Notes

Enzymatic Resolution of α-Alkyl *β*-Amino Acids Using Immobilized Penicillin G Acylase

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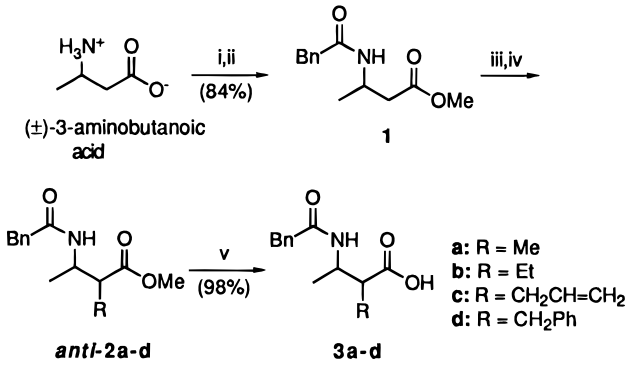
In recent years, increasing attention has been paid to the synthesis of enantiomerically pure α-substituted *β*-amino acids,[1] owing to their role as precursors of 3-substituted *β*-lactams and in the preparation of natural and unnatural biologically active polypeptides.

The synthesis of enantiomerically pure α-alkyl *β*-amino acids has been recently accomplished by the addition of chiral secondary amines to α,*β*-unsaturated esters,[2] by the condensation of disubstituted imines,[3] by homologation of the corresponding α-analogues,[4] or by the functionalization at C-5 of chiral 6-alkylperhydropyrimidin-4-ones.[5] This method allowed us to obtain (*S*,*S*)- or (*R*,*R*)-α-alkyl *β*-amino acids with high stereocontrol and in high yields.

A very simple alternative procedure for the preparation of these compounds is reported here, as the enzymatic hydrolysis of racemic *N*-phenylacetyl α-alkyl *β*-amino acids with penicillin G acylase (PGA). This enzyme is widely distributed among microorganisms and is used on an industrial scale for the production of 6-aminopenicillanic acid.[6] Since it exihibits a high affinity for the phenylacetyl moiety,[7] the hydrolysis of different phenylacetic acid derivatives has been reported. Among them, the resolution of racemic *β*-amino acids is catalyzed by PGA,[8] preferentially hydrolyzing the *S* isomer.

Scheme 1[a]



[a] Reagents and conditions: (i) $PhCH_2COCl$ (1.2 equiv), NaOH (2 equiv), acetone/H_2O, 0 °C, 1 h; (ii) $SOCl_2$ (2 equiv), MeOH, −15 °C, 2 h; (iii) LiHMDS (1 M solution in THF) (2 equiv), 0 °C, 1 h; (iv) RX (1.5 equiv), −78 °C to rt, 16 h; (v) K_2CO_3 (2 equiv), H_2O, reflux, 2 h, then 1 M HCl.

Table 1. Diastereomeric Product Ratios and Chemical Yields for the Alkylation Reaction of Methyl (±)-3-[(Phenylacetyl)amino]butanoate 1

entry	RX	yield (%)	*anti*/*syn* ratio[a] (%)
1	MeI	68	93:7
2	EtI	75	>99:1
3	AllylBr	80	>99:1
4	BnBr	84	>99:1

[a] Determined by ^{1}H NMR and GC−MS analysis.

In order to test the versatility of PGA toward α-substituted *β*-amino acids and to depict a simple method for the preparation of these substrates, the *N*-(phenylacetyl)-amides **2a**−**d** were synthesized from the commercially available (±)-3-aminobutanoic acid, following the procedure reported by Seebach[9] (Scheme 1). This alkylation reaction occurs with high *anti* selectivity. Indeed, by treatment of the lithium salt of **1** with alkyl halides at −78 °C in dry THF, the corresponding alkyl derivatives were obtained with high yield and selectivity (Table 1). Analysis by ^{1}H NMR and GC−MS of the reaction mixtures for entries b−d show, in each case, the presence of a single product with the *anti* configuration, which was assigned by comparisons of the ^{1}H NMR spectra with the data reported in the literature.[9] Only for the smaller methyl group was a small amount of *syn* adduct obtained.

The methyl ester of **2a**−**d** was then simply hydrolyzed in quantitative yield by reaction with potassium carbonate in refluxing water to afford amide acids **3a**−**d**.

This procedure is particularly convenient because the phenylacetyl moiety acts both as a protecting group of the amino functionality during the alkylation reaction and as a fragment that can be hydrolyzed during the subsequent enzymatic resolution.

Although the optimum rate of hydrolysis of penicillin G acylase is reported to occur at pH = 8.2, we found that under these conditions complete hydrolysis of both (*S*)- and (*R*)-3-aminobutanoic acid was accomplished by reaction at 40 °C for 5 h with *E. coli* PGA immobilized on

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S0022-3263(96)01350-3 CCC: $12.00

Scheme 2

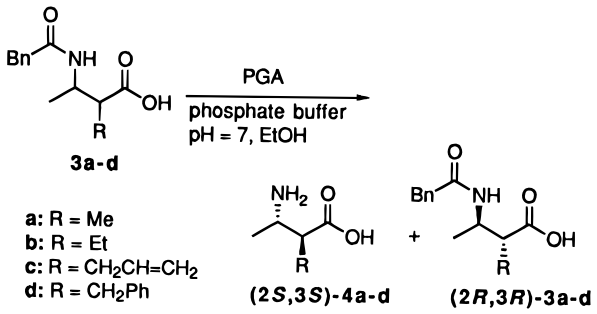

Table 2. Chemical Yields and Reaction Conditions for the Hydrolysis of *anti*-(±)-2-Alkyl-3-[(phenylacetyl)-amino]butanoic Acids 3a−d

entry	R	time (h)	*T* (°C)	phosphate buffer/ EtOH ratio	conversn (%)[a]
a	CH_3	5	30	10:1	50
b	CH_2CH_3	5	30	10:1	47
c	$CH_2CH{=}CH_2$	6	35	5:1	53
d	CH_2Ph	6	35	5:1	49

[a] The conversion refers to the amount of phenylacetic acid produced and was determined by comparison of the ^{1}H NMR peak of methylene group of starting material (δ 3.59 ppm) and of phenylacetic acid (δ 3.67 ppm).

Eupergit. To overcome this reactivity problem, several reaction conditions were tested.

The amide acids **3a**−**d** (100 mg) were treated with immobilized PGA (10 mg) in a solution of 0.1 M phosphate buffer (10 mL) with a variable amount of ethanol as a cosolvent (Scheme 2). The phosphate buffer was adjusted to pH = 7 before addition of the cosolvent and the enzyme, and thereafter the pH was not regulated. The reaction proceeded for 5−8 h at 30 or 35 °C, depending on the substrate. With an increase in the steric hindrance of the R group, the reaction temperature, the reaction time, and the amount of ethanol used were increased, owing to the reduced water solubility of the substrate (Table 2).

For each reaction, after the scheduled reaction times, the mixture was concentrated under reduced pressure to eliminate the ethanol, the pH was adjusted to 3, and the water layer was extracted three times with ethyl acetate. The unhydrolyzed amide acids **2a**−**d** and the phenylacetic acid were recovered from the organic layers, while the water layers were concentrated under reduced pressure to afford the free amino acids (2*S*,3*S*)-**4a**−**d**. These acids were dissolved in a small amount of water and purified on a cation-exchange resin, using 1.5 M NH_4OH as eluant.

The specific rotations of (2*S*,3*S*)-**4a**−**d** were measured and compared with the data reported in the literature.[5c,10] As expected, the absolute configuration of the hydrolyzed amino acids was confirmed to be 2*S*,3*S*; the determination of the enantiomeric purity was troublesome because the specific rotations of these molecules are sensitive to conditions of purification and of measurement. Since the gas chromatographic separation of racemic phenylacetamido derivatives **2a**−**d** and **3a**−**d** on a chiral support failed, (2*S*,3*S*)-**4a**−**d** were transformed into the corresponding acetamide methyl esters (2*S*,3*S*)-**5a**−**d**, as reported in Scheme 3. The products were analyzed by chiral GC chromatography on a MEGADEX 5 column

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Scheme 3

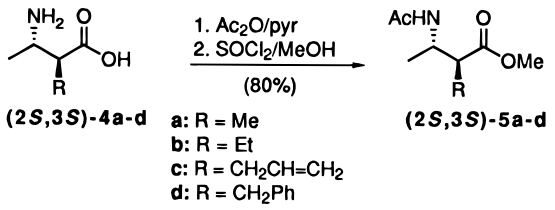


Table 3. Specific Rotations and Enantiomeric Excesses for Products (2*S*,3*S*)-4 and (2*S*,3*S*)-5

entry	product	$[\alpha]_D$	product	$[\alpha]_D$	ee[a]
a	(2*S*,3*S*)-**4a**	+10.0 (*c* 1.2, H_2O)	(2*S*,3*S*)-**5a**	−8.1 (*c* 0.1, $CHCl_3$)	100
b	(2*S*,3*S*)-**4b**	+2.4 (*c* 0.5, H_2O)	(2*S*,3*S*)-**5b**	−16.0 (*c* 0.2, $CHCl_3$)	100
c	(2*S*,3*S*)-**4c**	+12.5 (*c* 0.8, H_2O)	(2*S*,3*S*)-**5c**	−37.5 (*c* 0.2, $CHCl_3$)	94.5
d	(2*S*,3*S*)-**4d**	−14.1 (*c* 0.5, H_2O)	(2*S*,3*S*)-**5d**	−46.7 (*c* 0.7, $CHCl_3$)	100

[a] The enantiomeric excesses have been determined with chiral GC utilizing a MEGADEX 5 column with 2,3-dimethyl-5-pentyl-β-cyclodextrin.

Scheme 4

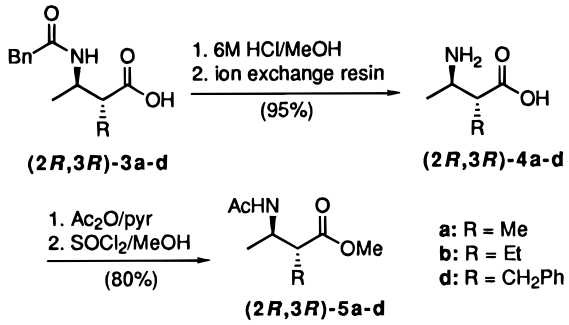


Table 4. Specific Rotations and Enantiomeric Excesses for Products (2*R*,3*R*)-4 and (2*R*,3*R*)-5

entry	product	$[\alpha]_D$	product	$[\alpha]_D$	ee[a]
a	(2*R*,3*R*)-**4a**	−8.7 (*c* 1.2, H_2O)	(2*R*,3*R*)-**5a**	+7.5 (*c* 0.1, $CHCl_3$)	100
b	(2*R*,3*R*)-**4b**	−3.5 (*c* 0.3, H_2O)	(2*R*,3*R*)-**5b**	+14.3 (*c* 0.3, $CHCl_3$)	94.3
c	(2*R*,3*R*)-**4c**	−6.6 (*c* 1.2, H_2O)	(2*R*,3*R*)-**5c**	+39.4 (*c* 0.1, $CHCl_3$)	100
d	(2*R*,3*R*)-**4d**	+21.0 (c 0.1, H_2O)	(2*R*,3*R*)-**5d**	+47.5 (*c* 0.1, $CHCl_3$)	100

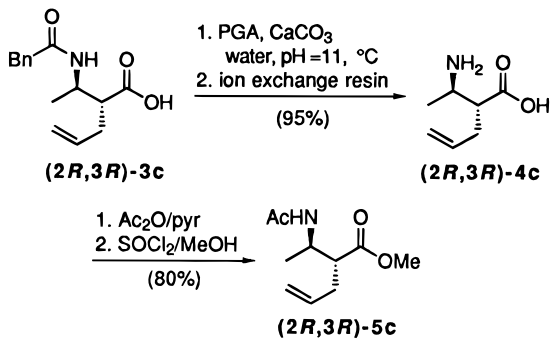
[a] The enantiomeric excesses have been determined with chiral GC utilizing a MEGADEX 5 column with 2,3-dimethyl-5-pentyl-β-cyclodextrin.

filled with 2,3-dimethyl-5-pentyl-β-cyclodextrin (Table 3).

On the other hand, (2*R*,3*R*)-**3a**, (2*R*,3*R*)-**3b**, and (2*R*,3*R*)-**3d** were recovered from the organic layers and dissolved in a 1:1 6 M HCl/methanol mixture and refluxed for 30 h (Scheme 4) to obtain the free amino acids (2*R*,3*R*)-**4a**, (2*R*,3*R*)-**4b**, and (2*R*,3*R*)-**4d**. The mixture was concentrated under reduced pressure to eliminate the methanol and the excess of HCl and dissolved in a small amount of water. The free amino acids were purified on a cation-exchange resin using 1.5 M NH_4OH as eluant and fully characterized as their acetamido methyl ester derivatives (2*R*,3*R*)-**5a**, (2*R*,3*R*)-**5b**, and (2*R*,3*R*)-**5d**. These compounds were analyzed by chiral GC utilizing a MEGADEX 5 column with 2,3-dimethyl-5-pentyl-β-cyclodextrin (Table 4).

Since the acid hydrolysis of the allyl derivative (2*R*,3*R*)-**3c** afforded a cyclization product,[9] the hydrolysis was

Scheme 5



carried out with immobilized PGA under basic conditions. Indeed, (2*R*,3*R*)-**3c** (100 mg) was hydrolyzed in water (5 mL) and ethanol (1 mL) with immobilized PGA (50 mg) and $CaCO_3$ (100 mg) (pH = 11). The reaction proceeded for 96 h at 35 °C in 95% yield (Scheme 5). The reaction mixture was acidified to pH = 3, and then (2*R*,3*R*)-**4c** was purified on a cation-exchange resin using 1.5 M NH_4OH as eluant and was fully characterized as its acetamido methyl ester derivative (2*R*,3*R*)-**5c** (Table 4).

In conclusion, we have demonstrated that immobilized penicillin G acylase is an effective reagent for the kinetic resolution of α-alkyl β-amino acids. The reaction time, the reaction temperature, the solvent, and the pH proved to be crucial for the yield and the enantiomeric purity of the products and should be attentively evaluated for each substrate.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 300 or 200 MHz. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be δ 7.27 ppm. Infrared spectra were recorded with an FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with Merck silica gel 60 (230−400 mesh). THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5. The enantiomeric excesses have been determined with chiral GC utilizing a MEGADEX 5 column with 2,3-dimethyl-5-pentyl-β-cyclodextrin (stationary phase SE52; film thickness 0.1 μm; length 25 m; internal diameter 0.32 mm; column material fused silica; upper temperature limit 370 °C). Penicillin G acylase supported on Eupergit was obtained by Recordati S.p.A. Unità De.Bi. (Lot. 940-1606; 252.9 IU/g wet; 890 IU/g dry).

Methyl (±)-*N*-(Phenylacetyl)-3-aminobutanoate (1). Phenylacetyl cloride (12 mmol, 1.59 mL) in acetone (10 mL) was added dropwise to a stirred solution of (±)-3-aminobutanoic acid (10 mmol, 1.03 g) and NaOH (0.8 g) in distilled water (30 mL) at 0 °C. The mixture was stirred at rt for 1 h, the acetone was removed under reduced pressure, and the residue was extracted with ethyl acetate. Then 2 M HCl was added to the aqueous layer until the solution reached pH = 1, and the mixture was extracted with ethyl acetate. The second organic layer was dried over Na_2SO_4 and concentrated. A solution of $SOCl_2$ (20 mmol, 1.46 mL) in methanol was stirred for 2 h at −15 °C, and then the acid previously obtained was added in one portion. The mixture was stirred overnight and left to warm to room temperature. The solution was concentrated under reduced pressure, and compound **1** was obtained in 84% overall yield after flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1 as eluant).

1: mp = 40−41 °C; IR (nujol) 3296, 1729, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* = 6.8 Hz, 3H), 2.51 (d, *J* = 5.5 Hz, 2H), 3.57 (s, 3H), 3.67 (s, 2H), 4.33 (m, 1H), 5.98 (d, *J* = 7.0 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.4, 39.6, 41.8, 42.8, 50.9, 126.3, 128.0, 128.6, 134.9, 169.9, 171.1; HRMS calcd for (M^+) $C_{13}H_{17}O_3N$ 235.120 843 6, found 235.120 900 5.

(±)-*anti*-*N*-(Phenylacetyl)-2-alkyl-3-aminobutanoic Acid 3a−d. To a stirred solution of ester **1** (2 mmol, 0.47 g) in dry THF (10 mL) was added LiHMDS (1 M solution in THF, 4 mmol, 4 mL) in one portion under argon at 0 °C. After 1 h, the alkylating agent (1.5 equiv) was added at −78 °C and the solution was allowed to stir overnight while being warmed to room temperature. The reaction was quenched with a saturated solution of NH_4Cl, and the solvent was removed under reduced pressure and replaced with dichloromethane, which was then washed twice with water. The organic layer was dried over Na_2SO_4 and concentrated. Compounds **2a−d** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9:1 as eluant) and then added to a solution of K_2CO_3 (2 equiv) in water. The mixture was refluxed for 2 h and then extracted with ethyl acetate. To the aqueous layer was added 1 M HCl until the solution reached pH = 1, and the mixture was extracted twice with ethyl acetate. After the solvent was removed under reduced pressure, compounds **3a−d** were obtained pure in 67−82% overall yield from **1**.

3a: mp = 121−124 °C; IR (Nujol) 3290, 1700, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H, *J* = 7.2 Hz), 1.13 (d, 3H, *J* = 6.8 Hz), 2.58 (dq, *J* = 4.1, 7.2 Hz, 1H), 3.58 (AB, 2H, *J* = 15.9 Hz), 4.15 (m, 1H), 6.49 (d,1H, *J* = 9.1 Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.6, 43.2, 43.3, 46.9, 127.0, 128.4, 129.0, 134.3, 171.8, 178.3; HRMS calcd for (M^+) $C_{13}H_{17}O_3N$ 235.120 843 6, found 235.120 821 3.

3b: mp = 91−92 °C; IR (Nujol) 3303, 1719, 1609 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.13 (d, 3H, *J* = 6.7 Hz), 1.52 (m, 2H), 2.35 (ddd, *J* = 6.1, 10.2, 12.3 Hz, 1H), 3.58 (s, 2H), 4.26 (m, 1H), 6.50 (d, 1H, *J* = 8.9 Hz), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.8, 19.4, 23.1, 43.4, 45.2, 50.9, 127.1, 128.7, 129.1, 134.3, 171.6, 178.1; HRMS calcd for (M^+) $C_{14}H_{19}O_3N$ 249.136 493 7, found 249.136 658 2.

3c: mp = 96−97 °C; IR (Nujol) 3382, 1714, 1619 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 3H, *J* = 6.8 Hz), 2.20 (m, 2H), 2.54 (m, 1H), 3.59 (s, 2H), 4.70 (m, 1H), 5.00 (m, 2H), 5.70 (m, 1H), 6.41 (d, 1H, *J* = 9.5 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.4, 34.0, 43.5, 45.2, 49.2, 117.6, 127.3, 128.5, 128.9, 134.1, 134.3, 171.7, 178.6; HRMS calcd for (M^+) $C_{15}H_{19}O_3N$ 261.136 493 7, found 261.136 524 9.

3d: mp = 103−106 °C; IR (Nujol) 3295, 1728, 1608 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, *J* = 6.7 Hz), 2.73 (m, 3H), 3.59 (AB, 2H, *J* = 15.6 Hz), 4.17 (m, 1H), 6.67 (d, 1H, *J* = 8.8 Hz), 7.27 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.4, 35.8, 43.5, 45.2, 51.2, 126.5, 127.3, 128.3, 128.7, 128.8, 129.2, 134.3, 138.0, 172.0, 177.3; HRMS calcd for (M^+) $C_{19}H_{21}O_3N$ 311.152 143 8, found 311.152 192 6.

General Procedure for the Enzymatic Hydrolysis of (±)-*N*-(Phenylacetyl)-2-alkyl-3-aminobutanoic Acid 3a−d. The amide acid **3** (100 mg) was added to a solution of 0.1 M phosphate buffer adjusted to pH = 7 (10 mL) and ethanol as cosolvent, containing penicillin G acylase from *Escherichia coli* immobilized on Eupergit (10 mg). The reaction mixture was stirred at the temperature and for the time reported in Table 2. Then the ethanol was removed under reduced pressure, and 2 M HCl was added to the aqueous solution until pH = 3. The mixture was extracted twice with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to recover phenylacetic acid and the unhydrolyzed amide. The aqueous layer was concentrated, and the residue was dissolved in water (1 mL) and adsorbed on cation-exchange resin. The resin was washed with water until the washing came out neutral and then was eluted with 1.5 M aqueous NH_4OH. The aqueous solution was concentrated under reduced pressure to recover the (*S*,*S*)-2-alkyl-3-amino acid in the zwitterionic form.

General Procedure for the Hydrolysis of (*R*,*R*)-*N*-(Phenylacetyl)-2-alkyl-3-aminobutanoic Acid 3a,b,d. The residue obtained from the organic layer of the enzymatic hydrolysis was dissolved in 6 M HCl and refluxed for 30 h. The mixture was then extracted with ethyl acetate to remove phenylacetic acid, and the aqueous layer was concentrated and treated with cation-exchange resin to recover the (*R*,*R*)-2-alkyl-3-amino acid in the zwitterionic form.

Hydrolysis of (*R*,*R*)-*N*-(Phenylacetyl)-2-allyl-3-aminobutanoic Acid (3c). The mixture of compound **3c** and phenylacetic acid (obtained from the organic layer of the enzymatic hydrolysis) and penicillin G acylase (50 mg) were suspended in a solution of $CaCO_3$ (100 mg) in water (5 mL) and ethanol (1 mL). The solution was stirred for 96 h at room temperature and then acidified with 2 M HCl until pH = 3. The mixture

was extracted twice with ethyl acetate to remove phenylacetic acid, and then the aqueous layer was concentrated under reduced pressure and treated with cation-exchange resin to recover (*R*,*R*)-*N*-(phenylacetyl)-2-allyl-3-aminobutanoic acid (**3c**) in the zwitterionic form in 95% yield.

General Procedure for the Preparation of Methyl *N*-Acetyl-2-alkyl-3-aminobutanoate (*S*,*S*)-5a−d and (*R*,*R*)-5a−d. The amino acid **4** was added in one portion to a stirred solution of pyridine (2 mL), acetic anhydride (2 mL), and (dimethylamino)pyridine (5 mg). The mixture was stirred at room temperature for 2 h and then quenched with water and extracted twice with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

A solution of $SOCl_2$ (2 equiv) in methanol (5 mL) was stirred for 2 h at −15 °C, and then the *N*-acetylamino acid previously obtained was added in one portion. The mixture was stirred overnight while slowly being warmed to room temperature. The solution was concentrated under reduced pressure, and compound **5** was obtained in overall 80% yield after purification with silica gel chromatography (cyclohexane/ethyl acetate 6:4 as eluant).

5a: IR (film) 3290, 1738, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 7.2 Hz), 1.99 (s, 3H), 2.63 (dq, 1H, J = 4.2 Hz, 7.2 Hz), 3.70 (s, 3H), 4.20 (m, 1H), 6.25 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 19.5, 23.5, 43.5, 46.8, 51.7, 169.6, 176.2; HRMS calcd for (M^+) $C_8H_{15}O_3N$ 173.105 193 5, found 173.105 234 1.

5b: IR (film) 3350, 1742, 1657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.4 Hz), 1.13 (d, 3H, J = 6.8 Hz), 1.62 (m, 2H), 1.99 (s,3H), 2.40 (ddd, 1H, J = 4.0, 6.8, 10.8 Hz), 3.72 (s, 3H), 4.25 (m, 1H), 6.4 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.0, 20.0, 23.5, 29.7, 45.1, 51.4, 51.6, 169.6, 176.2; HRMS calcd for (M^+) $C_9H_{17}O_3N$ 187.120 843 6, found 187.120 936 2.

5c: IR (film) 3120, 1733, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 3H, J = 6.8 Hz), 2.00 (s, 3H), 2.33 (m, 2H), 2.58 (m, 1H), 3.70 (s, 3H), 4.28 (m, 1H), 5.07 (m, 2H), 5.73 (1H, m), 6.38 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 23.3, 34.4, 45.3, 49.5, 51.6, 117.4, 134.5, 169.7, 175.4; HRMS calcd for (M^+) $C_{10}H_{17}O_3N$ 199.120 843 6, found 199.120 966 9.

5d: IR (film) 3290, 1720, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, 3H, J = 6.7 Hz), 2.01 (s, 3H), 2.81 (m, 2H), 2.95 (m, 1H), 3.61 (s, 3H), 4.23 (m, 1H), 6.66 (d, 1H, J = 8.7 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.8, 23.3, 36.1, 45.3, 51.4, 51.6, 126.6, 128.5, 128.9, 138.4, 170.5, 177.3; HRMS calcd for (M^+) $C_{14}H_{19}O_3N$ 249.136 493 6, found 249.136 442 2.

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Supporting Information Available: ^1H NMR of the crude mixture of **3c** hydrolysis and gas chromatograms of (2*R*,3*R*)-**5c** and (2*S*,3*S*)-**5c** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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