Synthesis of Enantiopure δ-Oxo α-Amino Esters and Prolines via Acylation of *N*-(Phenylfluorenyl)glutamate Enolates

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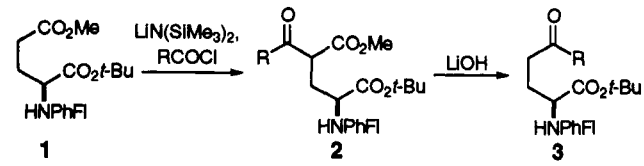
Acylation of the lithium γ-enolate of α-*tert*-butyl γ-methyl *N*-[9-(9-phenylfluorenyl)]glutamate (1) with different acid chlorides provides β-keto esters **2**. Selective γ-ester hydrolysis and decarboxylation furnishes good yields of enantiomerically pure δ-oxo α-amino esters **3** possessing primary, secondary, and tertiary alkyl, as well as aromatic δ-substituents. Acylation of **1** with methyl oxalyl chloride is followed by condensation of the ketone and amine of **2** to give *N*-(PhFl)-Δ^2-pyrroline triester **4** in 75% yield. Palladium-catalyzed hydrogenation of (2*S*)-*tert*-butyl 4-oxo-2-(*N*-(PhFl)amino)nonanoate (**3f**) yields >99.5% enantiopure (2*S*,5*S*)-5-butylproline *tert*-butyl ester (**5**), an intermediate in the synthesis of 2,5-dialkylpyrrolidine alkaloids.

In conjunction with our studies on the conformational affects of unnatural amino acids in small peptides, we require enantiomerically pure δ-oxo α-amino esters as synthetic intermediates to prepare substituted prolines.[1] δ-Oxo α-amino acid derivatives have been used to prepare a variety of non-proteinogenic amino acids; however, their asymmetric synthesis still remains a challenge.[2-4] Previous methods, which utilize glutamate-derived electrophiles such as *N*-protected glutamate γ-acid chloride and γ-imidazolide, as well as pyroglutamic ester equivalents, provide δ-oxo α-amino esters via acylation of organometallic, diazoalkane, and enolate reagents.[2,3] Restrictions on the use of these procedures exist because of the potential for racemization of chiral glutamate in the presence of basic organometallic reagents, the hazardous nature of diazoalkanes, and the poor reactivity of sterically demanding nucleophilic reagents.[2,3] We now report an alternative strategy that uses glutamate-derived nucleophiles and the acylation of glutamate γ-enolates followed by decarboxylation of the resulting β-keto esters **2** to provide enantiopure δ-oxo α-amino esters **3** with sterically bulky alkyl as well as aromatic δ-substituents (Scheme I).

α-*tert*-Butyl γ-methyl *N*-[9-(9-phenylfluorenyl)]glutamate (**1**) was prepared for our investigation in order to differentiate the carboxylates of glutamic acid.[5] The 9-(9-phenylfluorenyl) (PhFl) group for nitrogen protection was employed to achieve selective enolization of the γ-ester of glutamate **1** without racemization of the chiral α-amino

Scheme I. Synthesis of δ-Oxo α-Amino Esters 3



1 2 3

ester.[5,6] The steric bulk of the phenylfluorenyl group was also expected to shield the amine from acylation.

Previous studies have shown that reactions at glutamate γ-enolate anions with electrophiles are strongly dependent on the nature of the enolate counterion and the electrophile. Lithium enolates react with alkyl halides and aldehydes to provide γ-substituted glutamates in poor to moderate yields.[5,7] Potassium enolates are preferred for obtaining high yields of γ-substituted glutamates in alkylations with alkyl iodides and alkyl triflates.[5,7c] The γ-lithium enolate of dibenzyl *N*-tritylglutamate was shown to react with benzyl chloroformate; however, no yield was reported.[8]

We found lithium enolates to be essential for obtaining high yields of β-keto esters **2** in the acylation of the γ-ester of *N*-(phenylfluorenyl)glutamate **1** with acid chloride electrophiles. No β-keto ester product was isolated on treatment of the potassium enolate of **1** with acid chlorides.[9] β-Keto esters **2** were observed by proton NMR as pairs of diastereomers each exhibiting a γ-proton appearing as a doublet of doublets between 3.5 and 4.8 ppm. Yields of chromatographically isolated β-keto esters **2** obtained

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(9) At this time it is unclear whether the potassium enolate of **1** is unreactive to acid chlorides or if acylation is occurring on oxygen to provide an *O*-acyl methyl ketene acetal which is subsequently hydrolyzed to starting material after aqueous workup. For previous examples of the acylation of lithium enolates with acid chlorides see: (a) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785. (b) Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531. (c) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (d) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953. (e) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. High yields obtained with 120 mol % of $LiN(SiMe_3)_2$ suggest that acylation precedes deprotonation of the β-keto ester **2** by the enolate of **1**. For a related example see: (f) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.

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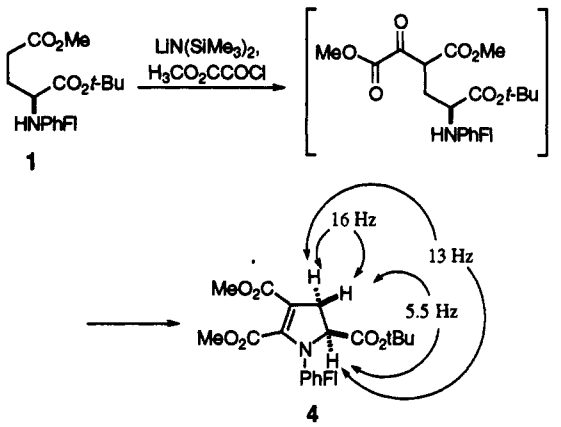
Table I. Yields for Acylation of 1 and Decarboxylation of 2[a]

entry	R	% yield of 2	% yield of 3	^{13}C for C=O of 3, ppm
a	Et	80	85	210.7
b	*iso*-Pr	68 (91)	82	214
c	*tert*-Bu	58 (89)	63	215.7
d	Ph	90	90	200
e	$PhCH_2$	65	95	208

[a] Refer to isolated material from chromatography on silica gel. Yields in parentheses based on consumed 1. Yields for 3 from LiOH reaction on 2.

Scheme II. Synthesis of Δ²-Pyrroline Triester 4



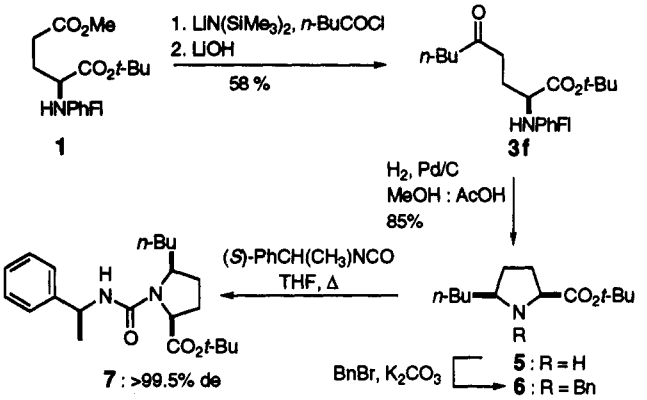
from acylation reactions with a variety of acid chlorides are reported in Table I.[10]

Selective hydrolysis of the γ-methyl ester and decarboxylation is achieved on exposure of β-keto esters 2 to lithium hydroxide (1000 mol %) in a 1:1 H_2O/THF solution to provide δ-oxo α-amino esters 3 (Table I). Potassium trimethylsilanolate (120 mol %) in ether also affects hydrolysis of methyl ester under milder conditions.[11] For example, hydrolysis of β-keto ester **2a** with LiOH in a THF/H_2O solution required heating at reflux for 10 h; on the other hand, $KOSi(CH_3)_3$ hydrolysis of **2a** was complete after stirring in ether for 4 h at room temperature. Chromatographic isolation of intermediates is not essential and δ-oxo α-amino esters **3** may be obtained in comparable yields by direct hydrolysis and decarboxylation of unpurified β-keto esters **2**.

Methyl oxalyl chloride reacted in the acylation of glutamate γ-enolate **1**, but the expected β-keto ester was not isolated. Instead, acylation of the γ-enolate was followed by condensation of the *N*-phenylfluorenylamine and ketone to give Δ²-pyrroline **4** in 75% yield after isolation by chromatography (Scheme II).[12] Triester **4** exhibits three aliphatic ring protons with geminal and vicinal coupling constants illustrated in Scheme II.

Intramolecular reductive amination of δ-oxo α-amino esters provides access to 2,5-disubstituted pyrrolidines, important molecules that serve as chiral auxiliaries,[13] chiral

Scheme III. Synthesis and Optical Purity of Proline 5



ligands,[14] chiral bases,[15] and synthetic intermediates.[16] To demonstrate the utility of δ-oxo α-amino esters **3** we prepared 5-*n*-butylproline *tert*-butyl ester (**5**), an intermediate in Rapoport's synthesis of the 2,5-dialkylpyrrolidine alkaloids of certain ant venoms (Scheme III).[17,18] This was accomplished by acylation of **1** with valeryl chloride under conditions described above and subsequent decarboxylation with LiOH in a THF/H_2O/MeOH solution to provide γ-keto α-amino nonanoate **3f** in 58% overall yield. Hydrogenation of **3f** with palladium-on-carbon in a 9:1 methanol/acetic acid solution proceeds by cleavage of the phenylfluorenyl group, intramolecular imine formation, protonation, and hydrogen addition to the less-hindered face of the iminium ion intermediate to selectively furnish (2*S*,5*S*)-5-*n*-butylproline *tert*-butyl ester (**5**).[2f,17] Proline ester **5** was obtained in 85% yield after purification by column chromatography and converted to its *N*-benzyl derivative **6** for an additional comparison.[17] The (2*R*,5*R*)-enantiomer of proline **5** was similarly prepared starting from D-glutamic acid.

Enantiomeric purity of **5** was ascertained after preparation of diastereomeric ureas **7** on reaction of both (2*S*,5*S*)- and (2*R*,5*R*)-**5** with (*S*)-α-methylbenzyl isocyanate.[5,19]

(10) Acid chlorides without α-hydrogens were added directly to the enolate solution. Acylation of **1** with pivaloyl chloride on 5× larger scale (5 mmol) resulted in 12% lower conversion to **2c**.

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(17) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. No *trans*-diastereomer was detected after the hydrogenation of **3f** to **5**; however, 2–5% of (2*S*)-5-butyl-Δ⁴-dehydroproline *tert*-butyl ester from incomplete hydrogenation of **3f** was occasionally isolated by chromatography: HRMS calcd for $C_{13}H_{23}NO_2$ (M^+) 225.1729, found 225.1751.

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(19) Lubell, W.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824. Attempts to determine enantiomeric purity of **5** by coupling to 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) in CH_3CN and examination of the diastereomeric tetraacetylglucose thioureas on HPLC were unsuccessful.

Observation of the *tert*-butyl ester singlets in the proton NMR during incremental additions of the opposite isomer demonstrated ureas **7** to be of >99.5% diastereomeric purity. Hence δ-oxo α-amino esters **3** and proline **5** arepresumed to be of >99.5% enantiomeric purity.

An effective route to furnish δ-oxo α-amino esters has been achieved via acylation of the lithium γ-enolate of *N*-phenylfluorenylglutamate diester **1** and subsequent hydrolysis and decarboxylation of the resulting β-keto esters **2**. We are now attempting to extend this methodology to aspartate and α-amino dicarboxylates with longer carbon chains, as well as to synthesize 5- and 4,5-substituted prolines via intramolecular reductive amination of β-keto esters **2** and δ-oxo α-amino esters **3**.[1]

Experimental Section

General. Unless otherwise noted all reactions were run under an nitrogen or argon atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately before use; 1,1,1,3,3,3-hexamethyldisilazane was distilled from CaH_2. Final reaction mixture solutions were dried over Na_2SO_4. Column chromatography was performed on 230–400 mesh silica gel; TLC was performed on aluminum-backed silica plates. Melting points are uncorrected. Mass spectral data, HRMS (EI), were obtained by the Université de Montréal Mass Spec. facility. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$). Chemical shifts for aromatic carbons are not reported.

General Procedure for Synthesis of δ-Oxo α-Amino Esters 3. A solution of *n*-butyllithium in hexane (0.6 mL, 2 M, 120 mol %) was added to a −78 °C solution of 1,1,1,3,3,3-hexamethyldisilazane (425 μL, 2 mmol, 200 mol %) in THF (8 mL), stirred for 15 min, and then treated with a solution of *N*-[9-(9-phenylfluorenyl)]glutamate diester **1**[5] (457 mg, 1 mmol, 100 mol %) in THF (2 mL). The resulting solution was stirred for 1 h and then added via Teflon tubing into a −78 °C solution of the acid chloride (200 mol %, freshly filtered through a pad of silica gel) in 1 mL of THF.[10] After stirring at −78 °C for 1–1.5 h the mixture was partitioned between EtOAc (20 mL) and 1 M NaH_2PO_4 (20 mL). The aqueous phase was extracted with EtOAc (20 mL), and the combined organic layers were washed with brine, dried, and evaporated to a residue which was chromatographed on silica gel eluting with a gradient of 0–10% EtOAc in hexanes. Concentration of the collected fractions provided β-keto esters **2** as oils which were observed by proton NMR to exist as mixtures of diastereomers.

β-Keto ester **2** (0.6–1 mmol) was redissolved in THF (5 mL), treated with a 2 M solution of lithium hydroxide (5 mL), and stirred at room temperature or heated at reflux until TLC showed complete disappearance of starting **2** and formation of a new higher R_f product. The mixture was partitioned between EtOAc (20 mL) and water (20 mL). The aqueous phase was extracted with EtOAc (20 mL); the organic layers were combined, washed with brine, dried, and evaporated to an oil which was chromatographed by eluting with a gradient of 0–10% EtOAc in hexanes.

(2*S*)-*tert*-Butyl 5-oxo-2-[*N*-[9-(9-phenylfluorenyl)]-amino]heptanoate (3a): a solid (68% from 1); mp 68 °C; $[\alpha]^{20}_D$ −153° (*c* 0.1, $CHCl_3$); ^1H NMR δ 1.07 (t, 3 H, *J* = 7.3 Hz), 1.22 (s, 9 H), 1.78 (m, 2 H), 2.35–2.65 (m, 5 H), 3.24 (br s, 1 H), 7.23–7.86 (m, 13 H); ^{13}C NMR δ 7.4, 27.5, 29, 35.5, 38, 54.8, 72.5, 80.3, 174.7, 210.7. HRMS calcd for $C_{30}H_{33}NO_3$ (M^+) 455.2460, found 455.2461.

(2*S*)-*tert*-Butyl 6-methyl-5-oxo-2-[*N*-[9-(9-phenylfluorenyl)]amino]heptanoate (3b): an oil (56% (75%) from 1); $[\alpha]^{20}_D$ −212° (*c* 0.2, $CHCl_3$); ^1H NMR δ 1.08 (d, 3 H, *J* = 6.9 Hz), 1.09 (d, 3 H, *J* = 6.9 Hz), 1.18 (s, 9 H), 1.66 (m, 2H), 2.33–2.63 (m, 4H), 7.18–7.69 (m, 13H); ^{13}C NMR δ 18.2, 27.8, 29.3, 36.4, 38.9, 40.8, 55.3, 72.9, 80.6, 175, 214; HRMS calcd for $C_{31}H_{36}NO_3$ (MH^+) 470.2695, found 470.2711.

(2*S*)-*tert*-Butyl 6,6-dimethyl-5-oxo-2-[*N*-[9-(9-phenylfluorenyl)]amino]heptanoate (3c): an oil (37% (56%) from 1); $[\alpha]^{20}_D$ −173° (*c* 0.8, $CHCl_3$); ^1H NMR δ 1.13 (s, 9H), 1.19, (s, 9H), 1.59 (m, 2H), 2.35 (m, 1H), 2.48 (t, 1H, *J* = 6.3 Hz), 2.76 (m, 1H), 7.69–7.18 (m, 13H); ^{13}C NMR δ 26.4, 27.8, 29.6, 33.2, 44, 55.3, 72.8, 80.6, 175.1, 215.7; HRMS calcd for $C_{32}H_{37}NO_3$ (M^+) 483.2773, found 483.2783. Anal. Calcd for $C_{32}H_{37}NO_3$: C, 79.47; H, 7.71; N, 2.9. Found: C, 79.52; H, 7.86; N, 2.86.

(2*S*)-*tert*-Butyl 5-phenyl-5-oxo-2-[*N*-[9-(9-phenylfluorenyl)]amino]pentanoate (3d): a solid (81% from 1); mp 124 °C; $[\alpha]^{20}_D$ −129° (*c* 0.2, $CHCl_3$); ^1H NMR δ 1.2 (s, 9 H), 1.85, (m, 2H), 2.56 (m, 1 H), 2.95 (m, 1 H), 3.12 (m, 1 H), 3.25 (br s, 1 H), 7.1–8.05 (m, 18 H); ^{13}C NMR δ 27.75, 27.8, 35, 55.1, 72.9, 80.7, 175.1, 200; HRMS calcd for $C_{34}H_{34}NO_3$ (MH^+) 504.2539, found 504.2559.

(2*S*)-*tert*-Butyl 6-phenyl-5-oxo-2-[*N*-[9-(9-phenylfluorenyl)]amino]hexanoate (3e): an oil (62% from 1) $[\alpha]^{20}_D$ −44 (*c* 0.7, $CHCl_3$); ^1H NMR δ 1.14 (s, 9H), 1.6 (m, 2H), 2.40 (m, 2H), 2.59 (m, 1H), 3.05 (br s, 1 H), 3.66 (s, 2H), 7.6–7.15 (m, 18H); ^{13}C NMR δ 27.7, 29.1, 38.1, 50.2, 55, 72.8, 80.6, 174.9, 208; HRMS calcd for $C_{35}H_{36}NO_3$ (MH^+) 518.2695, found 518.2686.

(2*S*)-*tert*-Butyl 4-Oxo-2-[*N*-[9-(9-phenylfluorenyl)]amino]nonanoate ((*S*)-3f). Crude β-keto ester **2f** (obtained from acylation of **1** (2 mmol) with valeryl chloride (4 mmol)) was redissolved in a THF (5 mL)/MeOH (5 mL) solution and treated with a 2 M solution of lithium hydroxide (5 mL). The solution was stirred until TLC showed complete disappearance of starting **2**. The mixture was partitioned between EtOAc (20 mL) and water (20 mL). The aqueous phase was extracted with EtOAc (20 mL) and the organic layers were combined, washed with brine, dried, and evaporated to an oil which was chromatographed by eluting with a gradient of 0–10% EtOAc in hexanes. Evaporation of the collected fractions gave 560 mg of **3f** (58% from 1) $[\alpha]^{20}_D$ −110° (*c* 0.5, $CHCl_3$); ^1H NMR δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.18 (s, 9H), 1.3 (m, 2 H), 1.5–1.66 (m, 4H), 2.34–2.51 (m, 5H), 3.09 (br s, 1H), 7.2–7.7 (m, 13H); ^{13}C NMR δ 13.8, 22.3, 25.9, 27.8, 29.3, 38.7, 42.5, 55.2, 80.7, 174.9, 210.8; HRMS calcd for $C_{32}H_{38}NO_3$ (MH^+) 484.2852, found 484.2827. **(2*R*)-*tert*-Butyl 4-oxo-2-[*N*-[9-(9-phenylfluorenyl)]amino]nonanoate ((*R*)-3f)** was prepared by the same conditions from D-glutamic acid: $[\alpha]^{20}_D$ 197° (*c* 0.45, $CHCl_3$).

(5*S*)-*tert*-Butyl 1-*N*-[9-(9-phenylfluorenyl)]-2,3-bis-[(methyloxy)carbonyl]-Δ²-pyrroline (4). Acylation of the lithium enolate of **1** (1 mmol) with methyl oxalyl chloride (0.183 mL, 2 mmol, direct addition), according to the general procedure, provided after chromatography 385 mg (75%) of **4**: $[\alpha]^{20}_D$ 14.3° (*c* 0.8, $CHCl_3$); ^1H NMR δ 1.32 (s, 9H), 2.42 (dd, 1H, *J* = 5.2 Hz, *J* = 16 Hz), 2.79 (dd, 1H, *J* = 16 Hz, *J* = 13 Hz), 3.27 (s, 3H), 3.36 (dd, 1H, *J* = 13 Hz, *J* = 5.2 Hz), 3.62 (s, 3H), 7.1–8.4, (m, 13H); ^{13}C NMR δ 27.8, 33.6, 51.1, 51.9, 61.9, 81, 163.9, 164.1, 171.6; HRMS calcd for $C_{32}H_{31}NO_6$ (M^+) 525.2151, found 525.2158.

(2*S*,5*S*)-5-Butylproline *tert*-Butyl Ester (*S*-5). A solution of δ-keto α-amino ester **3f** (200 mg, 0.4 mmol) in MeOH (9 mL) and AcOH (1 mL) was treated with palladium-on-carbon (10 wt %, 40 mg) and stirred under a balloon of hydrogen for 24 h. The mixture was filtered on Celite, the catalyst was washed with MeOH (5 mL), and the combined organic phase was evaporated to an oil that was purified on column chromatography using a gradient of 0–50% EtOAc in hexanes to give 88 mg (87%) of **5** as an oil: $[\alpha]^{20}_D$ −18.75° (*c* 0.8, EtOH); lit.[17] $[\alpha]^{20}_D$ −16° (*c* 3.4, EtOH); ^1H NMR δ 0.9 (t, 3 H, *J* = 7 Hz), 1.2–1.4 (m, 6 H), 1.46 (s, 9 H), 1.8–1.9 (m, 2 H), 2.0–2.1 (m, 2 H), 3 (m, 1 H), 3.6 (dd, 1 H, *J* = 9 Hz, *J* = 5 Hz); ^{13}C NMR δ 13.9, 22.6, 27.9, 29.3, 30.4, 31.4, 35, 60.3, 60.4, 81.4, 173.9. 5-*n*-Butylproline *tert*-butyl ester **5** was converted according to the literature procedure into its *N*-benzyl derivative **6** (87%): $[\alpha]^{20}_D$ −10° (*c* 0.3, EtOH); lit.[17] $[\alpha]^{20}_D$ −1.6° (*c* 5.3, EtOH); ^1H NMR δ 0.86 (t, 3H), 1.33 (s, 9H), 1.26–2.0 (m, 10H), 2.7 (m, 1H), 3.15 (m, 1H), 3.74 (d, 1H, *J* = 14 Hz), 3.83 (d, 1H, *J* = 14 Hz), 7.2–7.3, (m, 5H). **(2*R*,5*R*)-5-Butylproline *tert*-butyl ester ((*R*)-5)** was prepared by the same conditions from (*R*)-**3f**: $[\alpha]^{20}_D$ 1.37° (*c* 5.6, EtOH).

Enantiomeric Purity of 5-Butylproline *tert*-Butyl Ester (5). Either (2*S*,5*S*)- or (2*R*,5*R*)-proline ester **5** (10 mg, 0.041 mmol) in 2 mL of THF was treated with (*S*)-α-methylbenzyl isocyanate (0.082 mmol, 0.012 mL) and heated at a reflux for 2 h. Removal of the volatiles under vacuum left a residue which was directly examined by ^1H NMR in which the *tert*-butyl ester singlets were clearly differentiated. The limits of detection were determined

by incremental doping experiments with ureas **7** after purification on a 100-μm plate of silica gel. This method demonstrated (*S*)- and (*R*)-**5** to be of >99.5% diastereomeric purity. **Urea (*S*)-7**: ^{1}H NMR δ 0.88 (t, 3 H, J = 7 Hz), 1.28 (m, 2 H), 1.36 (s, 9 H), 1.43 (m, 2 H), 1.48 (d, 3 H, J = 6.5 Hz), 1.6–2.15 (m, 6 H), 3.92 (m, 1 H), 4.17 (dd, 1 H, J = 5.5 Hz, J = 7.7 Hz), 5.03 (m, 2 H), 7.2–7.4 (m, 5 H). **Urea (*R*)-7**: ^{1}H NMR δ 0.88 (t, 3 H, J = 7 Hz), 1.27 (m, 2 H), 1.48 (s, 9 H), 1.48 (d, 3 H, J = 7 Hz), 1.55–2.2 (m, 8 H), 3.91 (m, 1 H), 4.14 (dd, 1 H, J = 5 Hz, J = 7.6 Hz), 5 (quint, 1 H, J = 7 Hz), 5.16 (broad d, 1 H, J = 7 Hz), 7.2–7.4 (m, 5 H).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for of **2–7** (27 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.