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An efficient stereoselective synthesis of methyl (*S*)-3-amino-3-(3-pyridyl)propanoate

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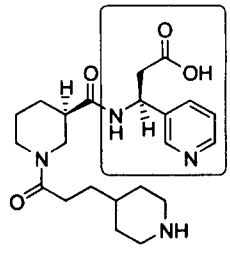
Abstract

Methyl (*S*)-3-amino-3-(3-pyridyl)propanoate (**2**) is a key starting material in the synthesis of RWJ-53308 (**1**), an orally active antagonist of the platelet fibrinogen receptor (GP IIb/IIIa antagonist). Herein, we describe an efficient stereoselective synthesis of **2** by the hydrogenation of enantiomeric enamine **8** with $Pd(OH)_2/C$, followed by the removal of the chiral auxiliary under mild conditions, a novel procedure that employs the combination of formic acid and triethylsilane.

Keywords: amino acid derivatives; enamines; stereoselective reductions.

RWJ-53308 (**1**) is a parenterally (iv) and orally active antagonist of the platelet fibrinogen receptor (GP IIb/IIIa antagonist) for the treatment of thrombotic disorders such as restenosis post-angioplasty, unstable/stable angina and myocardial infarction.[1]



RWJ-53308 (1)

The preparation of enantiomerically enriched methyl (*S*)-3-amino-3-(3-pyridyl)propanoate (**2**), a key starting material in the synthesis of **1**, was identified as a critical factor in our process devel-

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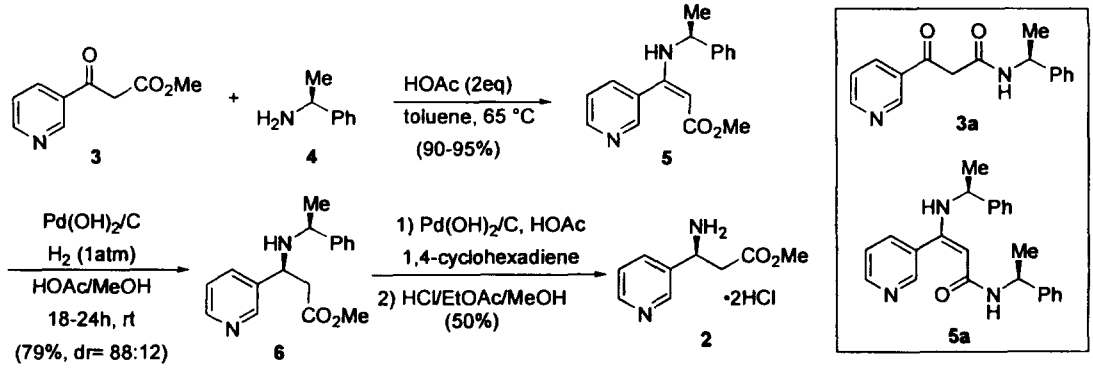
opment. Initially, compound **2** was prepared by the resolution of racemic *N*-Boc-(*S*)-3-amino-3-(3-pyridyl)propanoic acid. To meet the demand of large quantities of drug substances for development activities, we needed to develop an efficient synthesis to prepare this key starting material.

Several methods have been reported in the literature for the synthesis of enantiomerically pure β-amino acids or esters.[2] Some of the recent approaches are the Michael-type addition of enantiomeric lithium amides to α,β-unsaturated carboxylic esters,[3] the addition of *C*-nucleophiles to enantiomeric sulfinimines,[4] the reduction of enantiomeric enamines,[5] the stereoselective ring opening of chiral oxazolidines by Reformatsky reagents,[6] the addition of silyl enol ethers to enantiomeric imines with one equivalent of chiral non-racemic Lewis acids,[7] and the enantioselective hydrogenation of β-acylamino acrylic acids with chiral non-racemic catalysts.[8] These approaches are largely applicable to the synthesis of aliphatic and simple aromatic β-amino esters.

The β-(3-pyridyl) group in our target molecule **2** posed a challenge because of its potential interference with some of these reaction conditions, such as the reduction of the pyridine ring under catalytic hydrogenation conditions[9] and interaction with Lewis acid catalysts. After thoroughly evaluating the literature precedent, we decided to pursue the stereoselective reduction of a properly substituted enantiomeric enamine for the synthesis of our target compound. As illustrated in Scheme 1, (*S*)-α-methylbenzylamine (**4**), was used as a chiral auxiliary to prepare the enantiomeric enamine **5** by condensation with methyl nicotinoylacetate (**3**). Two major impurities were observed during the reaction in refluxing toluene, which were identified as the aminolysis product **3a** and **5a**. To minimize the formation of the amide by-products, we carried out the reaction under reduced pressure to remove water azeotropically at lower temperature. These conditions resulted in the formation of enantiomeric enamine **5** in 90–95% yield, containing no detectable amide by-products. The crude enamine **5** was used for the next step without further purification.



Scheme 1.

The diastereoselective reduction of enantiomeric enamine **5** was carried out under various conditions as summarized in Table 1. In our experiments, the reduction of **5** with $NaBH_4$ or $NaB(OAc)_3H$[5] gave poor (entry 1) to moderate (entry 3) diastereoselectivity. The palladium catalyzed hydrogenation of **5** gave better diastereoselectivity (entries 4–7, Table 1). The best diastereoselectivity (de=76%) was obtained by utilizing $Pd(OH)_2/C$ as a catalyst under atmospheric pressure in MeOH/AcOH (entry 7, Table 1). The desired diastereomer was isolated easily in >98% de by conversion of the crude product to its HCl salt and recrystallization from ethyl acetate/methanol solution. The overall yield was about 45%. The low yield was caused mainly by the unwanted reduction of the pyridine ring as observed by MS analysis.

As found by other researchers, the removal of the α-methylbenzyl group was quite difficult.[3c,d] The reaction was attempted under different transfer hydrogenation conditions in acidic media. We also

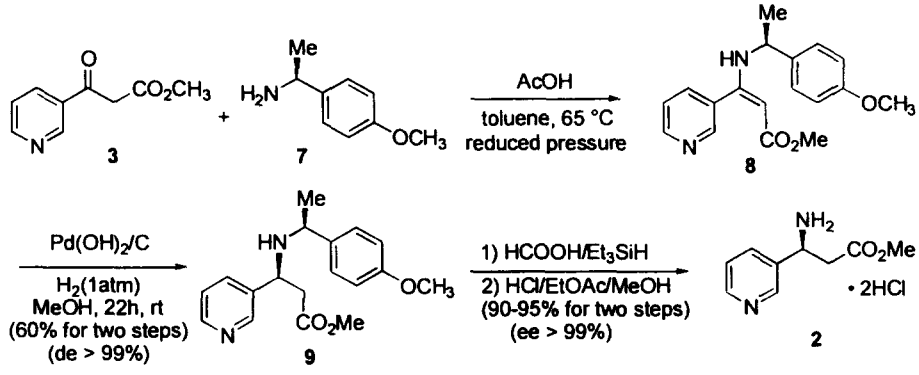
Table 1
Diastereoselective reductions of enantiomeric enamine **5** to amine **6**

Entry	Reaction Conditions	Yield[a]	*SS*:*SR*[b]
1	$NaBH_4$(4 eq), AcOH (2 eq), THF	72%	52:48
2	$NaBH_4$(2.5 eq), $ZnCl_2$(2.5 eq), THF	83%	37:63
3	$NaB(OAc)_3H$(2 eq), AcOH(2 eq), THF	---	73:27
4	H_2(40 psi), 10% $Pd(OH)_2$ (20% on C), MeOH/AcOH	76%	85:15
5	H_2(40 psi), 30% Pd (10% on C), MeOH/AcOH, 2 h	77%	79:21
6	H_2(10 psi), 30% Pd (10% on C), MeOH/AcOH, 4 h	87%	82:18
7	**H_2(1 atm), 10% $Pd(OH)_2$ (20% on C), MeOH/AcOH**	**79%**	**88:12**

a) Yields were determined by GC analysis of the isolated crude products. b) Diastereomeric ratios were determined by GC and HPLC analyses.

found that the best conditions were to use 100% load of $Pd(OH)_2$ (20% on C) as a 'catalyst' and 1,4-cyclohexanediene as a hydrogen source in glacial AcOH to give the product **2** in 50% isolated yield.

Because of the difficulties associated with the removal of this chiral auxiliary, we investigated the use of other amines, such as (*S*)-1-(4-methoxyphenyl)ethylamine (**7**), (*S*)-1-(2-methoxyphenyl)ethylamine, (*S*)-1-(3,4-dimethoxyphenyl)ethylamine, as chiral auxiliaries. We hoped that the higher electronic density on the aromatic ring would facilitate removal of the chiral auxiliary, possibly by a cationic process.[10] The sequence for the synthesis of **2** by utilizing **7** as a chiral auxiliary is illustrated in Scheme 2.[11]



Scheme 2.

The enantiomeric enamine **8** was prepared by heating methyl nicotinoylacetate (**3**) with one molar equivalent of (*S*)-1-(4-methoxyphenyl)ethylamine (**7**) in toluene in the presence of 2.5 equivalent of glacial AcOH at 60–65°C under reduced pressure. The crude enamine **8** was isolated in high purity by extractive work-up and was used directly in the reduction step without further purification.

Using our optimized conditions discussed above for the reduction of enamine **5**, the hydrogenation of the enantiomeric enamine **8** in the presence of 10% load of $Pd(OH)_2$ (20 wt.% on C) in methanol gave amine **9** in moderate diastereoselectivity (66–80% de) without any observed reduction of the pyridine ring. The pure diastereomer **9** was isolated by recrystallization from ethyl acetate/methanol in >99% de and 60% overall yield for the two steps. The removal of the 4-methoxy-α-methylbenzyl group was readily achieved by heating **9** in trifluoroacetic acid (TFA) to give the desired product **2** in 88–95% yields (entries 1 and 2, Table 2). However, from the process chemistry point of view, it is not desirable to use TFA for large scale production because of its high cost and corrosiveness. We explored the use of other acids and the results are summarized in Table 2.

Table 2
Removal of the 4-methoxy-α-methylbenzyl group

Entry	Reaction Conditions	Yield (HPLC area%)	ee
1	TFA/60 °C/2.5 h	94% (99%)	99.4%
2	TFA/anisole/60-70 °C/6 h	90% (99%)	99.6%
3	HCOOH/100 °C/30 min.	47% (87%)	99.6%
4	HCOOH/anisole/100 °C/1 h	67% (93%)	99.8%
5	HCOOH/HCl/100 °C/1 h	85% (97%)	99.8%
6	**HCOOH/Et_3SiH/90-100 °C/1 h**	**94% (98%)**	**99.4%**
7	AcOH/Et_3SiH/100 °C/12 h	79% (96%)	99.6%

We found that removal of the chiral auxiliary could be accomplished with other acids, such as formic acid and acetic acid. Heating **9** in formic acid at 100°C for 30 min (entry 3, Table 2) afforded the desired product. However, the attempted isolation of HCl salt of **2** was complicated by a solid by-product formed during the reaction. We speculate that the solid was obtained from the acid catalyzed polymerization of 4-methoxystyrene, formed from cleavage of the 4-methoxy-α-methylbenzyl moiety. This problem was overcome by the addition of triethylsilane (Et_3SiH), a cation scavenger, to trap/reduce the 4-methoxy-α-methylbenzyl cation and prohibit this polymerization process. Thus, the best result (entry 6, Table 2) was obtained by heating the amine **9** in a combination of formic acid and Et_3SiH at 90–100°C. After converting the crude product to its dihydrochloride salt by the treatment with methanolic HCl, the product **2** was easily isolated from EtOAc/MeOH solution in 90–95% yield and >99% ee.[12,13]

In conclusion, we have developed an efficient process to prepare enantiomerically enriched methyl (*S*)-3-amino-3-(3-pyridyl)propanoate (**2**). No chromatographic purification was used and the intermediate **9** and the final product **2** were isolated by simple recrystallization, which is suitable for large scale synthesis. The $Pd(OH)_2$ catalyzed hydrogenation of enantiomeric enamine **8** gave a good diastereoselectivity and an overall good chemical yield. The debenzylation of **9** was carried out using the combination of formic acid and triethylsilane, a novel procedure that may have wider scope in debenzylation reactions. The overall yield of the isolated product **2** was approximately 55% in >99% ee for the three-step sequence. Currently, we are further exploring this approach to various enantiomerically enriched β-amino esters and the results will be reported in a future publication.

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12. All new compounds prepared were characterized by spectroscopic methods and elemental analysis. The enantiomeric excess (ee) was determined by chiral HPLC analysis.
13. Experimental procedure for the removal of the 4-methoxy-α-methylbenzyl group: A solution of amine **9** (4.12 g, 10.6 mmol) and triethylsilane (1.45 g, 15.9 mmol) in formic acid (10 mL) was stirred at 90–100°C (oil-bath) under N_2. After 2 h, HPLC analysis showed the completion of the reaction. The volatiles were removed on a rotavapor at 50°C. The residual oil was diluted with EtOAc (20 mL) and MeOH (5 mL) and treated with 5.5 M HCl in MeOH (5.8 mL, 31.8 mmol). The excess MeOH was removed by evaporation on a steam-bath until the solution became cloudy again. The mixture was then stirred at rt overnight (ca. 16 h). More EtOAc (30 mL) was added to the suspension and the mixture was stirred for an additional 2 h. The solid was collected by filtration, washed with EtOAc (30 mL), and dried in vacuo for 1 h. The product **2** was obtained as a white powder (2.52 g, 94% yield, mp: 197.5–199.0°C).