl_2, -20 °C, overnight, 43%. 4) *B*-bromocatecholborane (3 equiv), CH_2Cl_2, -78 °C, 1 hr, 33%.

Scheme 3.

determined by conversion to **18** using Mosher's method. To the best of our knowledge, this is the first example of a kinetic resolution using an asymmetric Heck reaction. Moreover, this near perfect resolution is noteworthy because the relative stereochemistry of the allylic quaternary carbon center is controlled in a highly stereocontrolled manner during the kinetic resolution.

In conclusion, we have achieved an efficient synthesis of **16β**, a potential synthetic intermediate for wortmannin (**1**), in extremely high optical purity. Furthermore, we have discovered a variety of useful factors for controlling the stereochemistry in an intramolecular Heck reaction. Further studies are currently under investigation.

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[10] Addition of TBAB gave less satisfactory results.

[11] The structures of two of the by-products are shown below: