Highly Stereoselective Synthesis of *anti*-N-Protected-α-Amino Epoxides

Robert V. Hoffman,* Warren S. Weiner, and Najib Maslouh

Department of Chemistry and Biochemistry, New Mexico State University, North Horseshoe Drive, Las Cruces, New Mexico 88003-8001

rhoffman@nmsu.edu

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A simple and efficient method for the synthesis of *anti*-N-protected amino epoxides from carbamate-protected amino acids is described. The two key steps are the monobromination of a *β*-ketoester and chelation-controlled reduction of a bromomethyl ketone intermediate. Good overall yields, high diastereoselectivity, and excellent functional group compatibility are characteristic.

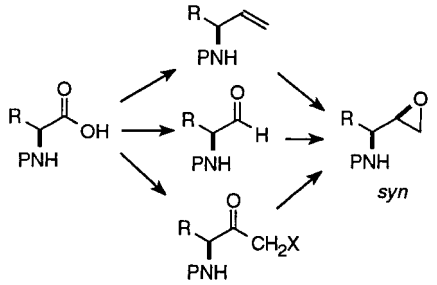
Introduction

Amino epoxides are versatile intermediates for the synthesis of a variety of densely functionalized compounds such as amino sugars, oxygenated amino acids, and hydroxyethylene peptide isosteres.[1] Although a variety of methods for their synthesis have been reported,[2] a very direct route is the conversion of N-protected amino acids into N-protected amino epoxides. This conversion requires the addition of a carbon atom, a reduction of the carboxylate oxidation level, and control of the stereochemistry in the epoxide ring. Three strategies have commonly been used to meet these requirements (Scheme 1).

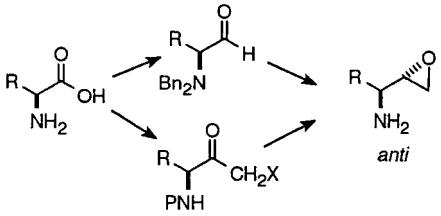
Conversion of the carboxylate to a vinyl group (often via the amino aldehyde) followed by peracid epoxidation can be used to give the *syn*-amino epoxide.[3] Reduction of the carboxylate to the aldehyde and reaction with sulfur ylids also has been used to produce the *syn*-amino-epoxide.[4] Finally, conversion of the carboxylate to a halomethyl ketone, stereocontrolled reduction of the ketone with Felkin−Anh control, and ring closure to the *syn*-aminoepoxide have been utilized.[1]

To produce *anti*-amino epoxides, the oxygenated secondary carbon must have the opposite configuration. This is usually achieved by using the *N*,*N*-dibenzyl protecting group[5] on the nitrogen of the amino acid (Scheme 2). Reduction to the aldehyde and addition of a sulfonium ylid thus produces the *anti*-amino epoxide.[6] Alternatively, conversion to a halomethyl ketone, stereocontrolled reduction with chelation control, and ring closure is a common way to access *anti*-amino epoxides.[1,7]

Scheme 1



Scheme 2



Although it is possible to prepare a variety of N-protected amino epoxides by these methods, problems with stereoselectivity, compatibility with side chain functional groups, and the use of problematic reagent systems (e.g., CH_2N_2, $LiCH_2Cl$) highlight the need for a more simple, general route to these compounds. Our interest in the synthesis[8] and reductions[8b,9] of N-protected α-amino ketones led to the synthetic plan shown in Scheme 3 for the synthesis of *anti*-amino epoxides. There are two key steps in the plan. Step *a* requires the monobromination of a *β*-ketoester and step *b* requires the stereoselective reduction of a protected aminoketone with chelation control to give the *anti*-amino alcohol. This synthetic approach was reported for a single compound

(1) (a) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696 is an excellent summary of the literature. See also: (b) Kurihara, M.; Ishii, K.; Kashara, Y.; Miyata, N. *Tetrahedron Lett.* **1999**, *40*, 3183. (c) Sengupta, S.; Sarma, D. S.; Das, D. *Tetrahedron Assymetry* **1999**, *10*, 1653.

(2) Albeck, A. *Drug Dev. Res.* **2000**, *50*, 425 is an extensive recent summary.

(3) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653.

(4) (a) Ashton, W. T.; Cantone, C. L.; Meurer, L. C.; Tolman, R. L.; Greenlee, W. J.; Patchett, A. A.; Lynch, R. J.; Schorn, T. W.; Strouse, J. F.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 2103. (b) Moore, W. J.; Luzzio, F. A. *Tetrahedron Lett.* **1995**, *36*, 6599.

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(6) (a) Reetz, M. T.; Binder, J. *Tetrahedron Lett.* **1989**, *30*, 5425. See also: Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *J. Org. Chem.* **1997**, *62*, 8902.

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(8) Amino ketones in the synthesis of sphingosines: (a) Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 3953. (b) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979. Aminoketones in the synthesis of peptidomimetics: (c) Hoffman, R. V.; Tao, J. *Tetrahedron* **1997**, *53*, 7119. (d) Hoffman, R. V.; Tao, J. *Tetrahedron, Lett.* **1998**, *39*, 4195. (e) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 126. (f) Hoffman, R. V.; Kim, H.-O. *Tetrahedron Lett.* **1992**, *33*, 3579. (g) Hoffman, R. V.; Kim, H.-O. *J. Org. Chem.* **1995**, *60*, 5107.

(9) Hoffman, R. V.; Maslouh, N. *J. Org. Chem.* in press.

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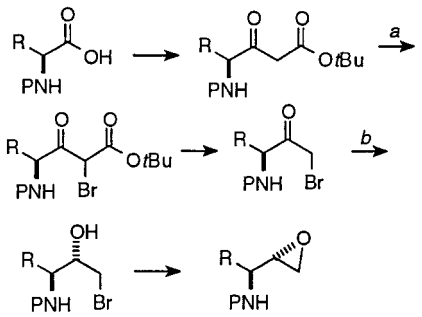
Scheme 3

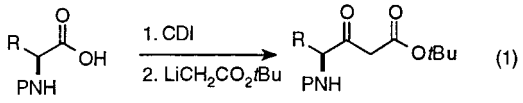


in the patent literature, but the yield was modest (~30%) and the reduction was not stereoselective.[10]

We felt that the simplicity of the approach warranted a second look. We are pleased to report that this strategy has been developed into a general, efficient, and highly stereoselective method for the synthesis of N-protected *anti*-amino epoxides from amino acids.

Results and Discussion

Using the method of Joullié,[11] a series of carbamate-protected amino acids was converted to the corresponding *tert*-butyl β-ketoesters (eq 1).[8c,9] This procedure is efficient and quite general, and it scales up very well.[12]



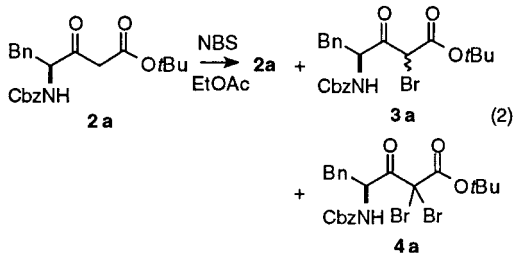
1a, R=$CH_2C_6H_5$, P= Cbz
1b, R= CH_3, P= Cbz
1c, R= *i*-Pr, P= Cbz
1d, R= $CH_2C_6H_4OBn$, P= Cbz
1e, R= $(CH_2)_4NHCbz$, P= Cbz
1f, R= $(CH_2)_2CO_2Me$, P= Cbz
1g, R= $CH_2C_6H_5$, P= Fmoc

2a-g
65-85%

(1)

Small scale brominations were used to develop a bromination protocol. Ketoester **2a** was reacted with $CuBr_2$ in refluxing ethyl acetate and in acetonitrile at 25 °C,[13] $CuBr_2$/ PhI(OH)OTs in acetonitrile at 0 °C,[14] and NBS in ethyl acetate at 25 °C.[15] NBS was found to be superior in terms of yield and convenience. Various solvents were evaluated, and crude yields were very high (>94%) for all of the solvents (EtOAc, THF, MTBE, CH_3CN, CH_2Cl_2, methanol, acetone, and toluene). NBS in ethyl acetate at room temperature was chosen as the standard bromination conditions.

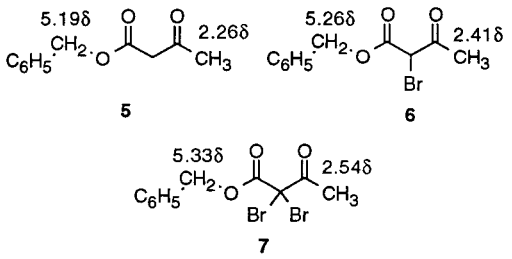
Reactions run at larger scales revealed that significant problems remained. First, use of 1 equiv of NBS with **2a** gave a product mixture consisting of unreacted starting material, monobrominated β-ketoester **3a**, and dibrominated product **4a** (eq 2). Second, the ratios of products



2a **3a** **4a** (2)

2a, **3a**, and **4a** were not consistent from run to run. Third, it appeared that the product ratio for a given run changed over time. At first this was attributed to instability of **2a**, since it had been reported that monobrominated β-ketoesters are unstable to storage.[16] Thus it became necessary to learn how to reliably carry out the monobromination of a β-ketoester. These results also suggest that the patent report of the bromination of γ-amino-*b*-ketoesters may be irreproducible as well.[10]

Benzyl acetoacetate **5** was chosen as a model β-ketoester substrate because it has a simple NMR spectrum (no multiplets) and is readily available. Moreover, the monobromo product **6** and the dibromo product **7** are easily distinguished and quantitated by the benzyl and methyl singlets. A solution of **5** in various solvents was treated with 0.8 equiv of NBS at room temperature, and the ratio of monobrominated **6** to dibrominated **7** was measured. The limited amount of NBS (0.8 equiv) was



5 **6** **7**

chosen in an attempt to avoid dibromination. The results are shown in Table 1, entries 1−4. Methanol appeared to be the superior solvent as it gave a 16:1 ratio of **6**:**7**. However, when 1 equiv of NBS was used (entry 5), the product ratio was inferior and significant amounts of unreacted **5** remained. Lowering the temperature (entry 6) improved the ratio only slightly. Different batches of NBS gave slightly varying ratios as well.

Table 1. Ratio of Monobromination to Dibromination of 5 by NBS

entry	solvent	time (h)	*T* (°C)	ratio **6**:**7**
1	CH_2Cl_2	18	25	2.4:1
2	EtOAc	19	25	0.9:1
3	acetone	20	25	2.4:1
4	MeOH	20	25	16:1
5	MeOH	12	25	1.7:1:0.7[a]
6	MeOH	12	0	2.3:1:0.7[a]

[a] One equivalent of NBS. Ratio is **6**:**7**:**5**.

Because the enol form is likely the species undergoing bromination, it appeared that the enol forms of **5** and **6**, which both are present in solution, must undergo bromination at somewhat comparable rates leading to

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(11) (a) Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron Lett.* **1987**, *25*, 2737. (b) Harris, B. D.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489.

(12) Hoffman, R. V.; Tao, J. *Methods in Molecular Medicine, Vol. 23, Peptidomimetics Protocols*; Kazmierski, W., Ed.; Humana Press: Totowa, NJ, 1999; p 103.

(13) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.

(14) Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett.* **1995**, *36*, 7735.

(15) Levai, L.; Ritvay-Emandity, K. *Chem. Ber.* **1959**, *92*, 2775.

(16) Shi, X.-X.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4596.

Table 2. Equilibration of a 6/7/5 Product Mixture in Methanol at 25 °C

initial ratio (**6**:**7**:**5**)	additive	final ratio
1.7:1:0.7	none	0.9:1:0.8
1.7:1:0.7	HOAc	0.3:1:0.7
1.7:1:0.7	2,6-lutidine	10.4:1:0.9
10.4:1:0.9	2,6-lutidine	13.2:1:0.9[a]

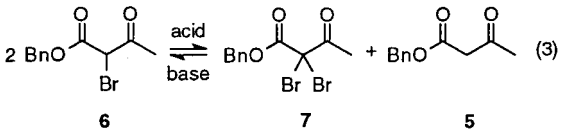
[a] After storage overnight at −20 °C.

mixtures of mono- and dibrominated products. Since the product ratios seemed to change with reaction time and with different batches of NBS, it also seemed possible that there is a disproportionation equilibrium between **5**, **6**, and **7** which changed the initial product ratios.

To test this hypothesis, three aliquots of a product mixture which had a **6**:**7**:**5** ratio of 1.7:1:0.7 were redissolved in methanol. The first contained no additives, the second contained ∼2% acetic acid, and the third contained ∼2% of 2,6-lutidine. Since it seemed likely that any equilibrium must be mediated by the enol forms, we sought to catalyze enolization and thus speed up the approach to equilibrium. The mixtures were allowed to stand for 9 h at room temperature, and the product ratios were redetermined (Table 2).

The results are unexpected and quite puzzling. In methanol alone the product ratio shifts in the direction of more dibrominated and unbrominated product. With acid present this shift is even greater, presumably as a result of the catalytic effect of acid in increasing the rate of disproportionation. However, most surprisingly, the presence of base causes a shift in the product ratio to favor the monobrominated product by a large amount. Simply put, the presence of acid shifts the product ratio in one direction, the presence of base shifts it in the other direction. If acid and base were merely serving as catalysts to achieve equilibrium more rapidly, then the change in product ratios should be in the same direction and should ultimately converge. This is does not seem to be the case.

On the basis of stoichiometry the disproportionation can be written as in eq 3. Not shown are the enol/enolate



tautomers that are also present in the mixture. One possible explanation for the divergent behavior with acid or base catalyst is that in the presence of base, a greater amount of the more acidic monobromo **6** is converted to the enolate and thus the equilibrium is shifted to the left. This system must be very sensitive to environmental effects, because only small amounts of a relatively weak acid or base apparently causes large changes in the product ratios. Moreover, cooling the solution overnight at −20 °C causes the **6**:**7**:**5** ratio to improve to 13.2:1:0.9.

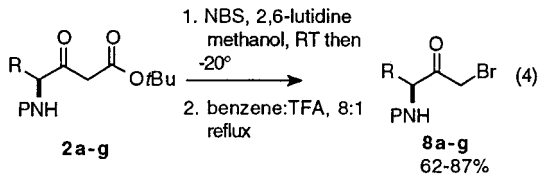
Treatment of **5** with *N*-chlorosuccinimide and 2,6-lutidine in methanol leads to a 1.1:1 ratio of monochlorinated to dichlorinated products. Moreover, the ratio does not change over the course of 13 h, indicating that disproportionation is not occurring. Thus chlorination of **2** is not a viable alternative for bromination in the preparation of amino epoxides by this strategy.[17]

Table 3. Reduction of Bromomethyl Ketones 8a−g

entry	ketone	$LiAlH(OtBu)_3$ *anti*:*syn* (% de)	$NaBH_4$ *anti*:*syn*
1	**8a**	43:1 (96)	4.6:1
2	**8b**	21:1 (92)	5.4:1
3	**8c**	>100:1[a] (>99)	35:1
4	**8d**	38:1 (95)	3.8:1
5	**8e**	36:1 (94)	7.3:1
6.	**8f**	35:1 (94)	7.0:1
7	**8g**	30:1 (93)	3.2:1

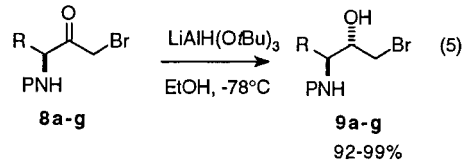
[a] Only one isomer was observed by HPLC.

Although more experiments are needed (and planned) to understand this intriguing system, the results in Table 2 provide a synthetic solution for monobrominating *β*-ketoesters. After some fine-tuning, a solution of **2a** in methanol containing 2 mol % 2,6-lutidine was treated with 1 equiv of NBS. After 2.5 h at room temperature, the reaction mixture was placed in the freezer for 20 h. After workup, the crude product was found to be a mixture of monobrominated **3a** and dibrominated **4a** in the ratio of 12.8:1. A single recrystallization from hexane gave pure monobromo **3a**. De-esterification/decarboxylation was carried in high yield out by refluxing **3a** in benzene/TFA (8:1) for 2 h. This procedure was used to convert *β*-ketoesters **2** to bromomethyl ketones **8** in good yields (eq 4). In practice the monobromo *β*-ketoester was



not purified but merely isolated and then decarboxylated to the bromomethyl ketone, which was recrystallized.

Chelation-controlled reduction of bromomethyl ketones **8a**−**g** by $LiAlH(OtBu)_3$ in ethanol at −78 °C gave the *anti*-amino bromohydrins **9a**−**g** in excellent yields (eq 5).



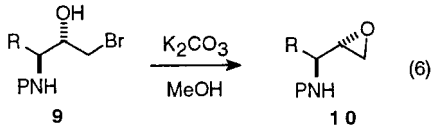
This reagent has recently been shown reduce *N*-carbamate-protected aminoketones to *anti*-amino alcohols with very high *anti* diastereoselectivity.[9] Only a single diastereomer was observed in the NMR spectra of the crude products, and this was assumed to be the *anti* isomer. This assumption was proven valid by conversion to known *anti*-amino epoxides (vide infra). We also assume that the enantiomeric purity of the products is high as well. We have prepared amino ketones from amino acids by this general route in several different contexts and, with the exception of phenyl glycine, have never observed significant epimerization of the amino group.[8]

Diastereomeric mixtures of **9a**−**g** were prepared for comparison purposes by reduction of **8a**−**g** with $NaBH_4$ in ethanol at −78 °C. The *anti* isomer was the major product, but the *syn* isomer could clearly be seen in the NMR spectrum. The diastereoselectivity was quantitated

(17) For an alternate route to analogous chloromethyl ketones, see: Wang, X.; Thottathil, J. K.; Polniaszek, R. P. *Synlett* **2000**, 902.

by HPLC, and the results are collected in Table 3. The data in Table 3 are for crude products. Recrystallization improves the ratio even more.

Treatment of amino bromohydrins **9** with potassium carbonate in methanol gave the corresponding amino-epoxide **10** in nearly quantitative yields (eq 6). Protected



9 **10** (6)

amino epoxides corresponding to **10a**,[18] **10b**,[19] **10c**,[7a] **10e**,[7c] **10f**,[7c] and **10g**[20] have all been reported recently in the literature. Thus epoxide formation from **9** was demonstrated for only a few representative examples, and these were found to have the *anti* stereochemistry.

This procedure for the preparation of protected amino epoxides is simple, efficient, and highly diastereoselective. It appears to be compatible with a variety of functionalized side chains and can be used with Cbz and Fmoc protecting groups (and presumably other acid-stable carbamate protecting groups).

Experimental Section

Infrared spectra were taken as a KBr pellets, as solution in $CHCl_3$, or as neat liquids. ^1H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation or by spraying with vanillan/H_2SO_4 and heating on a hot plate. Flash chromatography was performed using silica gel 60 (230−400 mesh). Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Acros, Aldrich, or Novabiochem and used as received. LiAlH(O*t*Bu)$_3$ was purchased from Fluka. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. *β*-Ketoesters **2a**−**g** were prepared by literature procedures.[8c, 9]

***β*-Ketoester 2e** was obtained as a clear, colorless oil: $[\alpha]^{25}_D$ +10.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3335, 1713, cm^{-1}; ^1H NMR *δ* 7.34 (m, 10 H), 5.54 (d(br), *J* = 8.3 Hz, 1 H), 5.2−5.0 (m, 4 H), 4.84 (m, 1 H), 4.45 (m, 1 H), 3.48 (d, *J* = 15.6 Hz, 1 H), 3.43 (d, *J* = 15.5 Hz, 1 H), 3.18 (m, 2 H), 1.91 (m, 1 H), 1.7−1.2 (m, 5 H), 1.45 (s, 9 H); ^{13}C NMR *δ* 202.0, 165.9, 156.6, 156.1, 136.7, 136.2, 128.5, 128.5, 128.2, 128.1, 128.0, 82.3, 67.1, 66.6, 59.9, 47.5, 40.4, 30.4, 29.5, 27.9, 22.1. Anal. Calcd for $C_{28}H_{36}N_2O_7$: C, 65.61; H, 7.08; N, 5.46. Found: C, 65.58; H, 7.03; N, 5.44.

***β*-Ketoester 2f** was obtained as a pale tan oil: $[\alpha]^{24}_D$ +10.5 (*c* 1.1, CH_2Cl_2); IR (neat) 3344, 1736, 1719 cm^{-1}; ^1H NMR *δ* 7.36 (m, 5 H), 5.56 (d(br), *J* = 7.5 Hz, 1 H), 5.11 (s, 2 H), 4.52 (m, 1 H), 3.66 (s, 3 H), 3.54 (d, *J* = 15.6 Hz, 1 H), 3.48 (d, *J* = 15.6 Hz, 1 H), 2.6−2.2 (m, 3 H), 1.89 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR *δ* 201.5, 173.2, 165.9, 145.1, 136.2, 128.5, 128.2, 128.1, 82.4, 67.1, 59.4, 51.8, 47.4, 29.7, 27.9, 26.0. Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 61.00; H, 6.93; N, 3.61.

***β*-Ketoester 2g** was obtained as a off white solid: mp 111.2−113.0 °C; $[\alpha]^{24}_D$ +6.4 (*c* 1.0, CH_2Cl_2); ^1H NMR *δ* 7.76 (m, 2 H), 7.6−7.1 (m, 11 H), 5.34 (d(br), *J* = 8.0 Hz, 1 H), 4.68 (m, 1 H), 4.43 (dd, *J* = 7.0, 10.6 Hz, 1 H), 4.36 (dd, *J* = 6.6, 10.5 Hz, 1 H), 4.17 (m, 1 H), 3.38 (m, 2 H), 3.18 (dd, *J* = 5.9, 14.1 Hz, 1 H), 3.02 (dd, *J* = 6.8, 14.1 Hz, 1 H), 1.45 (s, 9 H); ^{13}C NMR *δ* 201.6, 165.9, 155.7, 143.8, 141.4, 135.9, 129.3, 128.8, 127.8, 127.2, 127.1, 125.1, 120.0, 82.4, 67.0, 60.8, 48.2, 47.3, 37.2, 28.0. Anal. Calcd for $C_{30}H_{31}NO_5$: C, 74.21; H, 6.43; N; 2.88. Found: C, 74.25; H, 6.59; N, 3.00.

Bromo *β*-Ketoester 3a. Solid NBS (178 mg, 1.31 mmol) was added in one portion to a room-temperature solution of **2a** (520 mg, 1.31 mmol) and 2,6-lutidine (15 mL, 0.13 mmol, 10 mol %) in methanol (2.6 mL). After stirring for 2.5 h, the mixture was stored at −20 °C for 19 h. Ethyl acetate (20 mL) was added, and the mixture was extracted with 50% saturated NaCl (3 × 8 mL) and saturated NaCl (2 × 8 mL), dried with sodium sulfate, and evaporated to give a white crystalline product (96% yield) that was a 15.1:1:1.2 mixture of **3a**:**4a**:**2a**. Recrystallization from hexane gave pure **3a** (71%) as a 1.7:1 mixture of diastereomers: mp 78.7−81.5 °C. The two diastereomers had characteristic *tert*-butyl peaks at 1.43 and 1.47d. Anal. Calcd for $C_{23}H_{26}BrNO_5$: C, 57.99; H, 5.50; N, 2.94. Found: C, 58.13; H, 5.65; N, 3.09.

Bromomethyl Ketone 8a. Ketoester **3a** (601 mg, 1.26 mmol) was dissolved in 8:1 benzene/TFA (9 mL) and heated at reflux for 2 h. After cooling to room temperature, the mixture was extracted with water (2 × 4 mL), saturated $NaHCO_3$ (2 × 4 mL), and saturated NaCl (2 × 4 mL), dried ($MgSO_4$), and evaporated to give an orange crystalline product. Flash chromatography (200:1, CH_2Cl_2/*i*-PrOH) furnished **8a** as a white solid (84%): mp 95.7−96.5, ^1H NMR *δ* 7.4−7.1 (m, 10 H), 5.30 (d(br), *J* = 8.1 Hz, 1 H), 5.08 (s, 2 H), 4.82 (m, 1 H), 3.92 (d, *J* = 13.6 Hz, 1 H), 3.82 (d, *J* = 13.7 Hz, 1 H), 3.12 (dd, *J* = 5.5, 12.8 Hz, 1 H), 3.04 (dd, *J* = 6.0, 12.7 Hz, 1 H); ^{13}C NMR *δ* 200.4, 155.7, 135.9, 135.5, 129.1, 128.8, 128.4, 128.2, 128.0, 127.3, 67.1, 58.8, 37.6, 33.1. These data agree with the literature data.[18]

General Procedure for the Conversion of *β*-Ketoesters 2 to Bromomethyl Ketones 8. Solid NBS (1 equiv) was added to a solution of the *β*-ketoester **2** and 2,6-lutidine (10 mol %) in methanol (2 mL/mmol). After stirring for 2.5 h at room temperature, the mixture was stored in the freezer (−20 °C) for 20 h. The reaction mixture was extracted with 50% sat. NaCl (3 × 8 mL) and sat. NaCl (3 × 8 mL), dried ($NaSO_4$), and evaporated to give 2-bromo-*β*-ketoester **3** as a crude product. Crude product **3** was dissolved in 8:1 benzene/TFA (9 mL) and refluxed for 2 h. After cooling the reaction was extracted with water (2 × 4 mL), saturated $NaHCO_3$ (2 × 4 mL), and saturated NaCl (2 × 4 mL), dried ($MgSO_4$), and evaporated. The crude bromomethyl ketone was purified by flash chromatography

Preparation of 8b from 2b (517 mg, 1.61 mmol) by the above procedure (elution with CH_2Cl_2/MeOH 200:1) gave **8b** (73%) as a white crystalline solid: mp 77.0−79.1 °C (lit. mp 83−84 °C); ^1H NMR *δ* 7.36 (s, 5 H), 5.37 (d(br), *J* = 9.8 Hz, 1 H), 5.11 (s, 2 H), 4.68 (m, 1 H), 4.07 (d, *J* = 13.3 Hz, 1 H), 4.04 (d, *J* = 13.3 Hz, 1 H), 1.43 (d, *J* = 7.2 Hz, 3 H). These data match the NMR spectrum reported for this compound.[19] NMR examination of the crude product indicated a 39:1:1.3 ratio of **3b**:**4b**:**2b** in the bromination reaction.

Preparation of 8c from 2c (1.050 g, 3 mmol) by the above procedure (elution with toluene/EtOAc 20:1) gave **8c** (87%) as a white solid: mp 81.5−82.0 °C; $[\alpha]^{24}_D$ +41.2° (*c* 1.0, CH_2Cl_2); ^1H NMR *δ* 7.36 (m, 5 H), 5.31 (d(br), *J* = 8.8 Hz, 1 H), 5.11 (s, 2 H), 4.61 (dd, *J* = 4.5, 8.7 Hz, 1 H), 4.09 (d, *J* = 13.6 Hz, 1 H), 4.03 (d, *J* = 13.6 Hz, 1 H), 2.23 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR *δ* 200.6, 156.4, 136.1, 128.6, 128.3, 128.1, 67.3, 63.0, 32.7, 30.3, 19.7, 17.0. Anal. Calcd for $C_{14}H_{18}BrNO_3$: C, 51.23; H, 5.53; N, 4.27. Found: C, 51.13; H, 5.62; N, 4.12.

Preparation of 8d from 2d (986.7 mg, 1.96 mmol) by the above procedure gave **8d** as a white solid (71%) after silica gel chromatography eluting with toluene/EtOAc 20:1: mp 136.9−137.3 °C; $[\alpha]^{24}_D$ +17.6 (*c* 1.0, CH_2Cl_2); ^1H NMR *δ* 7.6−7.2 (m, 10 H), 7.06 (m, 2 H), 6.90 (m, 2 H), 5.29 (d(br), *J* = 7.6 Hz, 1 H), 5.09 (s, 2 H), 5.04 (s, 2 H), 4.79 (m, 1 H), 3.92 (d, *J* = 13.6 Hz, 1 H), 3.82 (d, *J* = 13.6 Hz, 1 H), 3.03 (m, 2 H); ^{13}C NMR *δ* 200.5, 158.2, 155.8, 136.9, 136.1, 130.2, 128.6, 128.4, 128.2, 128.0, 127.7, 127.5, 115.4, 70.1, 67.3, 59.0, 37.2, 33.0. Anal. Calcd for $C_{25}H_{24}BrNO_4$: C, 62.25; H, 5.01; N, 2.89. Found: C, 62.48; H, 5.09; N, 2.80.

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Preparation of 8e from 2e (805 mg, 1.57 mmol) by the above procedure gave **8e** as a white solid (74%) after purification by silica gel chromatography eluting with 7:2 toluene/EtOAc: mp 90.5−91.0 °C (lit. mp 89−90 °C);[18] $[\alpha]^{25}_D$ +9.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.34 (m, 10 H), 5.56 (d(br), J = 7.3 Hz, 1 H), 5.10 (s, 2 H), 5.07 (m, 2 H), 4.81 (m(br), 1 H), 4.61 (m, 1 H), 4.05 (m, 2 H), 3.19 (m, 2 H), 2.0−1.3 (m, 6 H). Anal. Calcd for $C_{23}H_{27}BrN_2O_5$: C, 56.22; H, 5.54; N, 5.70. Found: C, 56.50; H, 5.42; N, 5.58.

Preparation of 8f from 2f (1.0 g, 2.54 mmol) by the above procedure gave **8f** (84%) as a white solid. Purification by recrystallization from 5:2 hexanes/EtOAc gave an analytical sample: mp 104.3−104.6 °C; $[\alpha]^{25}_D$ +11.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.35 (m, 5 H), 5.57 (d(br), J = 7.6 Hz, 1 H), 5.11 (s, 2 H), 4.71 (m, 1 H), 4.12 (d, J = 13.4 Hz, 1 H), 4.08 (d, J = 13.4 Hz, 1 H), 3.66 (s, 3 H), 2.6−2.2 (m, 3 H), 1.94 (m, 1 H); ^{13}C NMR δ 200.2, 173.2, 156.1, 136.0, 128.6, 128.3, 128.1, 67.4, 57.3, 51.9, 31.7, 29.6, 26.6. Anal. Calcd for $C_{15}H_{18}BrNO_5$: C, 48.40; H, 4.87; N, 3.76. Found: C, 48.49; H, 4.87; N, 3.70.

Preparation of 8g from 2g (1.0 g, 2.06 mmol) by the above procedure gave **8g** (62%) as an off-white solid after purification by silica gel chromatography eluting with CH_2Cl_2: mp 132 °C (dec); $[\alpha]^{24}_D$ +5.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.77 (m, 2 H), 7.7−7.1 (m, 11 H), 5.28 (d(br), J = 7.4 Hz, 1 H), 4.79 (m, 1 H), 4.43 (app d, J = 6.8 Hz, 2 H), 4.18 (app t, J = 6.8 Hz, 1 H), 3.88 (d, J = 13.6 Hz, 1 H), 3.78 (d, J = 13.6 Hz, 1 H), 3.12 (dd, J = 6.6, 13.8 Hz, 1 H), 3.04 (dd, J = 7.0, 13.9 Hz, 1 H); ^{13}C NMR δ 200.3, 155.8, 143.7, 141.4, 135.6, 129.2, 129.0, 127.9, 127.4, 127.2, 125.0, 120.1, 67.0, 58.9, 47.3, 37.9, 32.8. Anal. Calcd for $C_{25}H_{22}BrNO_3$: C, 64.66; H, 4.78; N, 3.02. Found: c, 64.83; H, 5.00; N, 2.99.

General Procedure for the Reduction of Amino Ketones 8a−g to Bromohydrins 9a−g. Method A. Solid $LiAlH(OtBu)_3$ (2 equiv) was placed in a round-bottomed flask and cooled at −78 °C. Absolute ethanol (6 mL/mmol) was syringed slowly down the side of the flask, and the mixture was stirred vigorously. A cold solution of the bromomethyl ketone **8** in absolute ethanol (22 mL/mmol) was syringed slowly down the side of the reaction flask, and the reaction mixture was stirred for 1 h at −78 °C. The reaction was quenched with 5 mL of 1 M HCl and warmed to room temperature. The solvent was evaporated, and the slushy residue was triturated with ethyl acetate (8 mL). The organic extract was washed with 1 M HCl (2 × 3 mL) and then saturated NaCl (3 mL), dried ($MgSO_4$), and evaporated to give the bromohydrin **9**. The diastereomeric excess of the crude product was determinedby HPLC (normal phase, 20:1 dichloroethane/acetonitrile), and the crude product had excellent purity by NMR. A single recrystallization gave pure **9**.

Method B. In some cases the aminoketone was rather insoluble in cold ethanol and thus a cosolvent was needed to increase solubility. Tetrahydrofuran/ethanol 1:1 was found to serve this purpose well without diminution of either yield or diastereoselectivity. Solid $LiAlH(OtBu)_3$ (2 equiv) was placed in a round-bottomed flask and cooled at −78 °C. Tetrahydrofuran (3 mL/mmol) and then absolute ethanol (3 mL/ mmol) were syringed slowly down the side of the flask, and the mixture was stirred vigorously. A cold solution of the bromomethyl ketone **8** in a 1:1 mixture of tetrahydrofuran/absolute ethanol (22 mL/mmol) was syringed slowly down the side of the reaction flask, and the reaction mixture was stirred for 1 h at −78 °C. Quenching and workup were the same as in Method A.

Method C. A solution of amino ketone **8** in 1:1 tetrahydrofuran/absolute ethanol (30 mL/mmol) was cooled to −78 °C, and solid sodium borohydride was added in one portion. The mixture was stirred vigorously for 20 min at −78° and quenched with 5 mL of 1 M HCl. Workup was the same as in Method A.

Bromohydrin 9a was prepared from **8a** (50 mg, 0.13 mmol) by Method A. The crude product (97%) was pure by NMR. The ratio of diastereomers was 42.7:1 *anti:syn*. Recrystallization from hot EtOAc/hexane gave a pure sample (72%) with an *anti:syn* ratio of 141:1: mp 141 °C; $[\alpha]^{21}_D$ −13.9 (*c* 1.00, DMF); FTIR (KBr) 3336, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$ /few drops of methanol-d_4) δ 2.81 (dd, 1H, J = 9.0, 14.1 Hz), 3.01 (dd, 1H, J = 4.4, 14.0 Hz), 3.43 (dd, 1H, J = 6.4, 9.9 Hz), 3.51 (dd, 1H, J = 3.9, 10.5 Hz), 3.84 (m, 1H), 3.99 (m, 1H), 5.00 (s, 2H), 7.21−7.32 (m, 10H); ^{13}C NMR ($CDCl_3$ /few drops of methanol-d_4) δ 35.5, 35.8, 55.3, 66.6, 72.9, 126.4, 127.7, 127.9, 128.3, 129.3, 137.6, 156.3. Anal. Calcd for $C_{18}H_{20}BrNO_3$: C, 57.15; H, 5.33; N, 3.70. Found: C, 57.28; H, 5.47; N, 3.65. These data match the literature data.[21] Use of Method B gave **9a** in 95% crude yield with an *anti:syn* ratio of 41.8:1. Method C gave **9a** in quantitative yield with a 4.41:1 *anti:syn* ratio.

Bromohydrin 9b was prepared from **8b** (77 mg, 0.26 mmol) by Method A in 92% yield. The *anti:syn* ratio was 20.9:1. Recrystallization from 10:1 hexanes:/EtOAc gave a pure sample (71%): mp 110 °C; $[\alpha]^{21}_D$ −6.2 (*c* 1.00, $CHCl_3$); FTIR (KBr) 3315, 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H, J = 6.6 Hz), 3.38 (dd, 1H, J = 3.7, 10.5 Hz), 3.47 (dd, 1H, J = 8.1, 10.4 Hz), 3.86 (m, 1H), 3.89 (m, 1H), 5.01 (broad, 1H), 5.10 (s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.1, 36.1, 49.9, 67.1, 74.2, 128.2, 128.3, 128.6, 136.4, 156.1. Anal. Calcd for $C_{12}H_{16}BrNO_3$: C, 47.70; H, 5.34; N, 4.64. Found: C, 47.72; H, 5.55; N, 4.74. Method C gave **9b** in 94% yield with an *anti:syn* ratio of 5.41:1.

Bromohydrin 9c was prepared from **8c** (100 mg, 0.31 mmol) by Method A in 94% yield. Only a single diastereomer was observed in the HPLC of the crude product. Recrystallization from hexanes gave an analytical sample (76%): mp 74 °C; $[\alpha]^{21}_D$ +2.3 (*c* 1.00, $CHCl_3$); FTIR (KBr) 3425, 3345, 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 0.87 (d, 3H, J = 6.9 Hz), 0.95 (d, 3H, J = 6.9 Hz), 2.19 (m, 1H), 2.61 (s, 1H), 3.44 (dd, 1H, J = 7.7, 10.4 Hz), 3.62 (dd, 1H), 3.65 (m, 2H), 4.78 (d, 1H, J = 8.9 Hz), 5.10 (s, 2H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) d 16.3, 20.2, 27.9, 38.3, 58.9, 67.2, 72.5, 128.2, 128.3, 128.6, 136.3, 156.9. Anal. Calcd for $C_{14}H_{20}BrNO_3$: C, 50.92; H, 6.10; N, 4.24. Found: C, 51.19; H, 6.20; N, 4.35. Reduction of **8c** using Method C also gave only a single diastereomer (94%) by HPLC.

Bromohydrin 9d was prepared from **8d** (100 mg, 0.21 mmol) by Method B in 96% yield. The *anti:syn* ratio was 38.4:1. Recrystallization from chloroform gave a pure sample (46%): mp 159 °C; $[\alpha]^{21}_D$ −13.3 (*c* 1.00, DMF); FTIR (KBr) 3326, 1691, 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$ /few drops of methanol-d_4) δ 2.73 (dd, 1H, J = 9.2, 14.1 Hz), 2.97 (dd, 1H, J = 4.2, 14.1 Hz), 3.41 (dd, 1H, J = 7.1, 10.6 Hz), 3.50 (dd, 1H, J = 4.0, 10.6 Hz), 3.83 (m, 1H), 3.92 (m, 1H), 5.01 (s, 2H), 5.03 (s, 2H), 6.83−7.41 (m, 14H); ^{13}C NMR ($CDCl_3$ /few drops of methanol-d_4) δ 34.4, 35.6, 55.4, 66.4, 69.9, 72.8, 114.7, 127.3, 127.7, 128.2, 128.3, 130.2, 136.9, 156.3. Anal. Calcd for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41; N, 2.89. Found: C, 62.08; H, 5.51; N, 3.00. Method C gave **9d** (100%) with an *anti:syn* ratio of 3.77:1.

Bromohydrin 9e was prepared from **8e** (100 mg, 0.20 mmol) by Method A in 97% yield. The *anti:syn* ratio was 36.1:1. Recrystallization from toluene plus hexanes gave a pure sample: mp 105 °C; $[\alpha]^{21}_D$ −9.4 (*c* 1.00, $CHCl_3$); FTIR (KBr) 3316, 3026, 2957, 2907, 1696, 1546, 1465, 1312, 1292, 1262, 1152, 1067, 1033, 918, 848, 729, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 6H), 2.58 (broad, 1H), 3.11 (m, 2H), 3.33 (dd, 1H, J = 7.7, 10.6 Hz), 3.42 (dd, 1H, J = 3.5, 10.4 Hz), 3.70 (m, 1H), 4.77 (broad, 1H), 5.01 (m, ovelapping, 5H), 7.32−7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.7, 29.0, 29.7, 36.4, 40.5, 54.3, 66.8, 67.1, 74.2, 128.1, 128.3, 128.6, 136.4, 136.7, 156.7. Anal. Calcd for $C_{23}H_{29}BrN_2O_5$: C, 55.99; H, 5.92; N, 5.68. Found: C, 56.14; H, 6.14; N, 5.76. Method C gave **9e** (100%) with an *anti:syn* ratio of 7.26:1.

Bromohydrin 9f was prepared from **8f** (100 mg, 0.27 mmol) by Method B in 92% yield. The *anti:syn* ratio was 35.4:1. Recrystallization from 1,2-dichloroethane plus hexanes gave a pure sample (74%): mp 100 °C; $[\alpha]^{21}_D$ −9.4 (*c* 1.00, $CHCl_3$); FTIR (KBr) 3475, 3316, 1730, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 1H), 1.96 (m, 1H), 2.41 (t, 2H, J = 7.2 Hz), 2.90 (broad, 1H), 3.41 (dd, 1H, J = 8.0, 10.5 Hz), 3.50 (dd, 1H, J = 3.7,

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10.6 Hz), 3.63 (s, 3H), 3.78 (m, 1H), 3.83 (m, 1H), 5.08 (s, 2H), 5.19 (d, 1H, J = 8.6 Hz), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.7, 30.5, 36.4, 51.8, 54.0, 67.2, 74.0, 128.2, 128.3, 128.6, 136.3, 156.9, 174.0. Anal. Calcd for $C_{15}H_{20}BrNO_5$: C, 48.14; H, 5.39; N, 3.74. Found: C, 48.31; H, 5.45; N, 3.86. Method C gave **9f** (94%) with an *anti:syn* ratio of 6.98:1.

Bromohydrin 9g was prepared from **8g** (100 mg, 0.22 mmol) by Method B in 99% yield. Because separation of the diastereomers was incomplete, the *anti:syn* ratio could only be determined as >30:1. Recrystallization from toluene gave a pure sample (68%): mp 172 °C; $[\alpha]^{21}_D$ −16.8 (*c* 1.00, DMF); FTIR (KBr) 3326, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$ / few drops of methanol-d_4) δ 2.71 (dd, 1H, J = 9.1, 13.9 Hz), 2.92 (dd, 1H, J = 4.0, 13.9 Hz), 3.29 (dd, 1H, J = 7.6, 10.3 Hz), 3.37 (dd, 1H, J = 4.0, 10.6 Hz), 3.72 (m, 1H, overlapping), 3.84 (m, 1H), 4.01 (t, 1H, J = 6.6 Hz), 4.23 (m,2H), 7.09−7.69 (m, 13H); ^{13}C NMR ($CDCl_3$ / few drops of methanol-d_4) δ 35.3, 36.0, 47.1, 55.2, 66.3, 72.8, 119.8, 124.8, 126.4, 126.9, 127.6, 128.1, 128.3, 129.3, 137.6, 141.2, 143.7, 156.3. Anal. Calcd for $C_{25}H_{24}BrNO_3$: C, 64.38; H, 5.19; N, 3.00. Found: C, 64.50; H, 5.36; N, 2.97. Method C gave **9g** with an *anti:syn* ratio of 3.3:1.

Epoxide 10b was prepared from **9b** to demonstrate the method. A mixture of bromohydrin **9b** (60 mg, 0.2 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in methanol (2 mL) was stirred at room temperature for 30 min. After evaporation of the solvent, ethyl acetate (10 mL) was added. Extraction with water (5 mL) and saturated NaCl (5 mL), drying (Na_2SO_4), and solvent evaporation gave **10b** as a colorless oil (42 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3H, J = 6.8 Hz), 2.25 (m, 2H), 2.93 (m, 1H), 3.73 (m, 1H), 4.89 (broad, 1H), 5.09 (s, 2H), 7.34−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.5, 46.0, 48.1, 54.5, 66.9, 128.1, 128.2, 128.6, 136.5, 155.8. These data are in accord with the literature data for **10b**.[18]

Epoxide 10c was prepared by the same procedure from **9c** (40 mg, 0.12 mmol), K_2CO_3 (37 mg, 0.24 mmol), and methanol (2 mL) as a white solid (29.3 mg, 97%) crude): ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.85 (m, 1H), 2.74 (m, 2H), 2.89 (m, 1H), 2.29 (m, 1H), 4.74 (d, 1H, J = 8.1 Hz), 5.09 (s, 2H), 7.30−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.8, 19.2, 30.8, 45.6, 52.5, 58.0, 67.0,128.1, 128.2, 128.6, 136.5, 156.3.

Epoxide 10e was prepared from **9e** (40 mg, 0.081 mmol), K_2CO_3 (22.4 mg, 0.16 mmol), and methanol (2 mL) as a white solid (32.7 mg, 98% crude): ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 6H), 2.76 (m, 2H), 2.83 (m, 1H), 3.14 (m, 2H), 3.42 (m, 1H), 4.86 (broad, 1H), 5.07 (m, 5H), 7.32−7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.4, 29.7, 31.2, 40.5, 46.2, 52.7, 54.0, 66.7, 67.0, 128.1, 128.5, 136.5, 136.7, 156.2, 156.7. Anal. Calcd for $C_{23}H_{29}BrN_2O_5$: C, 55.99; H, 5.92; N, 5.68. Found: C, 56.14; H, 6.14; N, 5.76.

Epoxide 10f was prepared from **9f** (50 mg, 0.13 mmol), K_2CO_3 (37 mg, 0.26 mmol), and methanol (2 mL) as a colorless oil (37 mg, 97% crude): ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 1H), 1.96 (m, 1H), 2.43 (m, 2H), 2.75 (m, 2H), 2.89 (m, 1H), 3.52 (m, 1H), 3.64 (s, 3H), 5.04 (broad, 1H), 5.08 (s, 2H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.7, 30.4, 46.0, 51.7, 52.6, 53.7, 77.0, 128.1, 128.2, 128.6, 136.4, 156.1, 173.7.

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Supporting Information Available: ^{13}C NMR spectra of **10c** and **10f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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