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A Highly Stereocontrolled Asymmetric Synthesis of the Taxol C-13 side chain; (4S, 5R)-2,4-Diphenyloxazoline-5-carboxylic acid.

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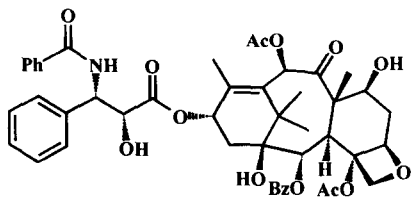
Abstract

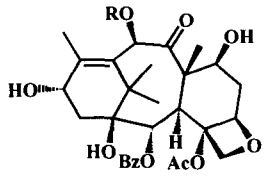
A stereoselective synthesis of (4S, 5R)-2,4-diphenyloxazoline-5-carboxylic acid, a precursor of the Taxol C-13 side chain was achieved using palladium-catalyzed oxazoline formation reaction from commercially available amino acid.

Keywords: oxazoline; palladium and compounds; asymmetric synthesis; taxoid.

Paclitaxel (Taxol®, **1**) isolated from the bark of the Pacific Yew *Taxus brevifolia*, is currently considered the most important anticancer agent and has been approved for treatment of metastatic ovarian and breast cancer[1-2]. The scarcity has led to the search for semisynthetic routes to taxol using other plant-derived products isolable in useful quantities.



1



2 R = Ac
3 R = H

Thus, a viable approach for the preparation of **1** is to utilize more accessible baccatin III(**2**) or 10-deacetylbaccatin III(**3**) as precursors via a semisynthetic route. Indeed, the successful applications of such semisynthetic strategies to the synthesis of **1** have been

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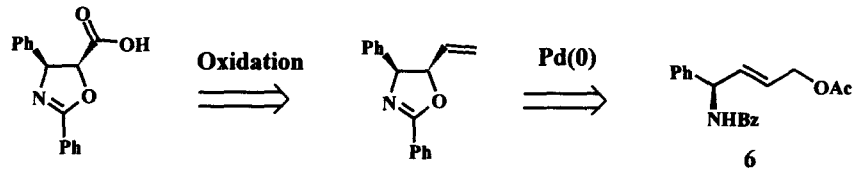
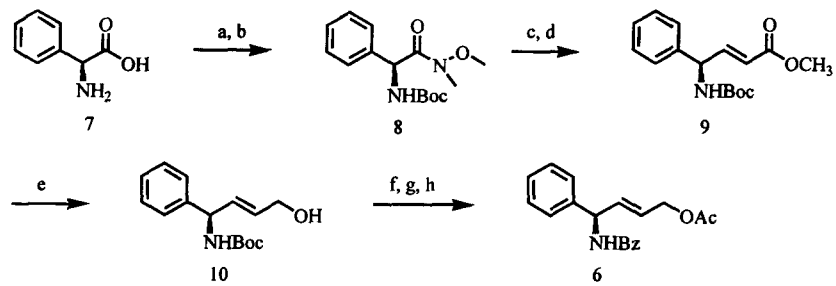
achieved[3-7], and these have prompted research into the development of Taxol side chain synthesis that is practical and adaptable to relatively large-scale production. As a part of program directed towards asymmetric synthesis of (4S, 5R)-2,4-diphenyloxazoline-5-carboxylic acid(**4**) of biological importance, we undertook a synthesis of the title amino acid in enantiopure form and report herein the details of the study(**scheme1**). The key step in our approach involves a highly enantioselective oxazoline formation catalyzed by palladium. The simplicity and low cost of starting material, and the ease of chromatographic separation may render this process the most practical route to enantiomerically pure oxazoline derivatives developed to date.



4 5 6

Scheme 1

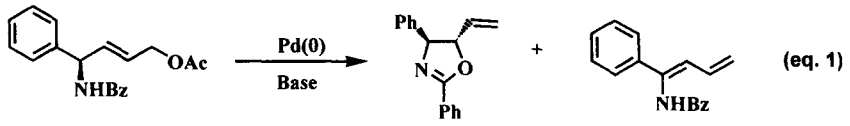
The requisite cyclization precursor (**6**) is straightforwardly prepared in high yield from the commercially available L-phenylglycine by 8 step sequences(overall 45%) as shown in **scheme 2**. L-phenylglycine (**7**) was treated with di-*tert*-butyl-dicarbonate to afford the corresponding N-Boc-phenylglycine, which was reacted with N,O-dimethylhydroxylamine hydrochloride in the presence of DCC and HOBT in CH_2Cl_2. The resulting amide (**8**) was reacted with lithium aluminium hydride at -40 ℃ to give the aldehyde[8], followed by a Wittig olefination using trimethylphosphonoacetate then led to the *E*-unsaturated ester (**9**). Thus, reduction of *E*-unsaturated ester, using DIBAL at -78 ℃ produced the corresponding allyl alcohol (**10**). Deprotection of the Boc group using aqueous hydrochloric acid followed by benzoylation of the resulting amino group formed the N-benzoyl alcohol. Acetylation of the hydroxy group yielded the key precursor (**6**) of cyclization.



7 8 9 10 6

Scheme 2. Reagents and conditions : a) Boc_2O, NaOH, *t*-BuOH, H_2O; b) $HNCH_3(OCH_3)$·HCl, DCC, HOBT, Et_3N, CH_2Cl_2, 81%(for 2steps); c) LAH, $(C_2H_5)_2O$, -40 ℃; d) $(CH_3O)_2POCH_2CO_2CH_3$, LiCl, diisopropylethylamine, CH_3CN, 80%(for 2steps); e) DIBAL, BF_3 OEt_2, CH_2Cl_2, -78 ℃, 89%; f) 3N-HCl in EtOAc; g) BzCl, Et_3N, THF, 0 ℃; h) Ac_2O, pyridine, CH_2Cl_2, 78%(for 3steps).

Although cyclization of enamides or enimidates by activation of the olefin with electrophiles has been well documented[9-11], there are few examples of palladium-catalyzed oxazoline formation reaction[12-13]. Conditions for the cyclization of oxazoline precursor (**6**) were intensively explored by examination of the effects of bases, ligands, and solvents as summarized in **Table 1**. CH_3CN or CH_2Cl_2 was an equally effective solvent, but DMF and THF gave a mixture of oxazoline (**5**) and elimination product (**11**). $Pd(PPh_3)_4$, K_2CO_3, and CH_3CN turned out to be the best condition for the highest conversion yield. Especially, cyclization of **6** with K_2CO_3 in the presence of 5mol% $Pd(PPh_3)_4$ in CH_3CN(entry 9) proceeded smoothly to afford a 6:1 mixture of **5** and **11** in favor of **5** as the desired compound. In all cases, *cis*-oxazoline was not obtained.



6 5 11

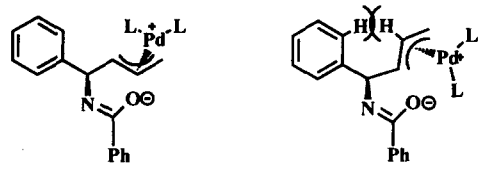
Table 1. Palladium-catalyzed oxazoline formation reaction

entry	Pd(0)	base[a]	solvent	Rx. Temp(°C)	Rx. Time(hr)	yield(%)[b](5:11)
1	$Pd(PPh_3)_4$(5mol%)	NaH	DMF	rt	8	30 : 45
2	Pd_2dba_3-$CHCl_3$(1mol%) PPh_3(8mol%)	NaH	DMF	rt	8	29 : 48
3	Pd_2dba_3-$CHCl_3$(1mol%) dppe(4mol%)	NaH	DMF	rt	8	0: 90
4	Pd_2dba_3-$CHCl_3$(1mol%) PPh_3(8mol%)	K_2CO_3	CH_3CN	reflux	8	63 : 10
5	Pd_2dba_3-$CHCl_3$(1mol%) PPh_3(8mol%)	K_2CO_3	CH_2Cl_2	reflux	8	19: 4
6	$Pd(PPh_3)_4$(5mol%)	K_2CO_3	DMF	60	24	40 : 38
7	$Pd(PPh_3)_4$(5mol%)	Hünig base	DMF	60	24	20 : 19
8	$Pd(PPh_3)_4$(5mol%)	K_2CO_3	CH_2Cl_2	reflux	24	70 : 25
9	$Pd(PPh_3)_4$(5mol%)	K_2CO_3	CH_3CN	reflux	24	78 : 13
10	$Pd(PPh_3)_4$(5mol%)	K_2CO_3	THF	rt	4	49 : 38

a. Bases were used as follows: NaH(1equiv.), K_2CO_3(2equiv.), Hünig base(2equiv.).

b. Yields refer to isolated and chromatographically pure products.

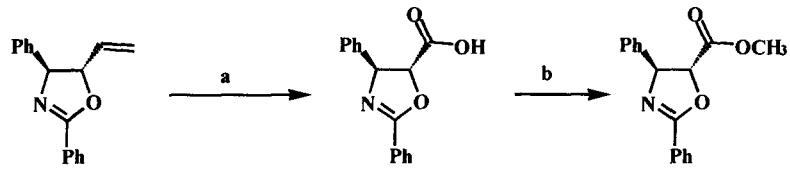
The high stereoselectivity in cyclization of **6** maybe arise due to the differences of steric interactions between the bulky phenyl group and hydrogen of π-allyl palladium complex in the transition state **A** and **B**. Consequently, cyclization proceeds through the more favored transition state **A** as shown in **Figure 1**.



A B

Figure 1.

Oxidative degradation of the vinyl group of oxazoline yielded the corresponding (4S, 5R)-2,4-diphenyloxazoline-5-carboxylic acid(**4**), which was then converted to its methyl ester (**12**)(**scheme 3**). From ^{1}H NMR studies, the observed coupling constant($J_{4,5}$ = 6.5Hz) between the two protons in the oxazoline ring indicated a *trans*-relationship. Optical rotation of **12** {$[\alpha]_D$ = +12.9 (c = 1, $CHCl_3$) : lit. $[\alpha]_D$ = +13 (c = 1, $CHCl_3$)[14]} was in good agreement with the reported value, which also conclusively proved the stereochemical assignment.



5 4 12

Scheme 3. Reagents and conditions : a) $RuCl_3$, $NaIO_4$, $NaHCO_3$, $H_2O/CCl_4/CH_3CN$, 2days, 78%; b) CH_2N_2, $(C_2H_5)_2O$, 100%.

In summary, a new synthesis of (4S, 5R)-2,4-diphenyloxazoline-5-carboxylic acid(**4**) was accomplished by using palladium-catalyzed oxazoline ring formation reaction.

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