Efficacious Preparation of Oppolzer's Glycylsultam via the Delépine Reaction

Alper Isleyen, Carolyn Gonsky, Robert C. Ronald, Philip Garner*

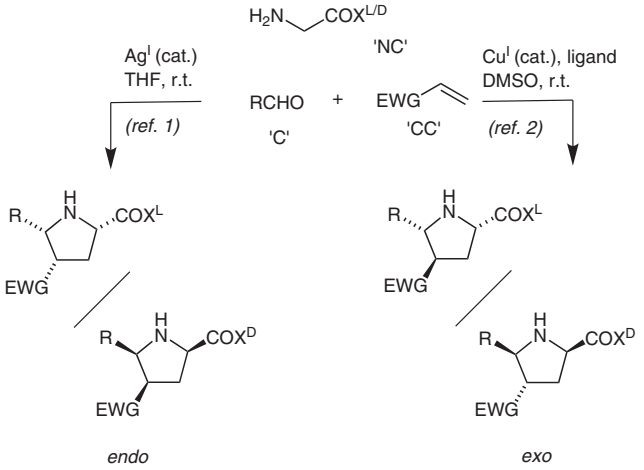
Department of Chemistry, Washington State University, Pullman, WA 99164-4630, USA
Fax +1(509)3358867; E-mail: ppg@wsu.edu

Received 10 September 2008; revised 15 December 2008

Abstract: A new preparative route to Oppolzer's glycylsultam, the 'NC' component in the asymmetric [C+NC+CC] coupling reaction leading to functionalized pyrrolidines, is described. The synthesis features a novel application of the Delépine reaction, providing a safe, efficient, and environmentally benign route to this useful chiral reagent for pyrrolidine synthesis.

Key words: asymmetric synthesis, chiral auxiliaries, chiral pool, Delépine reaction, Oppolzer's camphorsultam

We recently described a set of stereocomplementary multicomponent [C+NC+CC] coupling reactions that provide direct access to functionalized pyrrolidines (Scheme 1, 'C' can be a complex aldehyde).[1,2] Since the pyrrolidine ring is an important structural motif found in many bioactive molecules, the asymmetric [C+NC+CC] coupling reaction is expected to find widespread application in synthesis.[3] During the course of these studies, we required a supply of both the L- and D-versions of Oppolzer's glycylsultam[4,5] ($H_2NCH_2COX^*$, where X* = camphorsultam), which serves as the 'NC' component in the [C+NC+CC] coupling reaction. Prior syntheses of this glycylsultam were deemed unsuitable for our purposes. We now report an efficient, scalable, and environmentally friendly synthesis of Oppolzer's glycylsultam **6** (see Scheme 2) based on the Delépine reaction.



Scheme 1 Asymmetric [C+NC+CC] synthesis of pyrrolidines (X^L and X^D = antipodes of Oppolzer's camphorsultam)

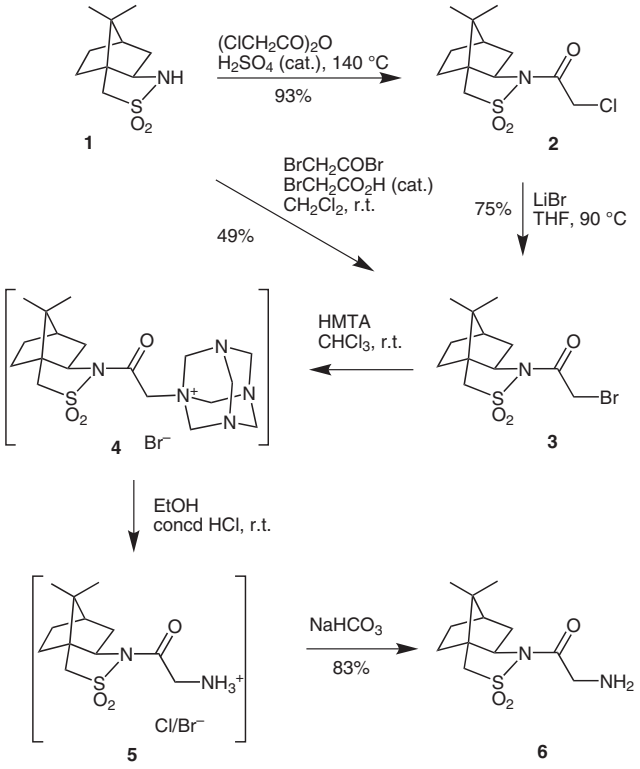
SYNTHESIS 2009, No. 8, pp 1261–1264
Advanced online publication: 16.03.2009
DOI: 10.1055/s-0028-1088021; Art ID: M05308SS

Initially, we employed a variation of Oppolzer's synthesis of α-amino acids to prepare the glycylsultam.[6] This synthesis involved trimethylaluminum-mediated acylation of the parent sultam using methyl *N*-[bis(methylsulfanyl)methylene]glycinate [$(MeS)_2C{=}NCH_2CO_2Me$][7] to give $(MeS)_2C{=}NCH_2COX^*$, which was hydrolyzed to provide the amine. Chassaing and co-workers[8] synthesized the ^{15}N-labeled hydrochloride salt of the glycylsultam via alkylation of labeled potassium phthalimide with $BrCH_2COX^*$ followed by N-deprotection. The sodiosultam could also be acylated with the mixed anhydride of labeled *N*-Boc-protected glycine, followed by N-deprotection. Dogan and co-workers reported acylation of the sodiosultam with azidoacetyl chloride to give the $N_3CH_2COX^*$, which was then subjected to a Staudinger reaction.[9] Our group subsequently developed an alternative route to $H_2NCH_2COX^*$ via S_N2 displacement of $BrCH_2COX^*$ with azide followed by hydrogenolysis.[10] Since this last sequence involved potentially explosive and/or toxic azides,[11] as well as flammable hydrogen gas, a safer and environmentally benign process was clearly desirable.

It was in this context that we began investigating a new route to the glycylsultam based on the Delépine reaction. Though often overlooked, this classical transformation[12] can provide an excellent route to primary amines on a preparative scale.[13] The mechanism of this two-step process involves (a) nucleophilic displacement of an activated halide by the inexpensive and relatively nontoxic hexamethylenetetramine (HMTA), followed by (b) decomposition of the intermediate quaternary hexamethylenetetramine salt with ethanolic hydrogen chloride. This reaction sequence results in a mixture of ammonium salts and diethoxymethane, from which the desired primary amine can be obtained after neutralization. The first step of the process is usually performed in a chlorinated hydrocarbon solvent, from which the quaternary hexamethylenetetramine salt precipitates. A simplified one-pot Delépine procedure using ethanol as the solvent for both steps has also been reported.[14]

We began by developing a more convenient and scalable synthesis of the known[15] chloroacetylsultam **2** (Scheme 2). Acid-catalyzed acylation of the parent L-camphorsultam **1**[16] with chloroacetic anhydride gave **2** in high yield. This compound had previously been made via N-metalation of **1** with sodium hydride followed by low-temperature acylation with chloroacetyl chloride. Although there was a precedent for the Delépine displacement of activated chlorides,[13b] compound **2** did not react

significantly with hexamethylenetetramine under a variety of reaction conditions. Conversion of chloride **2** into the more reactive bromoacetylsultam **3**[17] by use of lithium bromide in tetrahydrofuran (Scheme 2) solved this reactivity dilemma. Bromide **3** could also be formed directly from **1** – albeit in lower yield[18] – by acylation in the presence of a mixture of bromoacetyl bromide and catalytic bromoacetic acid (Scheme 2). Both of these routes to **3** were found to be more practical than the previously reported synthesis.



Scheme 2 Delépine route to Oppolzer's glycylsultam

Under optimized conditions, bromoacetylsultam **3** reacted cleanly with 1.1 equivalents of hexamethylenetetramine in chloroform at room temperature to give a quaternary hexamethylenetetramine salt (Scheme 2). In contrast to more typical Delépine salts, this compound was found to be fairly soluble in the reaction medium. Evaporation of the solvent gave a white solid whose ^{1}H NMR spectrum was consistent with the classical Delépine hexamethylenetetramine adduct **4**.[19] Decomposition of **4** was effected with hydrogen chloride in aqueous ethanol at room temperature (Scheme 2). After removal of precipitated ammonium halide, the filtrate was concentrated to give the ammonium salt **5**. It was essential to remove all of the diethoxymethane (or other volatile formaldehyde equivalents) at this stage to avoid the formation of a 1,3,5-triazinane in the next step.[20] Neutralization of **5** with sodium bicarbonate followed by extraction gave the desired free glycylsultam **6** in good yield (Scheme 2). This crude material invariably contained traces of camphorsultam **1**,[21] but was suitable for use in the [C+NC+CC] coupling reaction.

In conclusion, the Delépine reaction forms the basis for a convenient synthesis of Oppolzer's glycylsultam **6**. This short sequence proceeds in good overall yield (52% over 3 steps) on a multigram scale and does not require any chromatographic separations. The ready availability of **6** (as well as its antipode *ent*-**6**), made possible by this new procedure, will encourage use of the asymmetric [C+NC+CC] coupling technology.

Oven-dried glassware under Drierite drying tubes were used for nonaqueous reactions. Anhyd THF was distilled from Na/benzophenone ketyl under argon. Hexamethylenetetramine (HMTA) was recrystallized from 95% EtOH prior to use. All other commercial reagents were used as received. The progress of reactions was monitored by analytical TLC. Plates were visualized by charring with 5% anisaldehyde in EtOH–AcOH–H_2SO_4 (95:5:1). Melting points are uncorrected. Optical rotations were measured at 589 and 546 nm with a Jasco DIP-181 digital polarimeter calibrated with a sucrose standard. ^{1}H NMR spectra of samples in $CDCl_3$ were recorded at 300 MHz and are referenced to TMS. ^{13}C NMR spectra were recorded at 75 MHz and are referenced to $CDCl_3$ (δ = 77.00). Data from COSY, NOESY, and HMQC 2D experiments were used for making the ^{1}H and ^{13}C NMR assignments for compounds **2**, **3**, and **6**. MALDI-HRMS was carried out with an α-cyano-4-hydroxycinnamic acid matrix.

(3a*S*,6*R*,7a*R*)-1-(Chloroacetyl)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzothiazole 2,2-Dioxide (2)

Sultam **1** (20.5 g, 95.0 mmol) was added in five portions over 5 min to a stirred soln of chloroacetic anhydride (technical grade, 19.9 g, 0.105 mol) and concd H_2SO_4 (0.254 mL, 4.57 mmol) at 80 °C. The temperature was then increased to 140 °C, and the mixture was stirred until TLC analysis showed the reaction to be completed (ca. 2.5 h). The mixture was cooled to r.t. and then transferred to an Erlenmeyer flask containing a mixture of CH_2Cl_2 (200 mL) and H_2O (100 mL); it was then carefully neutralized with 0.712 M NaOH (200 mL, 0.142 mol) to pH 7.5. The aqueous layer was extracted further with CH_2Cl_2 (200 mL). The combined organic layers were dried ($MgSO_4$), filtered through a pad of charcoal and Celite, and concentrated under reduced pressure; this yielded crude **2** as a tan solid, which was used for the next step without further purification.

Yield: 25.8 g (93%); mp 115–120 °C (Lit.[15b] 120–122 °C); R_f = 0.44 (hexanes–EtOAc, 3:1).

A sample was recrystallized from *i*-Pr_2O–CH_2Cl_2 for optical rotation and combustion analysis; mp 131–134 °C; $[\alpha]_D^{23}$ –118.2, $[\alpha]_{546}^{23}$ –140.7 (*c* 2.16, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.50 (s, 2 H), 3.92 (dd, *J* = 7.5, 5.1 Hz, 1 H), 3.54 (d, *J* = 13.8 Hz, 1 H), 3.47 (d, *J* = 13.8 Hz, 1 H), 2.23–2.07 (m, 2 H), 1.99–1.84 (m, 3 H), 1.48–1.33 (m, 2 H), 1.15 (s, 3 H), 0.98 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 65.5, 52.6, 49.1, 47.9, 44.5, 42.3, 38.0, 32.7, 26.4, 20.7, 19.8.

Anal. Calcd for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.22; N, 4.80. Found: C, 49.60; H, 6.19; N, 4.64.

(3a*S*,6*R*,7a*R*)-1-(Bromoacetyl)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzothiazole 2,2-Dioxide (3) by Procedure A (from 2)

A soln of crude (chloroacetyl)sultam **2** (12.9 g, 44.1 mmol) in anhyd THF (20 mL) was added to a stirred soln of LiBr (38.1 g, 0.441 mol) in anhyd THF (67 mL) kept in a bath at 90–95 °C. The mixture was stirred at this temperature for 20 h, after which it was allowed to cool to r.t. and partitioned between H_2O (125 mL) and CH_2Cl_2 (250

mL). The aqueous layer was extracted further with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered through a pad of charcoal and Celite, and concentrated at reduced pressure; this yielded crude **3** as a light brown solid. Recrystallization from a mixture of *i*-Pr_2O (45 mL) and CH_2Cl_2 (50 mL) afforded (bromoacetyl)sultam **3** as colorless needles.

Yield: 10.9 g (79%); mp 111–115 °C (Lit.[17] 113 °C); $[\alpha]_D^{23}$ –101.8, $[\alpha]_{546}^{23}$ –120.7 (*c* 1.95, $CHCl_3$) [Lit.[17] $[\alpha]_D$ –118.5 (*c* 1, CH_2Cl_2)]; R_f = 0.45 (hexanes–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.35 (d, *J* = 12.9 Hz, 1 H), 4.21 (d, *J* = 12.9 Hz, 1 H), 3.92 (dd, *J* = 7.5, 5.1 Hz, 1 H), 3.54 (d, *J* = 13.8 Hz, 1 H), 3.47 (d, *J* = 13.8 Hz, 1 H), 2.21–2.04 (m, 2 H), 2.00–1.83 (m, 3 H), 1.49–1.31 (m, 2 H), 1.16 (s, 3 H), 0.99 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 65.4, 52.7, 49.0, 47.8, 44.5, 37.9, 32.7, 27.5, 26.4, 20.7, 19.8.

Anal. Calcd for $C_{12}H_{18}BrNO_3S$: C, 42.86; H, 5.40; N, 4.17. Found: C, 42.57; H, 5.25; N, 4.25.

Compound 3 by Procedure B (from 1)

Bromoacetyl bromide (7.5 mL, 86.0 mmol) was added to a stirred soln of camphorsultam **1** (15.0 g, 69.7 mmol) and bromoacetic acid (485 mg, 5 mol%) in CH_2Cl_2 (7.5 mL). The orange-colored mixture was stirred at r.t. for 3.5 h, at which point ^{1}H NMR analysis showed a 2:1 ratio of (bromoacetyl)sultam **3** to HBr addition product **7**.[18] The reaction mixture was partitioned between ice-cold CH_2Cl_2 (total volume 150 mL) and ice-cold, distilled H_2O (300 mL). The aqueous layer was extracted further with CH_2Cl_2 (150 mL). The combined CH_2Cl_2 layers were washed with H_2O (2 × 400 mL), dried ($MgSO_4$), filtered, and concentrated, to give a slightly yellowish oil, which solidified upon standing overnight (22.1 g). ^{1}H NMR analysis of this crude mixture showed a **3/1** ratio of 3:1. Recrystallization from CH_2Cl_2–absolute EtOH gave pure **3** as a colorless solid; yield: 11.52 g (49%); mp 114–115 °C. The filtrate was concentrated to give a yellow oil, which consisted of a **3/1** mixture in a 2:3 ratio.

(3a*S*,6*R*,7a*R*)-1-(Aminoacetyl)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzothiazole 2,2-Dioxide (6)

A mixture of (bromoacetyl)sultam **3** (10.0 g, 29.8 mmol) and HMTA (4.61 g, 32.8 mmol) in $CHCl_3$ (reagent grade, 50 mL) was stirred at r.t. for 20 h, and was then concentrated by rotary evaporation to give the crude Delépine adduct **4**. EtOH (95%, 25 mL) and 12 N HCl (7.5 mL) were added to this white solid. After stirring at r.t. for 6 h, the heterogeneous reaction mixture was cooled in an ice bath and filtered to remove NH_4Cl; the filter cake was washed with EtOH (95%, 200 mL). The filtrate and washings were concentrated by rotary evaporation to leave a solid, which was kept under vacuum (ca. 0.02 Torr) at 75 °C until it reached a constant weight (13.45 g). This crude ammonium salt **5** was partitioned between H_2O (200 mL) and CH_2Cl_2 (200 mL) to remove any neutral materials. The aqueous phase was then carefully neutralized to pH 7.5 with a soln of $NaHCO_3$ (3.27 g) in H_2O (220 mL), and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated; this gave glycylsultam **6** as a colorless solid. This material contained 5 mol% camphorsultam **1**.[21]

Yield: 6.09 g (75%); mp 112–117 °C; $[\alpha]_D^{23}$ –115.0, $[\alpha]_{546}^{23}$ –135.2 (*c* 2.00, abs EtOH); R_f = 0.51 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (d, *J* = 18.0 Hz, 1 H), 3.88 (dd, *J* = 7.5, 5.1 Hz, 1 H), 3.76 (d, *J* = 18.0 Hz, 1 H), 3.50 (d, *J* = 13.8 Hz, 1 H), 3.43 (d, *J* = 13.8 Hz, 1 H), 2.20–2.04 (m, 2 H), 1.95–1.83 (m, 3 H), 1.52 (br s, 2 H), 1.46–1.33 (m, 2 H), 1.15 (s, 3 H), 0.98 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 65.1, 52.7, 49.1, 47.8, 45.4, 44.6, 38.2, 32.8, 26.4, 20.7, 19.8.

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}N_2O_3S$: 273.1267; found: 273.1365.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

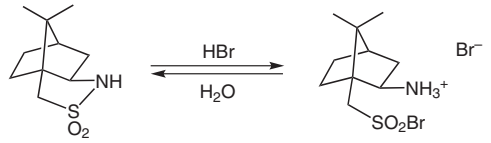
Acknowledgment

This research was supported by a grant from the National Science Foundation (Grant CHE-0553313). C. G. was the recipient of a WSU College of Sciences Undergraduate Student Research Mini-grant.

References

(1) Garner, P.; Kaniskan, H. Ü.; Hu, J.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *6*, 3647.
(2) Garner, P.; Hu, J.; Parker, C. G.; Youngs, W. J.; Medvetz, D. *Tetrahedron Lett.* **2007**, *48*, 3867.
(3) The value of our [C+NC+CC] coupling reaction in a complex synthetic scenario (synthesis of the natural products cyanocycline A and bioxalomycin β2) has already been demonstrated. See: Kaniskan, H. Ü.; Garner, P. *J. Am. Chem. Soc.* **2007**, *129*, 15460.
(4) (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009. (b) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363.
(5) Although Oppolzer did not actually report a synthesis of the parent glycylsultam, we feel that it is appropriate to refer to it as 'Oppolzer's glycylsultam' for descriptive reasons.
(6) Garner, P.; Dogan, Ö.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71.
(7) Hoppe, D.; Kloft, M. *Liebigs Ann. Chem.* **1980**, 1512.
(8) Martin, A.; Chassaing, G.; Vanhove, A. *Isot. Environ. Health Stud.* **1996**, *32*, 15.
(9) Dogan, Ö.; Öner, I.; Ülku, D.; Arici, C. *Tetrahedron: Asymmetry* **2002**, *13*, 2099.
(10) Kaniskan, H. Ü. *Ph.D. Dissertation*; Case Western Reserve University: Cleveland, OH, **2007**.
(11) Nicolaides, E. D.; Westland, R. D.; Wittle, E. L. *J. Am. Chem. Soc.* **1954**, *76*, 2887.
(12) Delépine, M. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 501.
(13) See: (a) Bottini, A. T.; Dev, V.; Klinck, J. *Org. Synth.* **1963**, *43*, 6. (b) Meyers, A. I.; Warmus, J. S.; Dilley, G. J. *Org. Synth.* **1996**, *73*, 246.
(14) Galat, A.; Elion, G. *J. Am. Chem. Soc.* **1939**, *61*, 3585.
(15) (a) Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885. (b) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368.
(16) For a very convenient synthesis of Oppolzer's camphorsultam that uses sodium borohydride rather than lithium aluminum hydride for reduction of the sulfoximine, see: Capet, M.; David, F.; Bertin, L.; Hardy, J. C. *Synth. Commun.* **1995**, *25*, 3323.
(17) Sweeney, J. B.; Cantrill, A. A.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3681.
(18) The modest yield of this reaction was due to competitive addition of HBr to **1** that resulted in an unstable compound tentatively identified as **7** on the basis of diagnostic peaks in its ^{1}H NMR spectrum: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (br s, NH_3^+), 5.28 (d, *J* = 14.2 Hz, 1 H), 3.94 (d, *J* = 14.2 Hz, 1 H). Attempts to suppress this side reaction were unsuccessful. In a separate control experiment, compound **7** was produced quantitatively by the action of HBr gas on **1**

dissolved in $CDCl_3$ (Scheme 3). Byproduct **7** reverts back to camphorsultam **1** upon exposure to water.

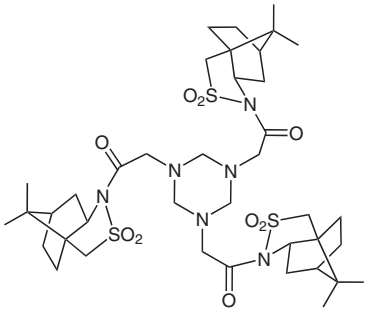


1 **7**

Scheme 3

(19) Monoalkylation of HMTA with the chiral bromide **3** breaks its T_d molecular symmetry, resulting in AB quartets for both sets of diastereotopic HMTA methylene protons in **4**. This Delépine salt was unstable, but these key HMTA signals could be observed in the ^{1}H NMR spectrum: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (d, *J* = 11.1 Hz, 3 H), 5.82 (d, *J* = 11.1 Hz, 3 H), 4.76 (d, *J* = 13.0 Hz, 3 H), 4.54 (d, *J* = 13.0 Hz, 3 H).

(20) The proposed structure of **8** (Figure 1) was supported by its exact mass (HRMS: *m*/*z* $[M - H]^+$ calcd for $C_{39}H_{59}N_6O_9S_3$: 851.3500; found: 851.2368) and the presence of an aminal carbon signal in its ^{13}C NMR spectrum: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 73.1.



8

Figure 1

(21) Solutions of the free glycylsultam **6** were found to be susceptible to nucleophile-induced deacylation to give back starting camphorsultam **1**. The level of contamination ranged from 3 mol% on a 0.5-g scale to 5 mol% on a 10-g scale of bromosultam **3**. However, a solid sample of **6** that had been kept at room temperature for more than one month showed minimal decomposition.