Expedient Asymmetric Synthesis of All Four Isomers of *N,N′*-Protected 2,3-Diaminobutanoic Acid

Andrea J. Robinson,* Pauline Stanislawski, and Dean Mulholland

School of Chemistry, Monash University, Clayton, Victoria 3800, Australia

Linnan He and Hui-Yin Li*,†

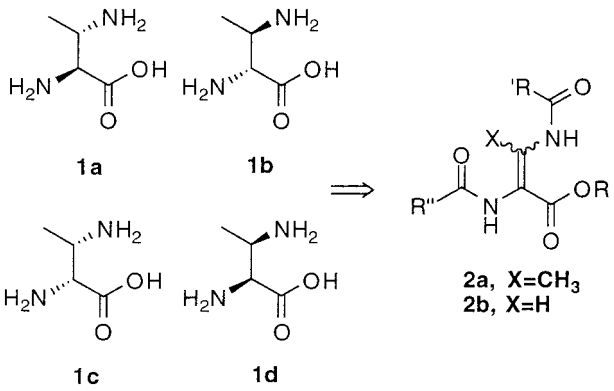
DuPont Pharmaceuticals Company, Chemical Process R&D, Experimental Station, Wilmington, Delaware 19880−0336

A.Robinson@sci.monash.edu.au

2,3-Diaminobutanoic acid (DAB) is found in several peptide antibiotics, toxins, and biologically active molecules. This paper describes the practical and highly enantioselective synthesis of all four *N,N′*-protected DAB stereoisomers using an asymmetric Rh(I)-phosphine-catalyzed hydrogenation of isomeric enamides as the key step. Thermal and photochemical isomerization of the enamide hydrogenation substrates coupled with catalyst-geometric isomer pairing allows targeted synthesis of single DAB isomers in maximum yield.

Optically active α,*β*-diamino acids are important structural components of many natural products and medicinal agents.[1] In particular, the *β*-branched nonproteinogenic amino acid 2,3-diaminobutanoic acid (DAB) (**1**) has attracted considerable attention because of its inclusion in several molecules possessing biological activity.[2] The (2*S*,3*S*)-epimer (**1a**) is a constituent of several tuberculostatic heptapeptide antibiotics, including the antrimycin and cirratiomycin classes,[3] and is also found in the highly potent antibiotic peptide lavendomycin, isolated from culture filtrates of *Streptomyces lavendulae*.[4] Interestingly, amphomycin, a peptide antibiotic isolated from *Streptomyces canus*, contains both (2*S*,3*S*)- and (2*S*,3*R*)-DAB.[5] The DAB unit is also found in plant extracts,[6] antifungal dipeptides,[7] toxins,[8,9] and other biologically active molecules.[10−12] Several syntheses of optically pure diaminobutanoic acid have been reported but only a few of these preparations offer easy access to both *syn* and *anti* isomers. Approaches to the *anti*-isomers (**1a** and **1b**) mainly capitalize on the ready availability of L- and D-threonine and introduce the *β*-*N*-substituent via a Mitsunobu reaction.[13] Routes starting from the more expensive *allo*-threonines, or a double inversion at the *β*-position of L- and D-threonine,[14] need to be employed to access the *syn*-diastereomers (**1c** and **1d**). More recent approaches to DAB (**1**) have included an asymmetric conjugate addition of a chiral lithium amide to *tert*-butyl crotonate,[9] asymmetric aminohydroxylation of *tert*-butyl crotonate[15] and Grignard addition to chiral nitrones derived from L-serine.[2] We were interested in investigating a stereodivergent synthesis of *all four* stereoisomers of DAB (**1**) from a common disubstituted crotonate precursor (**2a**, X = Me) using catalytic asymmetric hydrogenation as the key transformation (Scheme 1). We were encouraged by our previous studies on the reduction of the related 2,3-diamidopropenoate system (**2b**, X = H) where the use of rhodium(I) hydrogenation catalysts, incorporating chiral 1,2-bis(phospholano)benzene (DuPHOS)[16] and 1,2-bis(phospholano)ethane (BPE) ligands,[17] provided a highly efficient and enantioselective route (>98% ee) to both enantiomers.[18] Importantly, these same catalysts have also been employed in the asymmetric hydrogenation of *β*,*β*-disubstituted α-enam-

Scheme 1



* To whom correspondence should be addressed.

† Email: Hui-Yin.Li@dupontpharma.com.

(1) Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323−1326.

(2) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813−1816.

(3) Schmidt, U.; Riedl, B. *J. Chem. Soc., Chem. Commun.* **1992**, 1186−1187.

(4) Schmidt, U.; Mundinger, K.; Mangold, R.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1216−1219.

(5) Bodanszky, M.; Sigler, G. F.; Bodanszky, A. *J. Am. Chem. Soc.* **1973**, *95*, 2352−2357.

(6) Evans, C. S.; Qureshi, M. Y.; Bell, E. A. *Phytochemistry* **1977**, *16*, 565.

(7) Rane, D. F.; Girijavallabhan, V. M.; Ganguly, A. K.; Pike, R. E.; Saksena, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 3201−3204.

(8) Nakamura, Y.; Shin, C. *Chem. Lett.* **1992**, 49−52.

(9) Burke, A. J.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1996**, *7*, 621.

(10) Dunn, P. J.; Haner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017−5025.

(11) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *Chem. Commun.* **1996**, 633−634.

(12) Shigematsu, N.; Setoi, H.; Uchida, I.; Shibata, T.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 5147−5150.

(13) Schmidt, U.; Mundinger, K.; Riedl, B.; Haas, G.; Lau, R. *Synthesis* **1992**, 1201−1202.

(14) Nakamura, Y.; Hirai, M.; Tamotsu, K.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1369−1377.

(15) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045−2048.

(16) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 5, 10125−10138.

(17) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653−2655.

(18) Robinson, A. J.; Lim, C.-Y.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4141−4147.

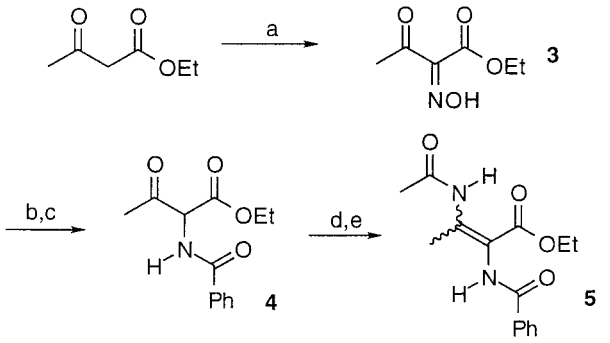
10.1021/jo001152f CCC: $20.00
Published on Web 01/16/2001

Table 1.

entry	substrate	ligand	reaction time, min	solvent	hydrogen pressure, psi	% yield	% ee[c]	absolute configuration[d]
1	*E*-**5**	*R,R*-MeDuPHOS	48	MeOH	60	100	71	2*R*,3*S*
2	*E*-**5**	*S,S*-MeDuPHOS	48	MeOH	60	100	69	2*S*,3*R*
3	*E*-**5**	*R,R*-MeDuPHOS	15	MeOH	90	100	72	2*R*,3*S*
4	*E*-**5**	*R,R*-MeDuPHOS	15	Ph-H	60	50[a]	>99	2*R*,3*S*
5	*E*-**5**	*R,R*-MeDuPHOS	12	Ph-H	90	70[a]	>98	2*R*,3*S*
6	*E*-**5**	*R,R*-MeDuPHOS	64	Ph-H	90	95	>98	2*R*,3*S*
7	*E*-**5**	*S,S*-MeDuPHOS	64	Ph-H	90	97	>98	2*S*,3*R*
8	*E*-**5**	*R,R*-MeBPE	72	Ph-H	90	92	96	2*R*,3*S*
9	*Z*-**5**	*R,R*-MeDuPHOS	15	MeOH	60	45[b]	-	-
10	*Z*-**5**	*S,S*-MeDuPHOS	15	MeOH	90	58[b]	-	-
11	*Z*-**5**	*R,R*-MeDuPHOS	16	Ph-H	90	100	96	2*R*,3*R*
12	*Z*-**5**	*R,R*-MeBPE	96	Ph-H	90	100	80	2*R*,3*R*
13	*Z*-**5**	*S,S*-MeBPE	96	Ph-H	90	100	80	2*S*,3*S*
14	*Z*-**5**	*R,R*-MeBPE	96	Hexane	90	1	-	-

[a] Isolated yield of **6c**; starting enamide (**5**) also recovered from the reaction mixture. [b] Expected butanoate (**6**) accompanied by unidentified isomeric compound. [c] Enantiomeric excess determined by chiral HPLC. [d] Absolute configuration determined by comparison to authentic samples of (**6a** and **6d**) derived from L-threonine.

Scheme 2



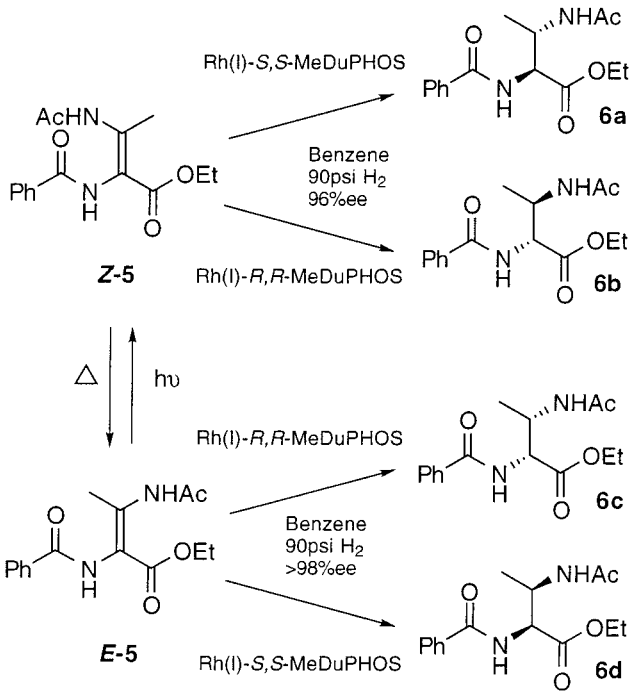
[a] Conditions: (a) $NaNO_2$, aq AcOH, 0 °C, 81%; (b) Al/Hg, THF; (c) BzCl, 63% over two steps; (d) NH_4OAc, MeOH, rt, 81%; (e) AcCl, pyridine, CH_2Cl_2/Et_2O, 58%.

ides to yield chiral β-branched amino acids[19] and can therefore accommodate increasing steric bulk at the β-position.

Hydrogenation substrates were easily assembled from ethyl acetoacetate. Thus, α-nitrosation gave the α-oximino-β-keto ester (**3**)[20] which was then reduced with aluminum amalgam and benzoylated in situ to give ketoester (**4**) in excellent yield. Careful control of the reaction temperature during the reduction step was needed to minimize concomitant reduction of the ketone. Subsequent treatment of **4** with ammonium acetate followed by acetylation installed the requisite β-amide group and afforded the *E*- and *Z*-enamides (**5**) as a 4:1 mixture (Scheme 2). The geometric isomers were readily separated by conventional column chromatography. On a larger scale, however, it was more convenient to isomerize the mixture into a single isomer: Thermal isomerization of *Z*-enamide gave pure *E*-enamide (*E*-**5**) and photochemical isomerization of the *E*-enamide at room temperature afforded pure samples of the *Z*-isomer (*Z*-**5**) (Scheme 3). This process eliminates the need for isomer separation prior to hydrogenation and significantly enhances the convenience and efficiency of this synthetic approach to DAB derivatives.

The results of the hydrogenation studies are summarized in Table 1. The conditions previously employed for the hydrogenation of α,β-diamidopropenoate substrates (MeOH, RT, 60−90 psi)[18] gave excellent chemical yields of α,β-diamidobutanoate (**6**). The Me-DuPHOS−Rh(I) triflate catalyzed hydrogenation of *E*-enamide (**5**) in methanol, however, gave disappointingly low enantioselectivities (69−71% ee, entries 1−3). The more sterically congested ligand, Et-DuPHOS, provided even poorer selectivity (65% ee). However, Me-DuPHOS−Rh(I)-catalyzed hydrogenation of *E*-enamide (**5**) in benzene gave butanoate (**6**) in >98% ee and excellent yield. A higher hydrogen pressure (90 psi) was employed to compensate for a reduced reaction rate in this solvent (entries 4−7). Enantiomeric excess was determined by chiral HPLC and assignment of absolute configuration was made by comparison with an authentic sample of (2*S*,3*R*)-**6d** obtained from L-threonine. Hence, hydrogenation of (*E*)-enamide (**5**) with [*R,R*]-Me-DuPHOS−Rh afforded (2*R*,3*S*)-diamidobutanoate (**6c**) whereas use of the ligand antipode, [*S,S*]-Me-DuPHOS, gave the enantiomeric *syn*-isomer, (2*S*,3*R*)-**6d** (Scheme 3). This sense of induction is analogous to that observed in the Rh(I)−DuPHOS-catalyzed hydrogenation of α-enamides[16,19] and α,β-diamidopropenoates.[18] Reduction with the more flexible Rh(I)-Me-BPE catalyst afforded butanoate (**6c**) in comparable yield and

Scheme 3



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

(20) Bouveault, L.; Locquin, R. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1159−1164.

enantiomeric excess (entry 8). Interestingly, hydrogenation of analogous β-substituted α,β-diamidoacrylates with Me-DuPHOS−Rh(I) hexafluorophosphonate was reportedly unsuccessful;[21] (2*S*,3*R*)-2,3-bis(acylamino)carboxylates were successfully prepared, however, with TRAP−Rh(I) complexes in 79−82% ee.

Hydrogenation of the *Z*-enamide (**5**) in methanol gave the required butanoate (**6**) under mild conditions (60psi H_2, 15 h) but was accompanied by an as yet unidentified and unstable byproduct which was isomeric with (**6**) (entries 9 and 10). In benzene, however, formation of this byproduct was completely eliminated and excellent yields of the desired *anti*-butanoates (**6a** and **6b)** were obtained with both the Rh(I)-DuPHOS and Rh(I)-BPE catalysts (entries 11−13). Hence, the *anti*-diamidobutanoate derivatives, (2*S*,3*S*)-**6a** and (2*R*,3*R*)-**6b**, were produced in 80% ee, respectively, via (*S*,*S*)- and (*R*,*R*)-Me-BPE-Rh(I)-catalyzed hydrogenation of the *Z*-enamide (*Z*-**5**) (Scheme 3). Furthermore, hydrogenation of *Z*-**5** using MeDuPHOS−Rh(I) catalysts gave *anti*-butanoates in 96% ee. Hydrogenation in hexane was unsuccessful (entry 14).

The high yields, excellent enantioselectivity, and mild hydrogenation conditions, coupled with the ability to access any one of the four DAB isomers from a common starting material, makes this synthetic approach to DAB derivatives particularly attractive. Notably, a variety of amine protecting groups are known to be compatible with the rhodium−DuPHOS/BPE catalysts and could be readily employed without major detriment to enantioselectivity. To access units suitable for natural product synthesis and antibiotic monobactams, such as aztreonam, we needed to demonstrate that the *Z*-enamide (*Z*-**5**) could be hydrogenated to give the *anti*-isomers, (2*R*,3*R*)-**6b** and particularly the (2*S*,3*S*)-**6a** stereoisomer. The slightly lower enantioselectivity (96% ee) observed in the hydrogenation of the *Z*-enamide compared with the *E*-enamide (>98% ee) is perhaps not surprising. Our previous ^{13}C-labeling experiments on the related α,β-diamidopropenoate system clearly showed the coordinative involvement of the α-amido group carbonyl during hydrogenation.[18] It is therefore reasonable to postulate that a *cis*-orientation of a bulky β-substituent may compromise the binding of the substrate to the rhodium metal center and result in lower enantioselectivity. In conclusion, we have successfully demonstrated the use of catalytic asymmetric hydrogenation and geometric isomer-ligand antipode matching to access all four stereoisomers of diamidobutanoate (**6**).

Experimental Section

General Procedures. Melting points were determined using a hot-stage melting point apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer as potassium bromide disks of solids (KBr) or as thin films of liquids (neat) between sodium chloride plates. Nuclear magnetic resonance spectra (^1H, ^{31}P, and ^{13}C NMR) were recorded on either 200, 300, or 400 MHz spectrometers. Electron impact ionization (EI) spectra (*m*/*z*) were recorded on a spectrometer operating at 200 °C/70 eV. Analytical thin-layer chromatography (TLC) was performed on plastic or glass slides coated with silica gel (Polygram SIL G/UV254). Column chromatography was performed using Merck silica gel 60, 0.063−0.200 mm (70−230 mesh). Degassed methanol and benzene (HPLC grade) were used in all hydrogenation reactions. Catalysts were used as received from the suppliers; Rh(I)−DuPHOS and Rh(I)−BPE refers to [(1,5-cyclooctadiene)Rh(I)(bis(2,5-dialkylphospholano)benzene)] triflate and [(1,5-cyclooctadiene)Rh(I)-(bis(2,5-dialkylphospholano)ethane)] triflate, respectively. In all Rh(I)-phosphine hydrogenations, high purity (<10 ppm) hydrogen and nitrogen were used and purified by passage through water, oxygen, and hydrocarbon traps. The enantiomeric excess of the hydrogenation products was determined via chiral HPLC analysis using Diacel Chiracel OJ and AS columns.

Preparation of Hydrogenation Substrates

Ethyl 2-Hydroxyimino-3-oxobutanoate (3). A solution of sodium nitrite (10.6 g, 0.153 mol) in water (20 mL) was added dropwise to a stirred solution of ethyl acetoacetate (20.0 g, 0.154 mol) in glacial acetic acid (40 mL) at 0 °C. After the addition was complete, the light yellow reaction mixture was allowed to warm to ambient temperature. After 0.5 h, TLC (light petroleum:ethyl acetate; 1:1) showed the disappearance of the starting material, and the reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (2 × 35 mL). The organic extracts were combined and washed with water (2 × 30 mL) and saturated sodium bicarbonate solution (2 × 30 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the oxime (**3**) (19.9 g, 81%) as a pale yellow oil. Spectroscopic analysis showed that the oxime (**3**) did not require purification. υ_{max} (neat): 3331bs, 1748s, 1701s, 1628m cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, J 7.1 Hz, 3H), 2.42 (s, 3H), 4.38 (q, J 7.1 Hz, 2H), 10.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 25.3, 62.5, 151.1, 162.0, 194.2. Mass spectrum (EI): *m*/*z* 159 (M^+, 7%), 131 (100). Accurate mass spectrum: *m*/*z* 159.0537, $C_6H_9NO_4$ requires 159.0532.

Ethyl 2-Benzoylamino-3-oxobutanoate (4). Aluminum turnings were activated according to the following procedure: Sodium hydroxide solution (1 M, 100 mL) was added to fine aluminum turnings (8.00 g, 0.297 mol) resulting in the evolution of hydrogen gas. The sodium hydroxide solution was decanted after 10−15 s, and the aluminum turnings were washed with water (100 mL). Aqueous mercury(II) chloride solution (0.5%, 50 mL) was then added to the aluminum and allowed to stand for 1−2 min before decanting. This procedure was repeated, and the amalgamated aluminum was washed in turn with water (100 mL), absolute ethanol (100 mL), and dry diethyl ether (100 mL). A solution of oxime (**3**) (10.0 g, 62.9 mmol) in tetrahydrofuran (50 mL) was added dropwise to a stirred suspension of the above aluminum amalgam in tetrahydrofuran (50 mL). A few drops of water were cautiously added to the reaction mixture. The temperature of the reaction was maintained below ca. 50 °C by periodic immersion of the flask in a cool water bath. After ca. 2 h, TLC (light petroleum: ethyl acetate; 2:1) showed the absence of the oxime (**3**). The reaction mixture was filtered, benzoyl chloride (8.1 mL, 70 mmol) was added dropwise to the filtrate, and the resulting solution was left to stir overnight. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (2 × 40 mL). The organic extracts were combined, washed with water (2 × 40 mL) and saturated sodium chloride solution (2 × 40 mL), and dried ($MgSO_4$). Evaporation under reduced pressure gave an orange oil (13.8 g). Purification by column chromatography (light petroleum:ethyl acetate; 1:1) first gave the title ketone (**4**) (9.80 g, 63%) as a yellow oil. υ_{max} (neat): 3359m, 1750s, 1727s, 1655s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J* 7.1 Hz, 3H), 2.46 (s, 3H), 4.31 (qd, *J* 5.3, 1.8 Hz, 2H), 5.45 (d, *J* 6.4 Hz, 1H), 7.35 (bd, *J* 5.5 Hz, 1H), 7.45 (t, *J* 6.7 Hz, 2H), 7.51−7.55 (m, 1H), 7.85 (d, *J* 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 28.1, 62.7, 63.5, 127.3, 128.6, 132.1, 133.3, 166.1, 166.9, 198.6. Mass spectrum (EI): *m*/*z* 249 (M^+, 0.2%), 105 (100), 77 (73). Accurate mass spectrum: *m*/*z* 250.1080 ($[M + H]^+$), $C_{13}H_{15}NO_4$ requires 250.1079. Further elution gave ethyl 2-benzoylamino-3-hydroxybutanoate (1.67 g, 11%) as a viscous yellow oil which crystallized on standing. υ_{max} (neat): 3325bs, 1742s, 1644s, 1602m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* 6.5 Hz, 3H), 1.34 (t, *J* 7.1 Hz, 3H), 4.29−4.34 (m, 3H), 4.89 (dd, *J* 6.7, 3.2 Hz, 1H), 7.16 (d, *J* 5.8 Hz, 1H), 7.45−7.50 (m, 2H), 7.55−7.57 (m, 1H), 7.83−7.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$)

(21) Kuwano, R.; Okuda, S.; Ito, Y. *Tetrahedron Asymmetry* **1998**, 2773−2775.

δ 14.2, 18.7, 58.9, 62.2, 69.4, 127.3, 128.7, 132.1, 133.2, 168.4, 170.3. Mass spectrum (EI): *m*/*z* 251 (M^+, 0.5%), 105 (100), 77 (49). Accurate mass spectrum: *m*/*z* 314.1400, $C_{13}H_{17}NO_4$ requires 314.1398.

Ethyl 2-Benzoylamino-3-amino-2-butenoate. A solution of ammonium acetate (25.8 g, 334 mmol) in methanol (60 mL) was added to the ketone (**4**) (8.29 g, 33.3 mmol), and the resulting light yellow solution was stirred overnight at ambient temperature. The reaction mixture was quenched with saturated sodium bicarbonate solution (100 mL), and the methanol was evaporated under reduced pressure. The mixture was extracted with dichloromethane (2 × 50 mL), and the combined organic extract was washed with saturated sodium chloride solution (2 × 40 mL) and dried (Na_2SO_4). Evaporation under reduced pressure gave the title enamine (6.68 g, 81%) as a pale yellow solid. Spectroscopic analysis showed that the enamine did not require purification. υ_{max} (KBr): 3428s, 1736m, 1642s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* 7.1 Hz, 3H), 2.01 (s, 3H), 4.13 (q, *J* 7.1 Hz, 2H), 7.02 (s, 1H), 7.47 (t, 7.3 Hz, 2H), 7.50−7.53 (m, 1H), 7.84 (d, *J* 7.0 Hz, 2H): NH_2 protons were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.6, 59.5, 93.8, 127.2, 128.6, 131.4, 135.1, 159.3, 167.6, 167.7. Mass spectrum (EI): *m*/*z* 248 (M^+, 35%), 105 (100).

Ethyl 2-Benzoylamino-3-acetylamino-2-butenoate (5). Acetyl chloride (0.32 mL, 4.4 mmol) was added dropwise to a stirred and ice-cooled solution of the enamine (1.00 g, 4.03 mmol) and pyridine (0.36 mL, 4.43 mmol) in dichloromethane (14 mL) and diethyl ether (7 mL). Once addition of acetyl chloride was complete, the reaction mixture was left to stir overnight at ambient temperature and then quenched with water (50 mL) and extracted with dichloromethane (2 × 20 mL). The organic extracts were combined, washed with 2 M sulfuric acid (2 × 20 mL) and saturated sodium chloride solution (2 × 30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a viscous orange oil (1.25 g). Purification by column chromatography (light petroleum:ethyl acetate; 2:1) first gave the *E*-butenoate (*E*-**5**) (0.504 g, 43%) as a colorless solid, mp 148−151 °C. υ_{max} (KBr): 3300s, 3200s, 1720s, 1672s, 1648s, 1615s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* 7.1 Hz, 3H), 2.17 (s, 3H), 2.46 (s, 3H), 4.20 (q, *J* 7.1 Hz, 2H), 7.19 (s, 1H), 7.46−7.49 (m, 2H), 7.53−7.57 (m, 1H), 7.84−7.87 (m, 2H), 11.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 16.8, 25.6, 61.1, 104.5, 127.2, 128.7, 131.9, 134.1, 153.9, 167.2, 167.23, 169.2. Mass spectrum (EI): *m*/*z* 290 (M^+, 3%), 105 (100). Microanalysis: Found; C 61.92%, H 6.44%, N 9.39%. $C_{15}H_{18}N_2O_4$ requires C 62.06%, H 6.26%, N 9.66%. Further elution gave the *Z*-butenoate (*Z*-**5**) (0.174 g, 15%) as a colorless solid, mp 76−78 °C. υ_{max} (KBr): 3297s, 1734s, 1703s, 1635s, 1578s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* 7.1 Hz, 3H), 2.13 (s, 3H), 2.30 (s, 3H), 4.23 (q, *J* 7.1 Hz, 2H), 7.46−7.50 (m, 2H), 7.54−7.58 (m, 1H), 7.88 (dd, *J* 7.1, 1.4 Hz, 2H), 8.67 (s, 1H), 8.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 18.5, 24.1, 61.4, 116.4, 127.4, 128.8, 132.1, 132.4, 135.6, 165.0, 166.5, 169.3. Mass spectrum (EI): *m*/*z* 290 (M^+, 2%), 105 (100), 77 (62), 51. Microanalysis: Found; C 62.18%, H 6.07%, N 9.56%. $C_{15}H_{18}N_2O_4$ requires C 62.06%, H 6.26%, N 9.66%.

Isomerization of Ethyl 2-Benzoylamino-3-acetylamino-2-butenoate (5). For the isomerization of *Z*-enamide into *E*-enamide, an *E*/*Z*-mixture of ethyl 2-benzoylamino-3-acetylamino-2-butenoate (**5**) (1−2 g) was dissolved in dichloromethane or toluene (100−150 mL) and heated at reflux until TLC showed the disappearance of the *Z*-isomer. After removal of the solvent under reduced pressure, ^1H NMR spectroscopy revealed the product to be 100% *E*-isomer (*E*-**5**). The *E*-isomer is stable at room temperature.

For the isomerization of *E*-enamide into *Z*-enamide, an *E*/*Z*-mixture of ethyl 2-benzoylamino-3-acetylamino-2-butenoate (**5**) (0.5−1 g) was dissolved in toluene (150 mL) and irradiated with ultraviolet light in a Hanovia photochemical reactor operating at 125 W using a medium-pressure mercury arc lamp. An internal condenser was used to maintain the reaction temperature between 10 and 20 °C. The isomerization was monitored by TLC and was typically complete after 3 h of continuous irradiation. After removal of solvent under reduced pressure, ^1H NMR spectroscopy revealed the product to be pure *Z*-enamide isomer (*Z*-**5**). To avoid isomerization into the *E*-isomer, the *Z*-isomer was stored at 0 °C.

Hydrogenation Study

General Hydrogenation Procedure. In a drybox, a Fisher-Porter tube was charged with catalyst (1 mg), deoxygenated solvent (∼5 mL), and substrate (50−200 mg). Three vacuum/N_2 cycles to purge the gas line of any oxygen followed by three vacuum/N_2 cycles of the vessel were carried out before the tube was pressurized with hydrogen to the required pressure (psi). The reaction was then stirred at room temperature for the specified period of time. The pressure in the vessel was then released, and the contents were evaporated to dryness under reduced pressure. The crude product (**6**) was passed through a short plug of silica prior to spectroscopic and chromatographic analysis. Hydrogenation experiments are described using the following format: substrate, solvent, catalyst, hydrogen pressure, reaction time, isolated yield, enantiomeric excess (assigned configuration), retention time (HPLC conditions) (See also Table 1).

(2*S*,3*R*)-Ethyl 2-Benzoylamino-3-acetylaminobutanoate (6d). [(2*E*)-Ethyl *2*-benzoylamino-3-acetylamino-2-butenoate (*E*-**5**), benzene, [(COD)Rh(I)((*S*,*S*)-Me-DuPHOS)]OTf, 90 psi H_2, 64 h; 97% yield, >98% ee (2*S*,3*R*-**6d**), t_R = 6.8 min (Chiralcel OJ, ambient temperature, flow rate = 1.0 mL/min, detection at 250 nm, eluent = 20% IPA:80% hexane)].

6d: Colorless solid, mp 102−103 °C: $[\alpha]^{25}_D$ +41.4° (*c* 1.6, $CHCl_3$). υ_{max} (KBr): 3422s, 3297s, 1736m, 1686w, 1654s, 1696s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, *J* 6.7 Hz, 3H), 1.29 (t, *J* 7.2 Hz, 3H), 1.91 (s, 3H), 4.22 (q, *J* 7.2 Hz, 2H), 4.49 (p, *J* 7.0 Hz, 1H, H3), 4.65 (t, *J* 7.5 Hz, 1H), 6.44 (bd, *J* 7.0 Hz, 1H), 7.36−7.51 (m, *J* 7.1 Hz, 3H), 7.72 (d, *J* 7.5 Hz, 1H), 7.83 (d, *J* 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 18.0, 23.2, 47.8, 58.4, 61.9, 127.0, 128.5, 132.0, 133.5, 167.7, 170.5, 171.0. Mass spectrum (ESI+, MeOH): *m*/*z* 315.1 ($[M + Na]^+$), 293.1 ($[M + H]^+$). Microanalysis: Found, C 61.57%, H 6.88%, N 9.63%. $C_{15}H_{20}N_2O_4$ requires C 61.61%, H 6.90%, N 9.59%.

(2*R*,3*S*)-Ethyl 2-Benzoylamino-3-acetylaminobutanoate (6c). [(2*E*)-Ethyl *2*-benzoylamino-3-acetylamino-2-butenoate (*E*-**5**), benzene, [(COD)Rh(I)((*R*,*R*)-Me-DuPHOS)]OTf, 90 psi H_2, 64 h; 95% yield, >98% ee (2*R*,3*S*-**6c**), t_R = 4.8 min (Chiralcel OJ, ambient temperature, flow rate = 1.0 mL/min, detection at 250 nm, eluent = 20% IPA:80% hexane)].

6c: Colorless solid, mp 102−103 °C: $[\alpha]^{25}_D$ −41.4° (*c* 1.7, $CHCl_3$). Accurate mass spectrum (ESI+, MeOH): *m*/*z* 315.1311 ($[M + Na]^+$), $C_{15}H_{20}N_2O_4Na$ requires 315.1314.

(2*S*,3*S*)-Ethyl 2-Benzoylamino-3-acetylaminobutanoate (6a). [(2*Z*)-Ethyl *2*-benzoylamino-3-acetylamino-2-butenoate (*Z*-**5**), benzene, [(COD)Rh(I)((*S*,*S*)-Me-BPE)]OTf, 90 psi H_2, 96 h; 100% yield, 80% ee (2*S*,3*S*-**6a**), t_R = 16.1 min (Chiralcel AS, ambient temperature, flow rate = 1.0 mL/min, detection at 250 nm, eluent = 10% IPA:90% hexane)].

6a: Colorless solid, mp 134−135 °C: $[\alpha]^{25}_D$ +10.8° (*c* 3.6, $CHCl_3$). υ_{max} (KBr): 3422s, 3297s, 1736m, 1654s, 1696s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, *J* 6.9 Hz, 3H), 1.31 (t, *J* 7.1 Hz, 3H), 2.01 (s, 3H), 4.26 (qd, *J* 7.1, 2.5 Hz, 2H), 4.51 (pd, *J* 7.1, 2.5 Hz, 1H), 4.75 (dd, *J* 6.4, 2.5 Hz, 1H), 6.82 (d, *J* 7.0 Hz, 1H), 7.46 (t, *J* 7.1 Hz, 2H), 7.53 (t, *J* 7.3 Hz, 1H), 7.82 (d, *J* 6.1 Hz, 1H), 7.86 (d, *J* 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1,16.5, 23.2, 48.4, 58.3, 62.0, 127.2, 128.7, 132.0, 133.2, 168.0, 170.0, 171.0. Mass spectrum (ESI+, MeOH): *m*/*z* 315.2 ($[M + Na]^+$), 293.1 ($[M + H]^+$). Microanalysis: Found, C 61.58%, H 7.09%, N 9.43%. $C_{15}H_{20}N_2O_4$ requires C 61.61%, H 6.90%, N 9.59%.

(2*R*,3*R*)-Ethyl 2-Benzoylamino-3-acetylaminobutanoate (6b). [(2*Z*)-Ethyl *2*-benzoylamino-3-acetylamino-2-butenoate (*Z*-**5**), benzene, [(COD)Rh((*R*,*R*)-Me-BPE)]OTf, 90 psi H_2, 96 h; 100% yield, 80% ee (2*R*,3*R*-**6b**), t_R = 23.1 min (Chiralcel AS, ambient temperature, flow rate = 1.0 mL/min, detection at 250 nm, eluent = 10% IPA:90% hexane)].

6b: Colorless solid, mp 134−135 °C: $[\alpha]^{25}_{D}$ −10.8° (*c* 2.5, $CHCl_3$). Accurate mass spectrum (ESI+, MeOH): *m/z* 315.1311 ($[M + Na]^+$), $C_{15}H_{20}N_2O_4Na$ requires 315.1321.

Acknowledgment. We would like to thank the Australian Research Council for their financial support of this research.

Note Added after ASAP Posting. The version of this paper posted on January 16, 2001, had incorrect author attributions and was withdrawn from the Web on January 31, 2001. The version with full authorship and affiliations was posted on May 22, 2001.

JO001152F