β-Amino Amides from β-Lactams: Application to the Formal Synthesis of a Peptide-Deformylase Inhibitor

Xinglong Jiang, Kapa Prasad,* Mahavir Prashad, Joel Slade, Oljan Repič, Thomas J. Blacklock

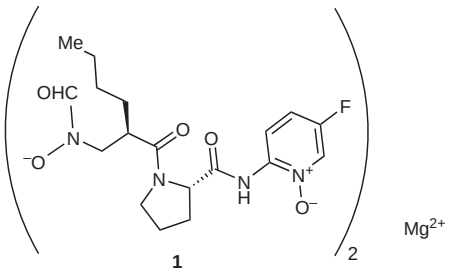
Process Research & Development, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936, USA
E-mail: Prasad.kapa@novartis.com

Received 16 June 2006

Abstract: A facile and a practical synthesis of peptide-deformylase inhibitor **1** is described using an acid-catalyzed aminolysis of β-lactam **12** with pyrrolidine **6** as the key transformation. In addition, simplified conditions for the conversion of a β-hydroxy acid to a β-lactam are reported.

Key Words: β-amino amides, β-lactams, peptide-deformylase inhibitor

Compound **1** is an extremely potent inhibitor of peptide deformylase (PDF)[1] in vitro while showing good antibacterial activity in vivo. It is active against pathogenic bacterial strains that have acquired resistance to other antibacterial agents. The PDF inhibitors of this class have the potential to be developed into an antibacterial agent with the ability to eradicate many bacterial respiratory infections.



1

Figure 1

Initial quantities of **1** that were needed for studies were made[1,2] utilizing a Michael addition of *O*-benzylhydroxylamine to compound **2** as the key step to generate the stereogenic center in the β-amino amide portion of the molecule (Scheme 1). This addition gave a mixture of diastereoisomers **3** in a 4:1 ratio. The desired isomer **4** was isolated in pure state as tosic acid salt by crystallization. As we needed a more expeditious synthesis to make larger quantity of **1**, we investigated the concept of arriving at β-amino amides from β-lactams (Scheme 2), and this led to a practical preparation of **1**.

The use of β-lactams in the preparation of β-amino acids and their subsequent conversion to β-amino amides is well documented in the literature.[3,4] Our strategy from the outset was to exclude the intermediacy of β-amino acids as it adds an additional step that requires the use of activation methodology needed for the formation of the peptidic bond from the carboxylic acid.

Instead, the N-oxygenated β-lactams in the present study are activated enough to facilitate direct aminolysis as reported earlier by Jin and Kim[5] using 10 equivalents of 40% methylamine solution. These results were encouraging enough to start our work but not yet practical as the amine component was used in large excess.

The β-lactam **12** was made in a high yield starting from **9** as shown in Scheme 3. Condensation of **9** with benzyloxyamine·HCl salt in water in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) gave **10** in quantitative yield.[6]

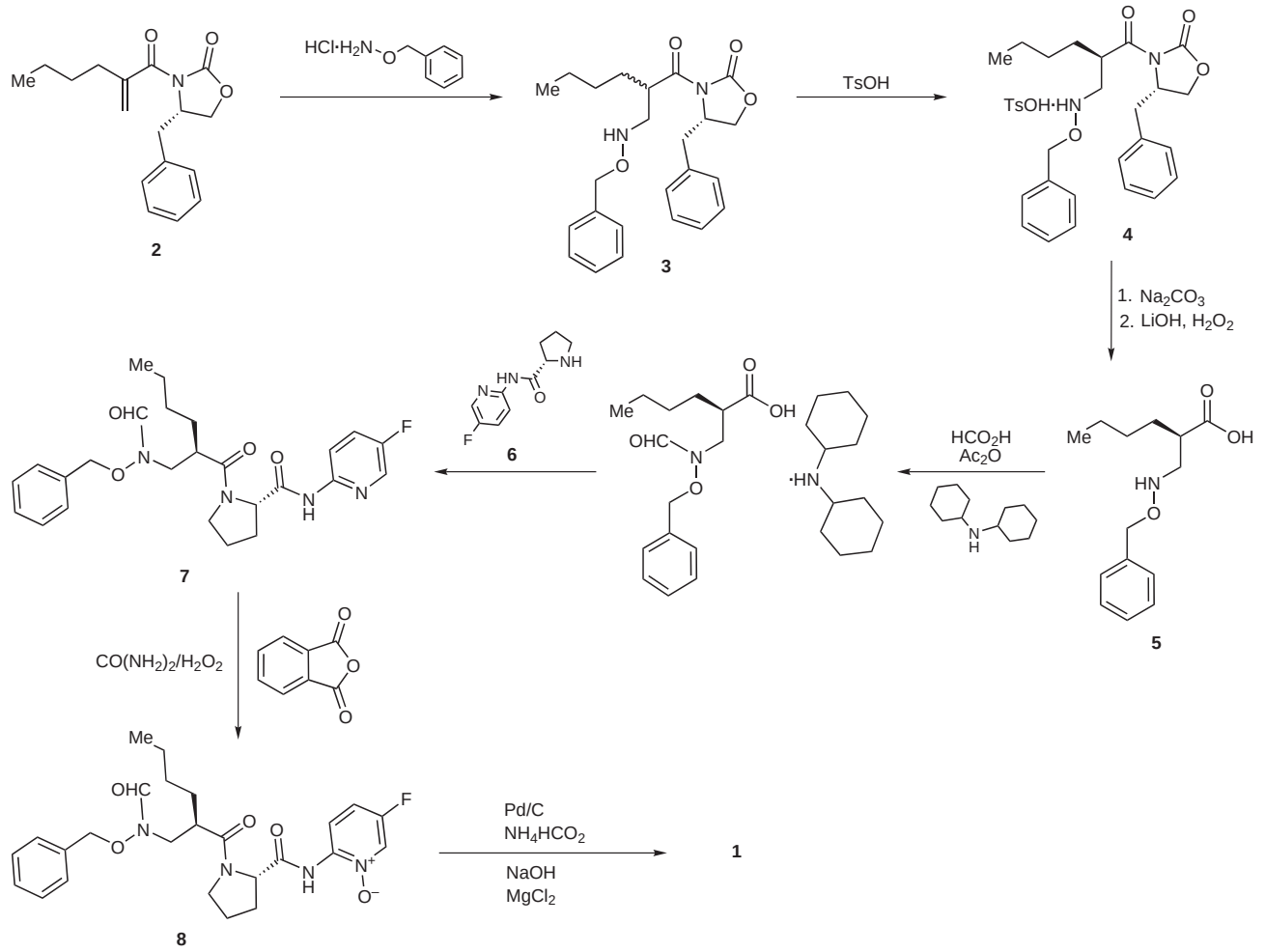
Conversion of **10** to mesylate **11** was accomplished in pyridine, and the product was isolated in >98% yield as a solid by quenching the reaction mixture with aqueous HCl. Finally, the β-lactam formation from **11** was accomplished by using potassium carbonate, tetrabutylammonium bromide in THF and heating the reaction mixture at 40 °C for 6 hours.[7] Pure product **12** was isolated after filtration and evaporation of the solvent and extraction with ethyl acetate and water.

Initial studies on the aminolysis (see Table 1) of **12** with 1.2 equivalents of **6** were disappointing. In neat methanol and 8% aqueous methanol the product formation was negligible. However, when a concentrated 40% aqueous methanol was used desired **13** was produced in 80% yield along with a by-product. The yield was dramatically improved to >96% by using 2-ethylhexanoic acid as the catalyst, and the preferred solvent was THF.

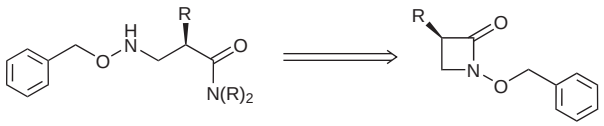
Having accomplished the preparation of β-amino amide **13** in high yield, the only step remaining for formal completion of the synthesis of **1** was the formylation. This was carried out in a straightforward manner using formic acid–acetic anhydride mixture in isopropyl acetate while maintaining the temperature at –7 °C. Product **7** was isolated as a crystalline solid in 80% overall yield starting from **11**, and its identity was confirmed by comparison with an authentic sample.

In conclusion, a highly efficient synthesis of **1** was described using aminolysis of a β-lactam intermediate as the key step. The stereochemical integrity of all chiral centers was preserved through out the synthesis, and the preparation of β-lactam itself was carried out in a highly practical manner from **9**.

SYNLETT 2006, No. 18, pp 3179–3181
Advanced online publication: 25.10.2006
DOI: 10.1055/s-2006-951499; Art ID: S14506ST



Scheme 1

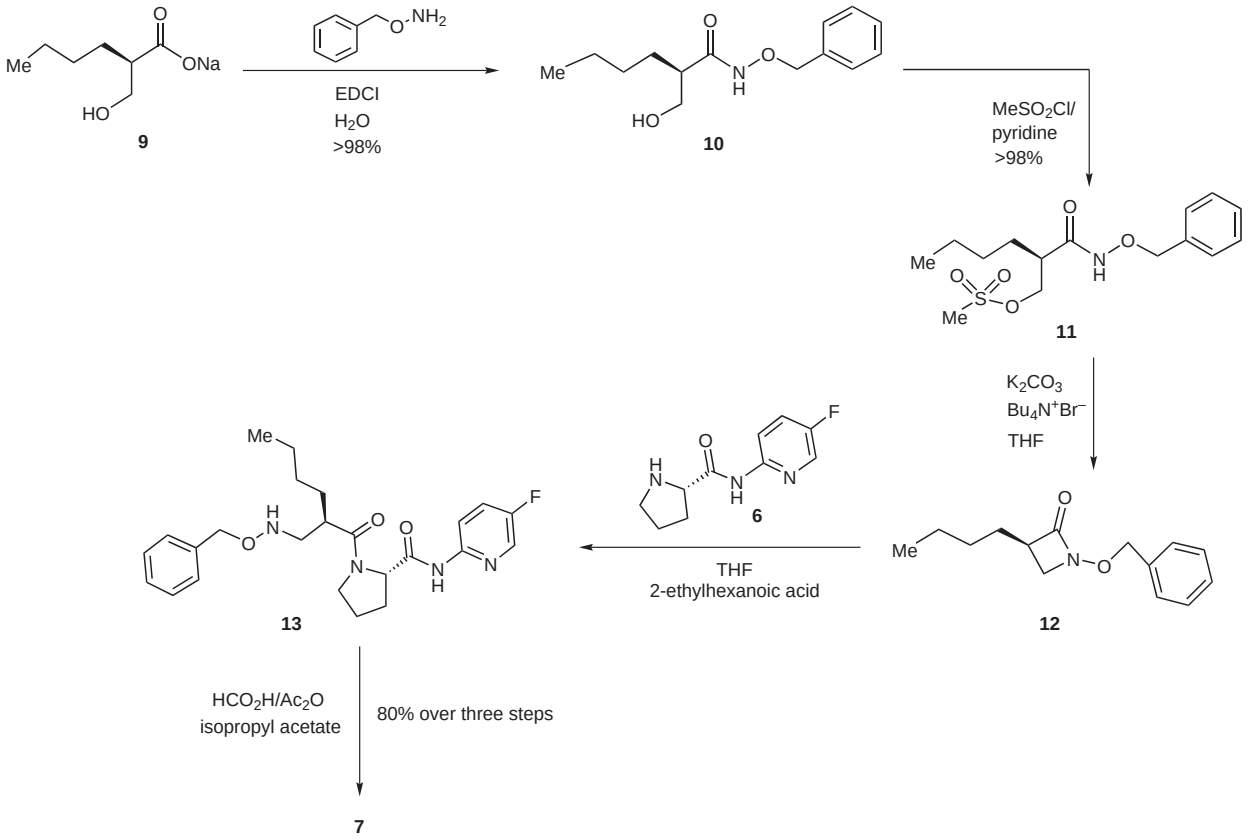


Scheme 2

Table 1 Aminolysis of **12** with **6**

Entry	Solvent	Additive	Temp (°C)	Time (h)	**13** (%)	Impurity (%)	Unreacted **12** (%)
1	MeOH (25 mL)	None	65	3	–[a]	–[a]	>95
2		H_2O (2 mL)	70	3	–[a]		>95
3	MeOH (5 mL)	H_2O (2 mL)	83	17	80	18	2
4	Toluene	None	reflux	4	–[a]		>95
5		1 equiv TMSCl	reflux	3	–[a]		>90
6		1 equiv 2-EHA	reflux	3	70	20	10
7	THF	0.5 equiv 2-EHA	72	7	>96	<2	<2
8	THF	0.5 equiv HCl (6 N)	68	4	15	5	80
9	Isopropyl acetate	0.5 equiv 2-EHA	72	8	90	8	2

[a] Not detected.



Scheme 3

References and Notes

(1) (a) Lopez, S.; Wu, C.; Blais, J.; Hackbarth, C.; Gomez, M.; Kubo, A.; Jain, R.; Sundaram, A.; Alvarez, S.; Bracken, K.; Dean, K.; Weidmann, B.; Patel, D.; Trias, J.; White, R.; Yuan, Z. *44th Annual Interscience Conference on Microbial Agents and Chemotherapy*; Washington, D.C., **2004**; October 20 – November 2, Poster No. *F1959*. (b) Patel, D. V.; Yuan, Z.; Jain, R. K.; Garcia Alvarez, S.; Jacobs, J. WO 2002102790, **2002**. (c) Jones, R. N.; Sader, H. S.; Fritsche, T. R. *Diagn. Microbiol. Infect. Dis.* **2005**, *51*, 139.

(2) Slade, J.; Parker, D. J.; Girgis, M.; Mueller, M.; Vivelo, J.; Liu, H.; Bajwa, J. S.; Chen, G.-P.; Carosi, J.; Lee, P.; Chaudhary, A.; Wambser, D.; Prasad, K.; Bracken, K.; Dean, K.; Boehnke, H.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2006**, *10*, 78.

(3) Xu, Y.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4314.

(4) Jin, Y.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3515.

(5) Jin, Y.; Kim, D. H. *Synlett* **1998**, 1189.

(6) Spectral data on new compounds are as follows.
Compound **10**: ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 4.12 Hz, 3 H), 1.18–1.26 (m, 5 H), 1.50–1.53 (m, 1 H), 2.10–2.23 (m, 1 H), 3.56–3.57 (s, 1 H), 3.60–3.62 (m, 2 H), 4.81–4.88 (m, 2 H), 7.31–7.37 (m, 5 H), 9.47 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 14.29, 23.01, 28.41, 29.73, 46.88, 63.96, 79.02, 128.70, 128.99, 129.60, 135.70, 173.56; $[\alpha]_D^{25}$ +0.556 (*c* 1.05, MeOH).
Compound **11**: ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.78 Hz, 3 H), 1.30–1.40 (m, 5 H), 1.58–1.60 (m, 1 H), 2.41–2.43 (m, 1 H), 2.97 (s, 3 H), 4.26–4.28 (m, 2 H), 4.93 (s, 2 H), 7.30–7.40 (m, 5 H), 8.52 (s, 1 H). ^{13}C ($CDCl_3$): δ = 13.78, 22.47, 28.02, 29.10, 37.23, 43.98, 70.21, 78.43, 128.66, 128.87, 129.31, 135.03, 170.06; $[\alpha]_D^{25}$ +5.901 (*c* 1.06, MeOH).
Compound **12**: ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.14 Hz, 3 H), 1.27–1.29 (m, 4 H), 1.43–1.48 (m, 1 H), 1.65–1.67 (m, 1 H), 2.81–2.83 (m, 1 H), 2.90 (dd, *J* = 2.46, 3.88 Hz, 1 H), 3.34 (dd, *J* = 2.46, 4.89 Hz, 1 H), 4.93 (s, 2 H), 7.35–7.39 (m, 5 H). ^{13}C NMR ($CDCl_3$): d = 13.85, 22.42, 28.49, 29.25, 45.11, 51.46, 77.94, 128.32, 128.69, 129.85, 135.31, 166.99; $[\alpha]_D^{25}$ +24.63 (c 1.02, MeOH).
Compound **13**: ^{1}H NMR ($CDCl_3$): δ = 0.78 (t, *J* = 6.90 Hz, 3 H), 0.82–0.90 (m, 1 H), 1.08–1.28 (m, 4 H), 1.31–1.38 (m, 1 H), 1.51–1.68 (m, 1 H), 1.69–1.73 (m, 1 H), 1.82–2.10 (m, 2 H), 2.32–2.42 (m, 1 H), 2.86–3.05 (m, 2 H), 3.20–3.31 (m, 1 H), 3.42–3.56 (m, 2 H), 4.68 (s, 2 H), 4.72–4.76 (m, 1 H), 7.20–7.42 (m, 6 H), 8.10–8.20 (m, 2 H), 9.75 (s, 1 H). ^{13}C ($CDCl_3$): δ = 13.91, 22.79, 24.33, 24.95, 29.60, 31.03, 42.36, 47.54, 53.83, 60.40, 75.85, 114.45, 114.50, 124.63, 124.89, 127.98, 128.45, 135.35, 135.69, 137.61, 147.72, 147.75, 154.58, 157.90, 169.53, 176.32; $[\alpha]_D^{25}$ –74.43 (*c* 1.01, MeOH).

(7) (a) In the literature, acetone in combination with potassium carbonate was typically used for the formation of these type of β-lactams, see ref. 7b. For practical reasons we preferred THF as the solvent and this necessitated the use of a phase-transfer catalyst. (b) Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 5160.