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Stereoselective synthesis of β-aryl-β-amino esters

Judith H. Cohen,* Ahmed F. Abdel-Magid, Harold R. Almond, Jr. and Cynthia A. Maryanoff

Johnson & Johnson Pharmaceutical Research & Development, Drug Evaluation, Welsh & McKean Rds, Spring House, PA 19477, USA

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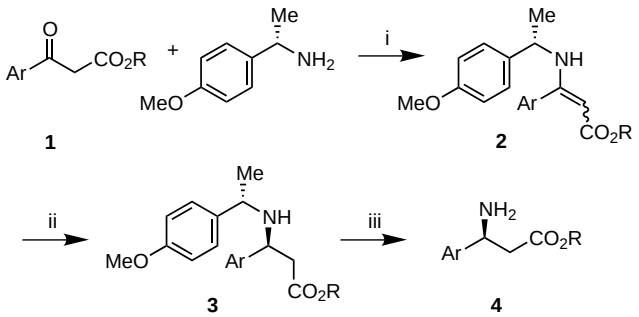
Abstract—An efficient stereoselective synthesis of β-aryl-β-amino esters via reduction of enantiomerically enriched *N*-(*p*-methoxy-α-methylbenzyl)enamines by catalytic hydrogenation followed by debenzylation is described. © 2002 Elsevier Science Ltd. All rights reserved.

β-Amino acids and esters are traditionally important molecules due to their unique pharmacological properties in free form, such as ethyl (*S*)-3-amino-2-phenyl propionate which exhibits neurological activity,[1] and because they are components of naturally occurring compounds such as the antifungal cyclic depsipeptide, Jasplakinolide.[2] Recently, there has been increased interest in the enantiomeric preparation of β-amino acids and esters as precursors for the synthesis of novel biologically active compounds such as non-peptide GP IIb/IIIa antagonists. These compounds, (which are potentially useful as antithrombotic agents for the prevention of acute myocardial infarction, unstable angina, and peripheral artery disease), are designed after the RGD (Arg-Gly-Asp) template found in adhesion ligands and contain chiral non-racemic β-amino acid residues.[3] We recently identified a series of interesting potent, orally active GP IIb/IIIa antagonists in which β-aryl-β-amino acids are essential components.[4] While there are several approaches to the synthesis of chiral non-racemic β-aryl-β-amino acids/esters,[5] the preparation of β-amino acids with pyridyl substituents is limited and in most part impractical.[6] As part of our research for RWJ-53308, we recently reported the large-scale asymmetric synthesis of enantiomerically pure, methyl (*S*)-3-amino-3-(3-pyridyl)propionate via stereoselective reduction of an enantiomeric enamine.[7] Based on the success of this synthesis, we expanded the scope of the process (Scheme 1) to include other aromatic substituted (*S*)-β-amino esters which are useful in the preparation of other analogs in this series. Herein we describe the research which led to an improved and general process for the synthesis of β-aryl-β-amino esters via stereoselective reduction of enantiomeric enamines.



Scheme 1. Ar = 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-Br-3-pyridyl, Ph, 4-CO_2Me-Ph, 4-F-Ph, 4-OH-Ph, 4-OMe-Ph. *Reagents and conditions*: (i) AcOH, toluene, reduced pressure, 60–75°C; (ii) 10 wt% of 20% $Pd(OH)_2$ on C, 1 atm; (iii) Et_3SiH, HCO_2H, 100°C.

The enantiomeric enamines **2**[8] were prepared by reacting the appropriate β-ketoester with one molar equivalent of (*S*)-1-(4-methoxyphenyl)ethylamine in toluene and glacial acetic acid. While the condensation of aliphatic ketones with amines is quite rapid, condensation of aryl ketones with amines is known to be very slow requiring higher temperatures and longer reaction times. Heating the mixture of β-aryl-β-ketoesters **1** in toluene with (*S*)-1-(4-methoxyphenyl)ethylamine at reflux temperature with azeotropic removal of water resulted in significant formation of amides, while lowered reaction temperatures (60–75°C) stopped amide formation but also slowed enamine formation considerably. To eliminate (or minimize) the formation of the amide by-products resulting from high reaction temper-

* Corresponding author. Tel.: 215-628-5059; fax: 215-628-7067; e-mail: jcohen@prdus.jnj.com

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ature and to facilitate enamine formation, we redesigned the reaction conditions. Specifically, the mixture was heated to reflux under reduced pressure so that water could be azeotropically removed between 60–70°C. This modification allowed us to prepare a variety of enamines in high yields (75–95%) and purities with very little or no amide formation. We verified the stereochemistry of the major enamine isomer being formed as *Z* based on NOE NMR experiments. However, in the case of the 3-pyridyl and 4-pyridyl compounds, the *Z*-enamines underwent isomerization to afford the *E*-isomers as well.

When we carried out the reductions of the *Z*-enamines **2** using the optimized procedure (atmospheric H_2 with 10 wt% of 20% $Pd(OH)_2$/C, no acid) for the 3-pyridyl compound,[7] we obtained varying results (Table 1).

While the reduction of the 3-pyridyl enamine occurred with moderately good selectivity to afford the desired *S*,*S* diastereomer **3** in 4:1 diastereomeric ratio (dr), the reduction of the other pyridyl-substituted enamines gave very poor results. Reduction of the 2-pyridyl compound (entry 2), required longer than 4 days for completion to afford the amine product **3** as a ~1:1 diastereomeric mixture. The 4-pyridyl compound (entry 3) was reduced within two days; however, the unwanted *S*,*R* diastereomer was isolated as the major product and reduction of the 5-bromo-3-pyridyl enamine (entry 4) resulted in loss of the 5-bromo group under a variety of catalytic hydrogenation conditions. The reduction of the phenyl and substituted phenyl compounds gave slightly better results (entry 5–9); the phenyl and 4-CO_2Me-phenyl compounds afforded the secondary amine **3** in ~2:1 dr while the 4-F, 4-OMe, and 4-OH-phenyl compounds afforded the secondary amines **3** in ~3:1 dr.

It is well known in literature that amines formed from hydrogenation of imines/enamines can act as inhibitors in catalytic reductions. Thus, addition of acids to these catalytic hydrogenations can greatly increase reaction rates by blocking this inhibiting effect.[9] In order to improve selectivity as well as increase the reaction rate, we investigated the catalytic hydrogenation of *Z*-enamines **2** under acidic conditions. From our previous work we had noted that catalytic hydrogenation of the 3-pyridyl enamine in the presence of excess acid led to formation of by-products resulting from reduction of the pyridine ring.[7] However, after further investigation, we observed no 'over-reduction' of the pyridine ring if the reaction was carried out using only 2 equiv. of acid.

Reductions of **2** in the presence of 2 equiv. AcOH yielded increased reaction rates and slightly improved selectivity as shown in Table 1. Specifically, the reduction of the 4-pyridyl-*Z*-enamine (entry 3) now favored formation of the desired *S*,*S* diastereomer in ~2:1 dr. However, for the reduction of **2** where Ar = 4-F, 4-OH, 4-OMe, and 4-CO_2Me-phenyl (entries 6–9), we observed significant loss of the *p*-methoxy-α-methylbenzyl group under long reaction times thus leading to difficulties with isolation and purification of the resulting β-aminoesters **4**. Therefore, we stopped these reactions prior to completion which led to higher chemical and diastereomeric purity but lower overall yields.

Although acetic acid offered a slight advantage in terms of reactivity and selectivity, we examined other acids (specifically Lewis acids) in the reduction in order to improve our results. We carried out the catalytic hydrogenation of the *Z*-enamines **2** in the presence of 2 equiv. of $BF_3{\cdot}Et_2O$ (Table 1) and noted three important observations: (1) unlike the reactions with AcOH, we did not observe any loss of the *p*-methoxy-α-methylbenzyl group even with the substituted phenyl compounds; (2) while most of the previous reductions took anywhere from 1–3 days for completion, the longest reaction with $BF_3{\cdot}Et_2O$ was only 6 h, and (3) most importantly, we observed an increase in selectivity for each reaction. The most significant improvement in selectivity was observed for the 2-pyridyl enamine (entry 2) going from a 1:1 mixture of diastereomers with no acid to 9:1 dr using $BF_3{\cdot}Et_2O$. Also, notable is the reduction of the 4-pyridyl enamine which increased to a 71:29 dr from 47:53 favoring the unwanted *S*,*R*

Table 1. Reduction of enamines **2**[a]

Entry	Ar	No Acid[b] SS:SR	AcOH[d] SS:SR	$BF_3{\cdot}Et_2O$[f] SS:SR
1	3-Pyridyl	80:20	83:17	88:12
2	2-Pyridyl	55:45	74:26	90:10
3	4-Pyridyl	47:53	58:42	71:29
4	5-Br-3-Pyr	NR[c]	–	–
5	Phenyl	67:33	77:23	85:15
6	4-CO_2Me-Ph	61:39	68:32[e]	85:15
7	4-OH-Ph	75:25	79:21[e]	86:14
8	4-OMe-Ph	74:26	80:20[e]	87:13
9	4-F-Ph	74:26	79:21[e]	86:14

[a] Diastereomeric ratios determined by HPLC and ^{1}H NMR.
[b] Reactions were carried out using 10 wt% of 20% $Pd(OH)_2$ on C under atmospheric pressure with no acid for 18–96 h.
[c] Reduction resulted in loss of Br group.
[d] Reactions were carried out using 10 wt% of 20% $Pd(OH)_2$ on C under atmospheric pressure with 2 equiv. AcOH for 1–36 h.
[e] Reactions stopped prior to completion resulting in low overall yields (30–40%).
[f] Reactions were carried out using 10 wt% of 20% $Pd(OH)_2$ on C under atmospheric pressure with 2 equiv. $BF_3{\cdot}Et_2O$ for 1–6 h.

diastereomer. All of the phenyl and substituted phenyl enamines (entries 5–9) showed an increase in selectivity as well to ~7:1 dr. Based on our results, addition of acid to the reduction leads to an increase in selectivity with 2 equiv. of $BF_3{\cdot}Et_2O$ affording the best diastereomeric ratios. In order to gain some insight into the reason for the increase, we examined the reduction of the 2-pyridyl *Z*-enamine more closely by HPLC analysis and NMR and noted an important difference between the three reduction conditions. When the reaction was carried out in the absence of acid, the *Z*-enamine was the major isomer in solution with very little *E*-enamine present (<5%) and the worst results for reaction rate and selectivity were observed. When 2 equiv. of AcOH was added to the reaction, there was some isomerization of the *Z*-enamine to the *E*-enamine (15–20%) and the selectivity increased slightly. However, when the reduction was carried out with 2 equiv. of $BF_3{\cdot}Et_2O$, the *E*-enamine becomes the major isomer (>70%) in solution via isomerization of the *Z*-enamine and the best results for selectivity are observed. Thus, a correlation between enamine stereochemistry and selectivity becomes evident for these reactions. In order to verify this, we carried out the three reductions (no acid, AcOH, and $BF_3{\cdot}Et_2O$) on the two compounds where we isolated both pure *E*- and *Z*-enamines as a direct comparison (Table 2).

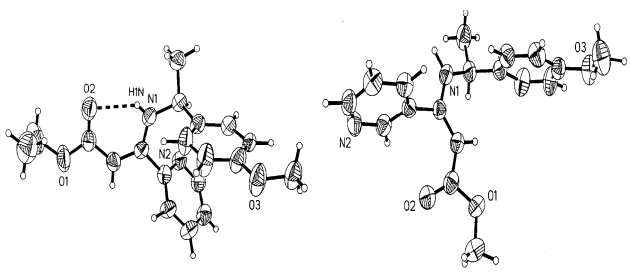
Reduction of the *Z*-enamines (entries 1–2) afforded the lowest selectivity in the absence of acid where the *Z*-enamine was the major isomer and the best selectivity upon addition of $BF_3{\cdot}Et_2O$ where isomerization to the *E*-enamine predominates. Conversely, reduction of the *E*-enamines (entries 3–4) afforded the best selectivity in the absence of acid as the *E*-enamine is the major isomer. Slightly less selectivity is observed upon addition of BF_3 Et_2O due to some isomerization to the *Z*-enamine. These results confirm our earlier observations verifying the relationship of enamine stereochemistry on selectivity for the reduction. Specifically, we obtain the best selectivity via reduction of the *E*-enamine versus the corresponding *Z*-isomer.

While there has been a lot of work reported on the reduction of enamines,[10] less attention has been paid to the importance of enamine stereochemistry on selectivity partially due to the problems associated with separation and isolation of pure *E*/*Z*-isomers. Specifically in the area of β-amino ester synthesis, this issue has not been fully addressed for acyclic systems such as ours, however, there has been some reports for cyclic systems[11] where it is easier to control both enamine stereochemistry and selectivity for the reduction. Based on our experimental results, we expanded the scope of our research to include a study of the differences between the *E*- and *Z*-enamines in both solid state and solution in order to explain the increase in selectivity when the *E*-enamine predominates throughout the reduction.

First we looked at the crystal structure of each enamine as shown in Fig. 1. The 2-pyridyl-*Z*-enamine shows hydrogen bonding between the NH of the enamine and the oxygen of the ester carbonyl making this a very rigid structure. Conversely, the 3-pyridyl-*E*-enamine shows no hydrogen bonding allowing for much more free rotation in this molecule. While the crystal structures give some insight into the differences of these two compounds in the solid state, we needed to examine the different confirmations of each enamine in solution in order to determine the effect of stereochemistry on selectivity during the reduction.

In order to do this, we carried out a conformational analysis on the 4-F-Ph-*E*/*Z*-enamines using the electrostatically driven Monte Carlo (EDMC) hydration shell method.[12] After the study was complete, we examined the minimal energy confirmations plus 1 kcal for each enamine, which accounts for approximately 80% of confirmations in solution. The *Z*-enamine as shown in Fig. 2 shows very little rotation suggesting there is also hydrogen bonding between the NH of the enamine and the oxygen of the ester carbonyl in solution as well. As a result of this rigid structure, the hydrogen during the reduction can approach either face of the enamine double bond with little differentiation thus accounting for the poor selectivity observed when the *Z*-enamine was the major isomer.

For the *E*-enamine (Fig. 3), there is no intramolecular hydrogen bonding thus allowing for free rotation espe-



(*Z*)-2-pyridyl (*E*)-3-pyridyl

Figure 1. Crystal structures for *Z*- and *E*-enamines.

Table 2. Reduction of 3-pyridyl and 4-pyridyl *Z*/*E*-enamines[a]

Entry	Ar	No acid SS:SR	AcOH SS:SR	$BF_3{\cdot}Et_2O$ SS:SR
1	3-Pyridyl (*Z*-isomer)	80:20	83:17	88:12
2	4-Pyridyl (*Z*-isomer)	41:59	58:42	90:10
3	3-Pyridyl (*E*-isomer)	92:8	85:15	71:29
4	4-Pyridyl (*E*-isomer)	71:29	61:39	85:15

[a] Reaction conditions are the same as reported in Table 1.

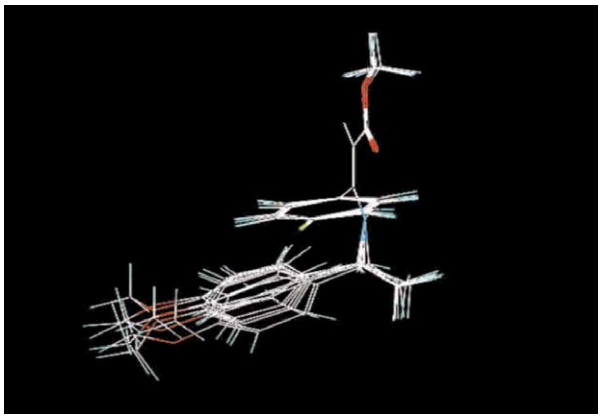


Figure 2. Confirmation analysis of (*Z*)-4-F-Ph-enamine.

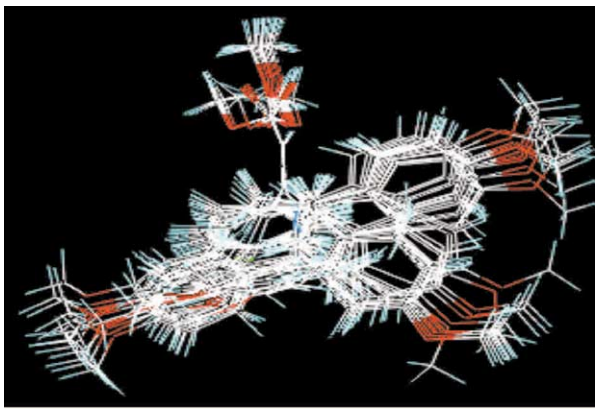


Figure 3. Confirmation analysis of (*E*)-4-F-Ph-enamine.

cially around the C–N bonds. As a result of the rotation, the α-methylbenzyl group can block the back face of the enamine double bond forcing the hydrogen to approach from the less hindered front face during the reduction. This affords the desired *S* stereochemistry for the new stereocenter being formed thus explaining the increase in selectivity when the *E*-enamine was reduced.

From our initial studies, it has become apparent that the difference in selectivity for the reduction between the *Z*- and *E*-enamines is based on steric effects resulting from the preference of hydrogen to approach the less hindered face of the enamine double bond.

Based on enamine stereochemistry, we conducted the reduction of enamines **2**[8] under different conditions to achieve the highest diastereomeric purity of the resulting secondary amines **3**.[8] For the *Z*-enamine, reduction was carried out using atmospheric catalytic hydrogenation with Pearlman's catalyst in the presence of 2 equiv. $BF_3{\cdot}Et_2O$ to effect isomerization to the *E*-enamine. However, reduction of the *E*-enamine was carried out using atmospheric catalytic hydrogenation with Pearlman's catalyst in the absence of acid. In this manner, we were able to predict conditions to favor formation of the desired *S*,*S* diastereomer of **3**, thus leading to greater overall yields. Using either reaction, the major *S*,*S* diastereomer of the secondary amines **3** were isolated in >98% de either by formation of a salt (HCl or fumarate worked best) or by crystallization from an appropriate solvent. The removal of the *p*-methoxy-α-methylbenzyl group was achieved by heating the purified secondary amines in formic acid with Et_3SiH to afford the corresponding β-amino esters **4** (75–95% yield), which are isolated as hydrochloride or fumarate salts. The overall yield for this process ranged from 30–60% and the products were isolated in >98% ee.

In summary, we have developed a general procedure for the synthesis of β-aryl-β-amino esters with high enantiopurity and good overall yields. Our current efforts focus on improving the diastereoselectivity of the key reduction step to increase overall yields.

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8. All new compounds show spectral/analytical data consistent with their structures. Representative examples: **2** (Ar = 4-pyridyl; *E*-isomer) ^{1}H NMR (THF-d_8) δ (ppm) 8.5 (d, 2H), 7.2 (d, 2H), 7.1 (d, 2H), 6.9 (d, 2H), 6.2 (d, 1H, NH), 4.6 (s, 1H), 4.5 (m, 1H), 3.7 (m, 5H), 1.4 (d, 3H), 1.0 (t, 3H); ^{13}C NMR (THF-d_8) δ (ppm) 164, 157, 155, 147, 145, 134, 125, 122, 112, 84, 56, 53, 51, 12. MS (ESI) m/z 327 (MH^+); **2** (Ar = 4-pyridyl; *Z*-isomer) ^{1}H

NMR (THF-d_8) δ (ppm) 8.9 (d, 1H, NH), 8.5 (d, 2H), 7.1 (d, 2H), 7.0 (d, 2H), 6.8 (d, 2H), 4.6 (s, 1H), 4.4 (m, 1H), 4.1 (q, 2H), 3.7 (s, 3H), 1.4 (d, 3H), 1.2 (t, 3H); ^{13}C NMR (THF-d_8) δ (ppm) 168, 160, 158, 149, 143, 135, 125, 121, 112, 86, 57, 53, 52, 12. MS (ESI) m/z 327 (MH^+); **3** (Ar = 4-pyridyl-2HCl salt) ^{1}H NMR (CD_3OD) δ (ppm) 8.8 (d, 2H), 8.3 (d, 2H), 7.4 (d, 2H), 6.9 (d, 2H), 4.6 (m, 1H), 4.1 (m, 2H), 3.7 (s, 3H), 3.5 (dd, 1H), 3.3 (dd, 1H), 1.8 (d, 3H), 1.2 (t, 3H); ^{13}C NMR (CD_3OD) δ (ppm) 170, 163, 156, 144, 131, 129, 129, 116, 63, 61, 58, 56, 38, 21, 15. MS (ESI) m/z 329 (MH^+)

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