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Asymmetric Hydrogenation of *N*-Sulfonylated-α-dehydroamino Acids: Toward the Synthesis of an Anthrax Lethal Factor Inhibitor

C. Scott Shultz,* Spencer D. Dreher,* Norihiro Ikemoto, J. Michael Williams, Edward J. J. Grabowski, Shane W. Krska, Yongkui Sun, Peter G. Dormer, and Lisa DiMichele

Department of Process Research and the Catalytic Reactions Discovery and Development Lab, Merck and Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

scott_shultz@merck.com

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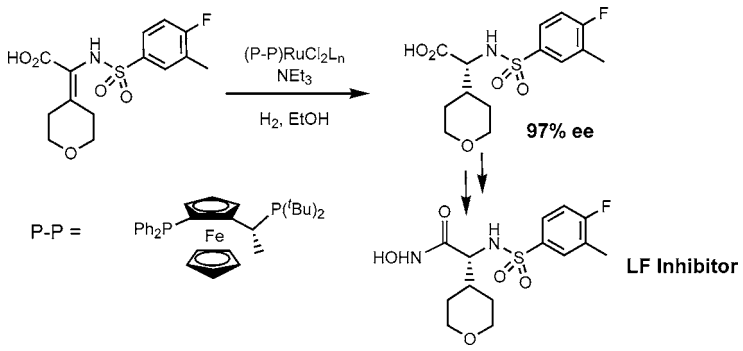
ABSTRACT

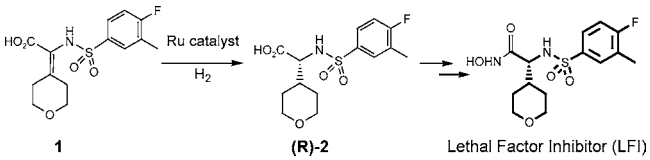


A novel and highly enantioselective Ru-catalyzed hydrogenation of *N*-sulfonylated-α-dehydroamino acids has been discovered and demonstrated in the synthesis of an anthrax lethal factor inhibitor (LFI). Herein, this methodology is used to prepare *N*-sulfonylated amino acids in up to 98% ee. This unprecedented hydrogenation uses a chiral Ru catalyst rather than Rh as typical for acylated dehydroamino acids and esters, and this work reports the first asymmetric hydrogenation of a tetrasubstituted dehydroamino acid derivative using a Ru catalyst.

The use of asymmetric catalysis in the synthesis of complex molecules has traditionally involved the preparation of simple, often protected, chiral building blocks that are subsequently transformed into more highly functionalized targets. A more efficient and cost-effective approach would shift chirality-inducing transformations toward the end of the synthesis. Such an approach would necessarily involve complex, highly functionalized substrates in the catalytic step and thus would push the boundaries of the scope of asymmetric catalysis.

Merck scientists have identified a promising synthetic lethal factor inhibitor (LFI) (Scheme 1) that has potent pre-exposure efficacy against *Bacillus anthracis* challenge in both mouse and rabbit infection models.[1] In an effort to streamline the synthesis of Merck's LFI for delivery of bulk material, we envisioned an unprecedented late-stage asymmetric hydrogenation of a tetrasubstituted *N*-sulfonyl-α-dehydroamino acid, **1**, leading in short order to the LFI. This synthetic strategy was realized, thus replacing a less efficient route proceeding through a highly enantioselective hydrogenation of the CBz-protected dehydroamino ester.[2,3]

Scheme 1. Proposed LFI Synthesis



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Despite a sizable body of literature demonstrating the biological activity of *N*-sulfonyl-α-amino acid derivatives,[4] there are no examples of asymmetric hydrogenation of *N*-sulfonyl-α-dehydroamino acid derivatives in the literature.[5] Additionally, hydrogenation of tetrasubstituted variants of amide- or carbamate-protected α-dehydroamino acid derivatives are less common as a result of the decreased reactivity caused by steric hindrance and have, in all cases, employed Rh catalysts.[6] The Me or Et ester derivative is almost exclusively used rather than the acid,[7] so we began our investigation by screening Rh catalysts for the hydrogenation of the Me ester of carboxylic acid **1** and found it to be quite unreactive. This led us to evaluate the hydrogenation of acid **1** with a Ru catalyst.[2] The use of Ru catalysts for the hydrogenation of α-dehydroamino acids has been known for some time;[8,9] however, to the best of our knowledge, there are no reported examples of tetrasubstituted substrates.[10]

Ru catalysts were found to have good reactivity for the hydrogenation of **1**,[11] and screening experiments identified the Josiphos ligand (*R*)-(*S*)-Ph_2P-F-C-P(^{t}Bu)$_2$ **A** (Figure 1) as the most enantioselective, giving 97% ee of desired (*R*)-**2** after optimization.[2] To investigate the generality of this Ru-mediated asymmetric hydrogenation reaction, we synthesized

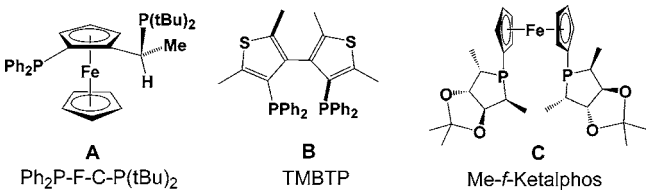
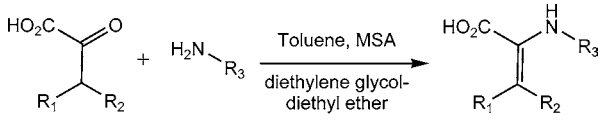


Figure 1. Phosphine ligand structures.

a variety of *N*-sulfonyl-α-dehydroamino acids, **3a**−**i** (Table 1). Compounds **3a**−**i** were all prepared by MSA-catalyzed condensation of an α-ketoacid with a sulfonamide in toluene with Dean−Stark removal of water.[12,13] No attempt was made to optimize the yields of **3a**−**i**. These compounds were taken to high purity by chromatography, recrystallization, or both.

Table 1. Synthesis of *N*-Sulfonyl-α-dehydroamino Acids **3a**−**i**



3

entry	no.	R_1	R_2	R_3	yield (%)
1	**3a**	-$(CH_2)_5$-		4-Me-C_6H_4-SO_2-	86
2	**3b**	-$(CH_2)_5$-		4-F-C_6H_4-SO_2-	62
3	**3c**	Me	Me	4-Me-C_6H_4-SO_2-	54
4	**3d**	Me	Me	4-OMe-C_6H_4-SO_2-	15
5	**3e**	Me	Me	4-F-C_6H_4-SO_2-	62
6	**3f**	Me	Me	C_6H_5-CH_2-SO_2-	51
7	**3g**	Me	Me	C_6H_5-$(CH_2)_3$-SO_2-	67
8	**3h**	Me	H	4-Me-C_6H_4-SO_2-	59
9	**3i**	iPr	H	4-Me-C_6H_4-SO_2-	57

Using conditions similar to those that proved optimal for the reduction of **1** (90 psig H_2, 0.5 equiv NEt_3, 25 °C, 1 mol % catalyst, EtOH solvent),[14] we found that the Josiphos ligand Ph_2P-F-C-P(^{t}Bu)$_2$ **A** worked well for substrates **3a** and **3b** (Table 2), which are structurally analogous to **1**. The Ts-valine substrate **3c**, however, gave unsuitably low enantioselectivity (49% ee) with the Josiphos ligand **A**. Catalyst screening identified the bis-thiophene atropisomeric ligand TMBTP **B**,[15] which gave very high enantioselectivity (96−97% ee) for **3c** and worked well for the other valine substrates **3d**−**g** as well. Both ligands **A** and **B** showed only modest stereoselectivity for trisubstituted substrate **3h** (**A** gave 67% ee, and **B** gave 70% ee[16]). Zhang's (*S*,*S*,*S*,*S*)-Me-*f*-Ketalphos **C**[17] gave useful enantioselectivity for the trisubstituted variants, reducing **3h** in 91% ee. The bulky *i*-Pr group in the dehydro-leucine substrate **3i** significantly reduced

(1) Shoop, W. L.; Xiong, Y.; Wiltsie, J.; Woods, A.; Guo, J.; Pivnichny, J. V.; Felcetto, T.; Michael, B. F.; Bansal, A.; Cummings, R. T.; Cunningham, B. R.; Friedlander, A. M.; Douglas, C. M.; Patel, S. B.; Wisniewski, D.; Scapin, G.; Salowe, S. P.; Zaller, D. M.; Chapman, K. T.; Scolnick, E. M.; Schmatz, D. M.; Bartizal, K.; MacCoss, M.; Hermes, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 7958−7963.

(2) Full details of these experiments are reported in an upcoming publication.

(3) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375−9376.

(4) For example, see: (a) Kottirsch, G.; Zerwes, H.-G.; Cook, N. S.; Tapparelli, C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 727. (b) O'Brien, P. M.; Ortwine, D. F.; Pavlovsky, A. G.; Picard, J. A.; Sliskovic, D. R.; Roth, B. D.; Dyer, R. D.; Johnson, L. L.; Man, C. F.; Hallak, H. *J. Med. Chem.* **2000**, *43*, 156. (c) Pikul, S.; Ohler, N. E.; Ciszewski, G.; Laufersweiler, M. C.; Almstead, N. G.; De, B.; Natchus, M. G.; L. C., H.; Janusz, M. J.; Peng, S. X.; Branch, T. M.; King, S. L.; Taiwo, Y. O.; G. E., M. *J. Med. Chem.* **2001**, *44*, 2499. (d) Dankwardt, S. M.; Abbot, S. C.; Broka, C. A.; Martin, R. L.; Chan, C. S.; Springman, E. B.; Van Wart, H. E.; Walker, K. A. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1233.

(5) Recently, Ito has reported the asymmetric hydrogenation of an *N*-sulfonylated indole with a Rh catalyst. Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213−2215.

(6) For example, see: (a) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem.* Soc. **1995**, *117*, 9602. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (c) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 3499. (d) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988−2989 (e) Blaser, H.-U.; Spindler, F.; Studer, M. *Appl. Catal., A* **2001**, *221*, 119−143. (f) Sheih, W.-C.; Xue, S.; Reel, N.; Wu, R.; Fitt, J.; Repic, O. *Tetrahedron: Asymmetry* **2001**, *12*, 2421. (g) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471 (h) Ohashi, A.; Kikuchi, S.-i.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535. (i) Lennon, I. C.; Moran, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855−875. (j) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (k) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(7) Asymmetric hydrogenation of tetrasubstituted amide-protected α-amino acids with Rh catalysts is known: (a) Takahashi, H.; Achiwa, K. *Chem. Lett.* **1989**, *2*, 305. (b) Nagel, U.; Kinzel, E. *Chem. Ber.* **1986**, *119*, 3326.

(8) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.

(9) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1571.

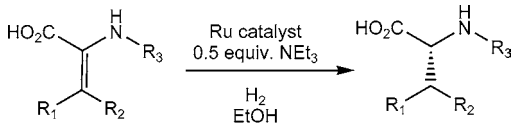
(10) A Ru catalyst has been used to hydrogenate a tetrasubstituted enamide; see: Dupau, P.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 331−334.

(11) Ru catalyst solutions were prepared by mixing [(cymene)$RuCl_2$]$_2$ + phosphine ligand in 3:1 EtOH/1,2-dichloroethane at 50 °C for ≥1 h. See Supporting Information for complete details.

(12) Yonezawa, Y.; Shin, C.; Ono, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2905.

(13) A small amount of high-boiling diethylene glycol diethyl ether was employed to keep the polar materials in solution during the reaction.

Table 2. Hydrogenation of *N*-Sulfonyl-α-dehydroamino Acids **3a**−**i** and *N*-Carbobenzoxy-α-dehydroamino Acids **5a,b**



3, 5 **4, 6**

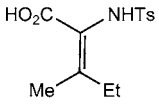
entry[a]	no.	R_1	R_2	R_3	ligand[b]	assay yield (%)[c]	ee (%)
1[d]	**3a**	-(CH2)5-		4-Me-C_6H_4-SO_2-	A	>99	95.9
2	**3b**	-(CH2)5-		4-F-C_6H_4-SO_2-	A	98	95.9
3	**3c**	Me	Me	4-Me-C_6H_4-SO_2-	B	>99	97.0
4	**3d**	Me	Me	4-OMe-C_6H_4-SO_2-	B	93	97.6
5	**3e**	Me	Me	4-F-C_6H_4-SO_2-	B	95	97.2
6	**3f**	Me	Me	C_6H_5-CH_2-SO_2-	B	>99	97.3
7	**3g**	Me	Me	C_6H_5-$(CH_2)_3$-SO_2-	B	98	98.1
8	**3h**	Me	H	4-Me-C_6H_4-SO_2-	C	96	91.4
9[e]	**3i**	iPr	H	4-Me-C_6H_4-SO_2-	C	>99	89.6
10	**5a**	Me	Me	CBz	B	94	99.1
11	**5b**	-(CH2)5-		CBz	A	95	91.4

[a] Typical Conditions: 1 mol % catalyst, approximately 150 mg of substrate, 0.5 equiv of NEt_3, 1.5 mL of EtOH, 90 psig H_2, 25 °C, 24 h. [b] See Figure 1 for ligand structure. [c] Determined by HPLC. [d] 2 mol % catalyst. [e] 5 mol % catalyst, 100 mg of substrate, 40 °C, 24 h.

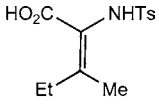
reactivity, and 5 mol % of the Me-*f*-Ketalphos catalyst was required for full converison. The enantioselectivity (89.6%), however, was largely unaffected by this change in reactivity.[18]

The reaction is remarkably tolerant of the sulfonamide structure and electronics. For the cyclohexyl substrates **3a** (4-Me) and **3b** (4-F) identical enantioselectivity was observed. Similarly in the valine series **3d**−**f** (4-Me, 4-OMe, and 4-F) minimal effect on the reaction ee was noted. Inserting methylene groups in **3f** and **3g** to isolate the olefin from electronic or steric effects of the aryl side chain also had negligible effect. The insensitivity of the hydrogenation of substrates **3a**−**g** to the electronic nature of the sulfonamide side chain led us to consider whether other, non-sulfonamide groups would be similarly tolerated, thus broadening the scope of this method. Hydrogenation of carbobenzoxy (CBz)-protected substrates **5a** and **5b**[19] under our standard conditions gave results similar to those of the sulfonamide cases. We were somewhat surprised to find no literature examples of the hydrogenation of a tetrasubstituted carbamate-protected dehydroamino acid using ruthenium catalysis, and this may prove to be a useful general asymmetric amino acid synthesis.

Table 3. Hydrogenation of Isoleucine Substrates (*E*)-**7** and (*Z*)-**7**



(*Z*)-7



(*E*)-7

entry	no.	*E*:*Z*[a]	ligand[b]	*T* (°C)	H_2 (psig)	ee[c] (%)	dr	conv[d] (%)	config[e]
1	***E*-7**	76:1	B	40	90	94.9	26:1	>99	(*R*,*S*)
2	***E*-7**	76:1	B	25	90	95.9	45:1	>99	(*R*,*S*)
3	***E*-7**	76:1	B	15	500	97.4	56:1	>99	(*R*,*S*)
4	***Z*-7**	1:135	B	40	90	85.3	1.5:1	>99	(*R*,*R*)
5	***Z*-7**	1:135	B	15	500	96.0	21:1	>99	(*R*,*R*)

[a] HPLC ratio (224 nm). [b] See Figure 1 for ligand structure. [c] ee of major diastereomer. [d] Typical assay yields for hydrogenation of (*E*)-**7** (93%) and (*Z*)-**7** (86%). [e] (*R*,*S*) denotes *R* stereochemistry at the α-carbon and *S* at the *β*-carbon, for example.

An important aspect of this work is the reduction of substrates that are prochiral at the *β*-position. We therefore prepared the dehydro-isoleucine substrates (*E*)-**7** and (*Z*)-**7**[20] and found that the hydrogenation reactions were more challenging (Table 3). High levels of enantioselectivity were observed; however, a significant amount of Ru-mediated *E*/*Z* isomerization led to a substantial loss in diastereoselectivity. At 90 psig H_2 and 40 °C, hydrogenation of (*Z*)-**7** gave a diastereomeric ratio (dr) of 1.5:1 compared to 26:1 observed in the hydrogenation of (*E*)-**7** (entries 1 and 5). This problem was mitigated by reducing the reaction temperature and increasing the H_2 pressure. Presumably, the rate of isomerization is largely unaffected by hydrogen pressure, whereas the hydrogenation rate is enhanced at higher pressure. At 500 psig H_2 and 15 °C, the dr increased to 20:1 for (*Z*)-**7** and 56:1 for (*E*)-**7**.[21]

It is possible that the Ru-catalyzed hydrogenation of both the *N*-sulfonyl-α-dehydroamino acids and the *N*-acyl-α-dehydroamino acids proceeds by a mechanism similar to that

(14) A number of solvents were examined, and alcoholic solvents such as methanol, ethanol, and trifluoroethanol were superior to polar aprotic and nonpolar solvents such as THF, EtOAc, and toluene (see Supporting Information for complete details). As was observed for the hydrogenation of **1**, the ee in the hydrogenation of **3c** decreased at >1.0 equiv of NEt_3, dropping to 86.3% and 84.4%, respectively, at 1.2 and 2.0 equiv. In addition to solvent studies, a DOE (design of experiments) study was carried out on **3c** to investigate the effect of base charge, H_2 pressure, and temperature on the reaction conversion and ee. (Standard conditions = 1 mol % catalyst, 24 h reaction time; see Supporting Information for details and plots.) As expected, the reaction conversion increases with increasing H_2 pressure; however, with respect to temperature there is a distinct maximum at approximatley 50 °C. The highest ee (96%) was observed at the upper end of the H_2 pressure range examined (100 psig) and lower limit of temperature range (25 °C). These data strongly indicate that there are catalyst stability problems at elevated temperatures. Increasing the NEt_3 charge (up to 0.95 equiv) gave only a slight increase in conversion (up to ~20%) at elevated H_2 pressure and had no effect on reaction ee.

(15) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 2043−2047.

(16) Hydrogenation of **3h** with TMBTP catalyst gave only 29% yield at 1 mol % catalyst, 25 °C, 24 h, 90 psig H_2.

(17) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471−4474.

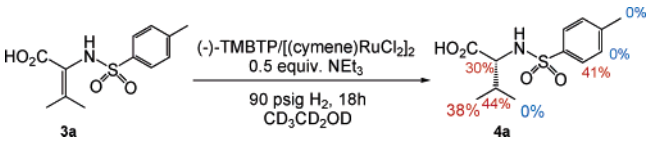
(18) Phenylalanine-derived substrates were briefly investigated and found to be somewhat unreactive (4−60% conversion) under standard conditions (S/C = 100, 90 psig H_2, 25 °C, 24 h), and the highest ee observed was approximately 30% with the TMBTP ligand.

(19) Compounds **5a** (52% isolated yield) and **5b** (43%) were prepared similar to: Yonezawa, Y.; Shin, C.; Ono, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2905.

(20) Dehydro-isoleucine substrates (*E*)-**7** and (*Z*)-**7** were prepared as a 1.25:1 (*E*/*Z*) mixture in 70% yield and separated via preparative SFC. See Supporting Information for details. Olefin geometry for (*E*)-**7** was determined on the basis of observed NOE (0.3%) at the *o*-phenyl of the Ts sulfonamide upon selective excitation of the methyl singlet.

(21) Diastereomer ratio reported is the ratio of the HPLC absorbance of each diastereomer at 224 nm.

Scheme 2. Extent of Deuterium Incorporation in the Hydrogenation of **3c** with H_2 in EtOD-d_6



proposed by Halpern for tiglic acid.[22] Two equivalents of substrate bind to the Ru center in an η^3 fashion through their carboxylate groups, and after activation of H_2, olefin insertion through an η^1 intermediate gives a five-membered chelate. Solvolysis of this chelate and substrate exchange completes the catalytic cycle.

Halpern observed that under H_2 in CD_3OD the product contains a single D at the β-position with predominantly H at the α-position.[22] This observation suggests that exchange between the Ru−H intermediate and CD_3OD prior to insertion of the C═C bond is slow relative to the hydrogenation reaction. Finally, solvolysis (by CD_3OD) of the Ru−Cβ bond leads to the major product. To see if our system exhibited similar behavior, we performed the hydrogenation of **3c** in H_2/EtOD-d_6 (Scheme 2).

In the present system deuterium incorporation was observed in both the α (30%) and β (44%) positions of **4c** with slightly more in the β position. The most likely explanation is that H/D exchange between solvent and H_2 gas is faster than hydrogenation. Whereas the hydrogenation of tiglic acid in Halpern's experiments was generally complete within about 1 h, complete conversion of **3c** required 18 h. Substantial deuterium incorporation was also observed in one of the two γ-methyl groups of **4c** (38%), and the two ortho sites of the Ts side chain (41%). Surprisingly, the γ-incorporation was only observed in one methyl group, implying that there is no olefin isomerization occurring under these conditions. This is in stark contrast to the results observed with the dehydro-isoleucine substrates (*E*/*Z*)-**5** where hydrogenation of either olefin isomer gave rise to both sets of diastereomers. It was not obvious from this experiment which of the two γ-methyl groups in **3c** was undergoing H/D exchange. However, we obtained this answer by carrying the hydrogenation of **3c** (in EtOD-d_6/H_2) to ca. 50% conversion and analyzing unreacted **3c**. A very high level of deuterium incorporation (>90%) was observed *only* in the methyl group cis to the −COOH in **3c**.[23] At this time, we are unsure of the mechanism of H/D exchange in the γ-position as it could be due to C−H activation of the proximal allylic methyl group or from insertion/isomerization.

In conclusion, we have demonstrated a novel asymmetric hydrogenation methodology for the synthesis of *N*-sulfonyl-α-amino acids using chiral Ru catalysts. This reaction is quite general with respect to the substitution at nitrogen; however, some limitations with unsymmetrical and bulky substrates are observed. Additionally, this methodology allowed us to efficiently set the stereochemistry in the synthesis of an anthrax lethal factor inhibitor while avoiding lengthy protection/deprotection strategies.

Acknowledgment. We thank Mirlinda Biba (assay development), Jimmy Dasilva (prep HPLC), J. Chris McWilliams (DOE), Jess Sager (DOE), and Thomas Novak (HRMS) for their assistance.

Supporting Information Available: Experimental procedures and spectroscopic data for the synthesis of **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050869S

(22) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589−594.

(23) The H/D ratio in the γ-position is approximately equal to H/D ratio in the system (hydrogenation vessel) at equilibrium. The amount of H (from H_2) in this experiment was much lower than in the previous experiment as a result of the use of a smaller hydrogenation vessel (smaller headspace volume). These observations are consistent with H/D exchange between solvent and H_2/D_2 gas being much faster than the rate of hydrogenation.