

## A Single-Pot, Mild Conversion of $\beta$ -Lactones to $\beta$ -Lactams

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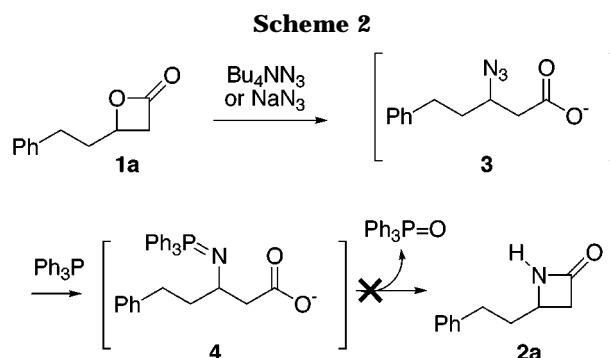
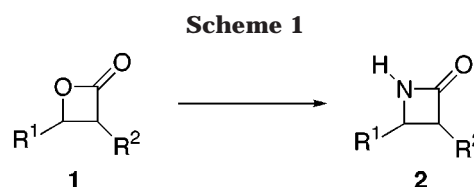
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### Introduction

$\beta$ -Lactams continue to be important synthetic targets because they are substructures of many antibiotics<sup>1</sup> and they are also versatile intermediates in synthesis.<sup>2</sup> As part of a program aimed at the development of new transformations of  $\beta$ -lactones and extensions of their utility in synthesis,<sup>3</sup> we now report a procedure for the single-pot conversion of  $\beta$ -lactones **1** to  $\beta$ -lactams **2** (Scheme 1).<sup>4</sup> Considering the importance of  $\beta$ -lactams, this procedure should find utility as an alternative method for their synthesis.<sup>5</sup> Ultimately, we envision that having found concise catalytic, asymmetric routes to  $\beta$ -lactones will also produce methods for the synthesis of a wide variety of optically active  $\beta$ -lactams, albeit in an indirect fashion.

### Results and Discussion

Initially, we reasoned that in analogy to the conversion of epoxides to aziridines,<sup>6</sup> treatment of a  $\beta$ -lactone with azide anion followed by addition of  $\text{PPh}_3$  would lead directly to a  $\beta$ -lactam (Scheme 2). The ring opening of  $\beta$ -lactones to the corresponding  $\beta$ -azido carboxylates (i.e., **3**) has been previously reported and is known to proceed



by O-alkyl fission rather than O-acyl fission.<sup>7</sup> We anticipated that this intermediate, without isolation, could be treated with triphenylphosphine in situ to deliver an aza-Wittig intermediate that could cyclize with concomitant loss of triphenylphosphine oxide to deliver the  $\beta$ -lactam **2a** directly. Several attempts to effect this reaction sequence beginning with the hydrocinnamaldehyde-derived  $\beta$ -lactone **1a** were unsuccessful leading to clean production of the corresponding  $\beta$ -amino carboxylic acid upon aqueous workup with no traces of  $\beta$ -lactam **2a** being produced.

We then considered application of the elegant procedure of Miller involving intramolecular Mitsunobu reactions of  $\beta$ -hydroxy hydroxamic acid derivatives leading to  $\beta$ -lactams, which we had successfully employed in our synthesis of (-)-pateamine A.<sup>8</sup> To accomplish this, we first needed to develop conditions for conversion of  $\beta$ -lactones to the corresponding *N*-benzyloxyhydroxamic acid derivatives **5**. We found that the ring-opening reaction was sluggish if in situ free-basing was attempted using *O*-benzyloxyamine hydrochloride salt with excess triethylamine. The free base was then employed, and screening of solvents including THF,  $\text{CH}_3\text{CN}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{C}_6\text{H}_6$ , and  $\text{Et}_2\text{O}$  indicated that the latter solvent gave the maximum conversion over a period of ~25 h. Subsequently, we determined that the reaction could be driven to completion by performing the ring-opening reaction neat or with minimal solvent.

With conditions established for the ring-opening step, we then studied the direct one-pot ring-opening/Mitsunobu sequence building on the work of Miller. After the ring-opening reaction was complete as judged by TLC analysis,  $\text{Et}_2\text{O}$  was added followed by sequential addition of  $\text{PPh}_3$  and diisopropyl azodicarboxylate (DIAD). After the mixture was stirred for ~24 h, the *N*-benzyloxy- $\beta$ -

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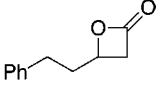
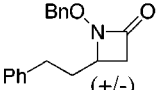
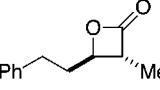
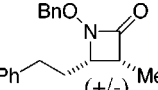
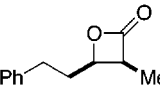
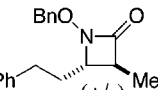
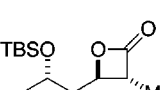
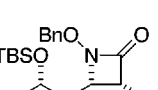
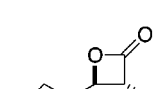
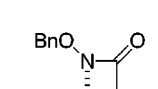
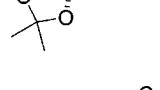
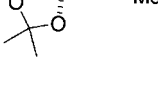
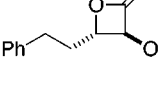
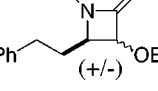
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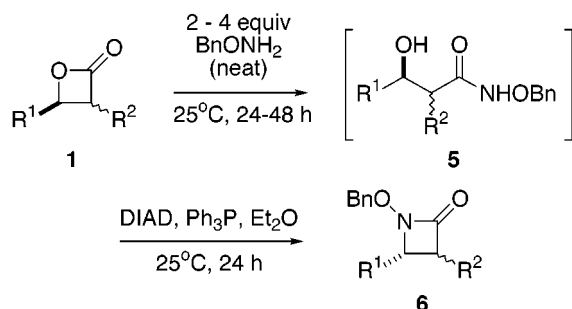
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**Table 1. One-Pot Conversion of  $\beta$ -Lactones **1** to *N*-Benzyloxy- $\beta$ -lactams **6****

Entry	$\beta$ -Lactones <sup>a</sup>	$\beta$ -Lactams	Cis/trans <sup>b</sup>	% Yield <sup>c</sup>
1	 <b>1a</b>	 <b>6a</b> (+/-)	-	74
2	 <b>1b</b>	 <b>6b</b> (+/-)	>19:1	87
3	 <b>1c</b>	 <b>6c</b> (+/-)	1:>19	72
4	 <b>1d</b>	 <b>6d</b>	>19:1 <sup>d</sup>	75
5	 <b>1e</b>	 <b>6e</b>	>19:1	72
6	 <b>1f</b>	 <b>6f</b> (+/-)	1.9:1	76
7 <sup>e</sup>	 <b>1g</b>	 <b>6g</b> (+/-)	-	45

<sup>a</sup> Starting  $\beta$ -lactones had a diastereomeric purity of >19:1 with the exception of **1d**. <sup>b</sup> Cis/trans ratios were determined or estimated by 300 MHz <sup>1</sup>H NMR of crude reaction mixtures. <sup>c</sup> Yield refers to overall yield for the single-pot, two-step conversion. <sup>d</sup> The starting  $\beta$ -lactone was a 3.8:1 mixture of anti-trans and syn-trans isomers, and this gave a 3.5:1 mixture of syn-cis and anti-cis isomers after purification. <sup>e</sup> The first step was performed at 52–55 °C.

**Scheme 3**

lactams **6a–g** were produced in good overall yields (Scheme 3 and Table 1).<sup>9</sup>

Analysis of the crude reaction mixtures by <sup>1</sup>H NMR (300 MHz) indicated that the ring-opening/Mitsunobu sequence had proceeded with high stereochemical fidelity with the exception of the  $\alpha$ -benzyloxy  $\beta$ -lactone **1f**. In this case, it appears that epimerization occurred during the Mitsunobu step leading ultimately to a 1.9:1 ratio of

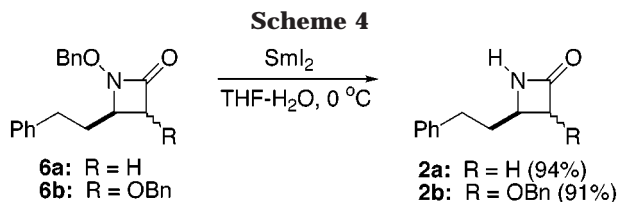
diastereomers (Table 1, entry 6). Furthermore, by analysis of coupling constants,<sup>10</sup> the Mitsunobu reactions were found to proceed as expected with inversion of configuration at the  $\beta$ -carbon, and this was verified by converting both cis and trans  $\beta$ -lactones **1b** and **1c** to the cis and trans- $\beta$ -lactams **6b** and **6c**, respectively. On attempted conversion of the  $\alpha$ -trimethylsilyl- $\beta$ -lactam **1g**, the initial ring opening was found to be extremely sluggish and required heating. This resulted in low overall yield of the  $\alpha$ -unsubstituted- $\beta$ -lactam **6g**; however, this cannot simply be attributed to steric effects since the starting  $\beta$ -lactone **1g** is cis-substituted.

Reductive cleavage of the N–O bond leading to the N-unsubstituted  $\beta$ -lactams **2** was readily accomplished using SmI<sub>2</sub> as employed previously by us<sup>8b</sup> and first described as a method for the reduction of *N*-benzyloxyamines and hydroxamic acid derivatives.<sup>11</sup> Thus, reduction of the *N*-benzyloxy- $\beta$ -lactam **6a** with SmI<sub>2</sub> in the presence of water led to the  $\beta$ -lactam **2a** in 94% yield (Scheme 4). Reductive cleavage of the N–O bond of  $\beta$ -lactam **6b** could be accomplished without concomitant

(9) The  $\beta$ -lactone substrates were prepared by the ZnCl<sub>2</sub>-promoted, tandem Mukaiyama aldol-lactonization (TMAL) reaction ( $\beta$ -lactones **1a, b** and **1d–f**; Yang, H. W.; Romo, D. *J. Org. Chem.* **1998**, *63*, 1344–1347; Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, *53*, 16471–16488), by the SnCl<sub>4</sub>-promoted reaction of aldehydes and silylketene acetals ( $\beta$ -lactone **1c**; Wang, Y.; Zhao, C.; Romo, D., submitted), or by the [2 + 2] cycloaddition of silylketenes and aldehydes ( $\beta$ -lactone **1g**; Yang, H. W.; Romo, D. *Tetrahedron Lett.* **1998**, *39*, 2877–2880).

(10) Coupling constants for trans-substituted  $\beta$ -lactams are typically in the range of  $J = 1.9$ – $2.0$  Hz while those for cis-substituted  $\beta$ -lactams are in the range of  $J = 5.3$ – $5.5$  Hz; see: Nelson, D. A. *J. Org. Chem.* **1972**, *37*, 1447–1448.

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cleavage of the  $\alpha$ -benzyloxy group as noted previously for  $\alpha$ -oxygenated esters.<sup>12</sup>

In summary, we have developed an expedient, single-pot conversion of  $\beta$ -lactones to  $\beta$ -lactams. This further expands the utility of  $\beta$ -lactones as intermediates in synthesis and with recent developments in the asymmetric synthesis of  $\beta$ -lactones,<sup>13</sup> this procedure will allow access to a variety of optically active  $\beta$ -lactams in addition to the ones described herein. This methodology complements existing methods for the direct preparation of  $\beta$ -lactams in optically active form.<sup>5</sup> We have also described further examples of the  $\text{SmI}_2$ -promoted, reductive N–O bond cleavage of *N*-benzyloxy- $\beta$ -lactams.

### Experimental Section

**General Methods.** The synthesis of the  $\beta$ -lactones employed in this study has been described previously.<sup>9</sup> Solvent purification/drying, flash chromatography, and thin-layer chromatography were performed as previously described.<sup>9</sup> All reactions were carried out under  $\text{N}_2$  in oven-dried glassware unless noted otherwise. *O*-Benzyloxyamine hydrochloride was purchased from Lancaster. Triphenylphosphine was purchased from Acros. Diisopropyl azodicarboxylate was purchased from Aldrich.  $\text{SmI}_2$  was prepared by the literature procedure immediately prior to use.<sup>14</sup>

**Representative Procedure for the Conversion of  $\beta$ -Lactones to  $\beta$ -Lactams As Described for the Synthesis of  $\beta$ -Lactam 6a.** A mixture of  $\text{BnONH}_2$  (250.8 mg, 2.02 mmol) and  $\beta$ -lactone **1a** (179.5 mg, 1.02 mmol) was stirred for 2 h at 25 °C, at which point the mixture could not be stirred due to the formation of white precipitates. Anhydrous ether (0.3 mL) was added, and the resulting white slurry was stirred for an additional 20 h at 25 °C or until judged complete by TLC analysis. Additional anhydrous ether (2 mL) was added to the mixture, and then solid  $\text{PPh}_3$  (541.3 mg, 2.04 mmol) and neat DIAD (95% purity, 0.43 mL, 2.07 mmol) were sequentially added at 0 °C. The resulting yellow-green solution was stirred for 23 h at 25 °C. The reaction was quenched with 1 N HCl solution, extracted with ether–EtOAc, dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated in vacuo, and purified twice by flash chromatography (EtOAc/Hex = 1:3 and  $\text{CH}_2\text{Cl}_2$ ) to afford the  $\beta$ -lactam **6a** (213.2 mg, 74% yield). Spectral data for this compound matched that previously reported.<sup>8</sup>

**$\beta$ -Lactam 6b.** This  $\beta$ -lactam was prepared in 87% yield (82.5 mg) from  $\beta$ -lactone **1b** (60.9 mg, 0.32 mmol):  $R_f$  0.41 (THF/ $\text{CHCl}_3$ /Hex = 0.4:1:3); IR (thin film) 1767  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10–7.45 (m, 10H), 4.98 (AB q,  $J$  = 11.1 Hz, 2H), 3.61 (dt,  $J$  = 5.7, 6.9 Hz, 1H), 2.95 (dq,  $J$  = 5.7, 7.2 Hz, 1H), 2.50–2.75 (m, 2H), 1.62–1.90 (m, 2H), 1.14 (d,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  167.4, 140.8, 135.1, 129.4, 128.9, 128.5, 128.4, 128.2, 126.1, 78.0, 61.0, 42.3, 32.6, 30.3, 8.9; FAB HRMS calcd for  $[\text{M} + \text{Na}]$  318.1470, found 318.1457.

**$\beta$ -Lactam 6c.** This  $\beta$ -lactam was prepared in 72% yield (77.6 mg) from  $\beta$ -lactone **1c** (71.3 mg, 0.36 mmol):  $R_f$  0.38 (THF/ $\text{CHCl}_3$ /Hex = 0.4:1:3); IR (thin film) 1770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300

MHz,  $\text{CDCl}_3$ )  $\delta$  7.08–7.41 (m, 10H), 4.96 (AB q,  $J$  = 11.4 Hz, 2H), 3.09 (ddd,  $J$  = 2.1, 5.1, 8.1 Hz, 1H), 2.51–2.71 (m, 2H), 2.44 (dq,  $J$  = 2.1, 7.2 Hz, 1H), 1.94–2.05 (m, 1H), 1.66–1.78 (m, 1H), 1.14 (d,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.8, 140.6, 135.1, 129.3, 128.9, 128.46, 128.40, 128.1, 126.1, 78.0, 65.8, 45.7, 33.5, 31.8, 12.9; FAB HRMS calcd for  $[\text{M} + \text{Na}]$  318.1470, found 318.1468.

**$\beta$ -Lactam 6d.** This  $\beta$ -lactam was prepared in 75% yield (54.1 mg) from  $\beta$ -lactone **1d** (51.2 mg, 0.20 mmol):  $R_f$  0.34 (THF/ $\text{CHCl}_3$ /Hex = 0.2:1:3);  $[\alpha]_D^{25}$  –1.0 (c 1.05,  $\text{CHCl}_3$ ); IR (thin film) 1770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.42 (m, 5H), 4.95 (AB q,  $J$  = 11.1 Hz, 2H), 3.72–3.87 (m, 2H), 2.93 (dq,  $J$  = 5.7, 7.2 Hz, 1H), 1.69 (ddd,  $J$  = 5.4, 7.5, 14.1 Hz, 1H), 1.45 (ddd,  $J$  = 5.4, 8.4, 14.1 Hz, 1H), 1.15 (d,  $J$  = 7.2 Hz, 3H), 1.06 (d,  $J$  = 5.7 Hz, 3H), 0.87 (s, 9H), 0.037 (s, 3H), 0.009 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  167.4, 135.2, 129.3, 128.9, 128.5, 77.9, 65.5, 58.3, 42.3, 37.6, 25.7, 23.9, 17.9, 9.3, –4.5, –4.9; FAB HRMS calcd for  $[\text{M} + \text{H}]$  364.2308, found 364.2296.

**$\beta$ -Lactam 6e.** This  $\beta$ -lactam was prepared in 72% yield (57.1 mg) from  $\beta$ -lactone **1e** (51.0 mg, 0.27 mmol):  $R_f$  0.23 (EtOAc/Hex = 1:2);  $[\alpha]_D^{25}$  –58.2 (c 0.98,  $\text{CHCl}_3$ ); IR (thin film) 1781  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.48 (m, 5H), 5.05 (s, 2H), 4.19 (app dt,  $J$  = 6.3, 7.8 Hz, 1H), 4.09 (dd,  $J$  = 6.6, 8.1 Hz, 1H), 3.68 (dd,  $J$  = 5.7, 7.8 Hz, 1H), 3.65 (dd,  $J$  = 6.3, 8.1 Hz, 1H), 2.99 (dq,  $J$  = 5.7, 7.5 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.15 (d,  $J$  = 7.5 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 135.0, 129.3, 128.7, 128.4, 110.0, 77.7, 75.2, 66.3, 63.4, 41.4, 26.7, 25.3, 9.4; FAB HRMS calcd for  $[\text{M} + \text{Na}]$  314.1368, found 314.1358. Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{O}_4\text{N}$ : C, 65.96; H, 7.26; N, 4.81. Found: C, 65.78; H, 7.34; N, 4.78.

**$\beta$ -Lactam 6f.** This  $\beta$ -lactam was prepared in 76% yield (79.4 mg) from  $\beta$ -lactone **1f** (76.1 mg, 0.27 mmol):  $R_f$  0.17 (EtOAc/Hex = 1:9); IR (thin film) 1767  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.08–7.39 (m, 15H), 4.98 (AB q,  $J$  = 11.1 Hz, 2H), 4.77 (AB q,  $J$  = 12.0 Hz, 2H), 4.45 (d,  $J$  = 5.1 Hz, 1H), 3.61 (dt,  $J$  = 4.8, 6.6 Hz, 1H), 2.61–2.68 (m, 2H), 1.88–1.95 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.4, 141.0, 136.9, 134.8, 129.2, 129.0, 128.6, 128.38, 128.36, 128.26, 127.9, 127.7, 126.0, 78.1, 77.8, 72.6, 63.0, 31.9, 29.6; FAB HRMS calcd for  $[\text{M} + \text{Na}]$  410.1732, found 410.1732.

**$\beta$ -Lactam 6g.** This  $\beta$ -lactam was prepared in 45% yield (17.6 mg) from  $\beta$ -lactone **1g** (34.7 mg, 0.14 mmol):  $R_f$  0.42 (THF/ $\text{CHCl}_3$ /Hex = 0.4:1:3); IR (thin film) 1770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.45 (m, 5H), 4.95 (AB q,  $J$  = 11.1 Hz, 2H), 3.47–3.54 (m, 1H), 2.70 (dd,  $J$  = 5.1, 13.5 Hz, 1H), 2.28 (dd,  $J$  = 2.4, 13.5 Hz, 1H), 1.20–1.40 (m, 12H), 0.88 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.2, 135.4, 129.2, 128.9, 128.5, 78.1, 58.1, 37.8, 32.4, 31.7, 29.3, 29.0, 25.4, 22.6, 14.1; FAB HRMS calcd for  $[\text{M} + \text{H}]$  276.1964, found 276.1971.

**$\beta$ -Lactam 2a.** To a solution of *N*-benzyloxy  $\beta$ -lactam **6a** (190.4 mg, 0.68 mmol) in THF (7 mL) and deoxygenated water (0.32 mL) was added a THF solution of  $\text{SmI}_2$  (0.187 M, 18 mL, 3.37 mmol) at 0 °C until a dark blue color persisted. After 1 h, the solution was partitioned between EtOAc and saturated  $\text{NaHCO}_3$  (enough to dissolve solids). The organic layer was washed with saturated  $\text{Na}_2\text{S}_2\text{O}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated in vacuo, and purified by flash chromatography (EtOAc/Hex = 1:2 to 1:1 to 2:1) to afford the  $\beta$ -lactam **2a** (111.4 mg, 94% yield): IR (thin film) 1745  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ - $\text{D}_2\text{O}$ )  $\delta$  7.16–7.35 (m, 5H), 5.93 (br s, 1H), 3.60–3.67 (m, 1H), 3.05 (ddd,  $J$  = 2.4, 5.1, 15.0 Hz, 1H), 2.60–2.76 (m, 2H), 2.56 (ddd,  $J$  = 1.2, 2.4, 15.0 Hz, 1H), 1.93–2.00 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  168.3, 140.6, 128.4, 128.1, 126.0, 47.5, 43.2, 36.8, 32.5; FAB HRMS calcd for  $[\text{M} + \text{Na}]$  198.0895, found 198.0886.

**$\beta$ -Lactam 2b.** This  $\beta$ -lactam was prepared in 91% yield (31.9 mg) from  $\beta$ -lactam **6b** (48.0 mg, 0.12 mmol) by the procedure described above for the synthesis of  $\beta$ -lactam **2a**:  $R_f$  0.04 (EtOAc/Hex = 1:4); IR (thin film) 1756  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ - $\text{D}_2\text{O}$ )  $\delta$  7.15–7.37 (m, 10H), 5.90 (br s, 1H), 4.78 (AB q,  $J$  = 12.0 Hz, 2H), 4.69 (dd,  $J$  = 2.7, 4.8 Hz, 1H), 3.74 (dt,  $J$  = 5.1, 8.1 Hz, 1H), 2.61–2.82 (m, 2H), 1.90–2.15 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  168.8, 141.0, 137.1, 128.5, 128.4, 128.3, 127.9, 127.8, 126.1, 82.4, 72.8, 54.5, 32.4, 31.8; FAB HRMS calcd for  $[\text{M} + \text{H}]$  282.1494, found 282.1483.

(12) For reviews on the use of  $\text{SmI}_2$  including its use for the reduction of C–X bonds of  $\alpha$ -heterosubstituted carbonyl compounds, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (b) Soderquist, A. *Aldrichim. Acta* **1991**, *24*, 15–23.

(13) For a review of methods for the synthesis of optically active  $\beta$ -lactones, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403–6434.

(14) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

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**Supporting Information Available:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of  $\beta$ -lactams **6b-g** and **2a,b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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