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Process Research on [(2*S*)-(3-Fluorophenyl)-(1*S*)-(5-oxotetrahydrofuran-2-yl)ethyl]carbamic Acid *tert*-Butyl Ester, a Lactone Intermediate for an Aspartyl Protease Inhibitor

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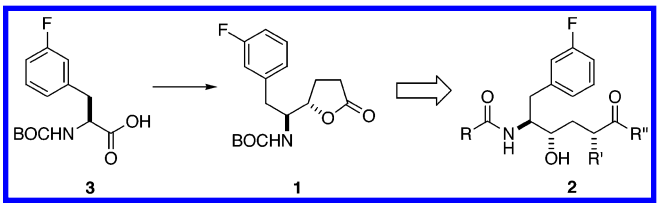
Abstract:

Two processes for the preparation of lactone [2*S*-(3-fluorophenyl)-1*S*-(5-oxotetrahydrofuran-2-yl)ethyl]carbamic acid *tert*-butyl ester 1 starting from *S*-BOC-(3-fluorophenyl)alanine 3 are described. (*S*)-(3-Fluorophenyl)alanine *N*-methyl-*N*-methoxy amide 10, the Weinreb amide of 3, was reacted with 2-(2-1,3-dioxanyl)ethylmagnesium bromide to provide key intermediate ketoacetal 11. To achieve high yields for this conversion, the N−H of the BOC group in Weinreb amino acid amide 10 was deprotonated first with a simple Grignard reagent (methyl or benzylmagnesium halide) followed by Barbier reaction with magnesium metal and 2-(2-bromoethyl)-1,3-dioxane. The acetal group in 11 was opened oxidatively with ozone, and the resulting ester 15 was reduced selectively at low temperature with *N*-Selectride. Alternatively, the ketone moiety in 11 was reduced diastereoselectively with aluminum triisopropoxide in 2-propanol to give the undesired (*R*,*S*)-diastereomeric alcohol. The alcohol was converted to the mesylate which was heated in solution to cause formation of oxazolidinone 19 through displacement of the mesylate group by the carbonyl moiety of the BOC group with loss of *tert*-butyl alcohol. This intramolecular reaction provided the desired (*S*,*S*)-diastereomer. Finally, acetal 19 was converted to nitrile 20 with hydroxylamine hydrochloride in ethanol with catalytic toluenesulfonic acid at reflux. Basic aqueous hydrolysis of nitrile 20 followed by treatment with di-*tert*-butyl dicarbonate provided 1. While the second process was longer, the inexpensive reagents, simple reaction conditions, and high yields made it the process of choice. Both processes have been run on a multikilogram scale.

Lactone intermediate **1** is used for the preparation of (4*S*)-hydroxy-(5*S*)-amino-6-(3-fluorophenyl)hexanoic acid **2**, a hydroxyethylene dipeptide isostere.[1] These isosteres are aspartyl protease inhibitors which have been studied in HIV[2] and for blood pressure control by interaction with renin receptors.[3] There are many syntheses of these lactones and these isosteres in the literature.[4] Recently, we described the observation of a novel dimer in the synthesis of title lactone **1** starting from amino acid **3** involving DIBALH reduction of the methyl ester of **3** and in situ reaction with the lithium salt of ethyl propiolate.[5] Process research led to elimination of the dimer and allowed the procedure to be conducted on a kilogram scale. While this supplied the initial needs for lactone **1**, the selectivity of the lithiated ethyl propiolate addition was moderate with a 6.5:1 ratio of the desired (*S*,*S*)-diastereomer formed. Since this process required low-temperature conditions, involved unstable intermediates, and had a low overall yield, a better process was needed. In this paper, we describe the work that lead to a new process to lactone **1** starting with (*S*)-BOC-(3-fluorophenyl)alanine **3** utilizing simple, inexpensive reagents and reaction conditions.



Since a bulk supplier of BOC-amino acid **3** had been identified, it was chosen as the starting material for our work. One synthesis of lactones such as **1** had been published by Diederich and Ryckman in the early 1990's starting from the Weinreb amide of *N*,*N*-dibenzylphenylalanine **4** and 2-(1,3-dioxanyl)ethylmagnesium bromide **5**[6] (Scheme 1). A key point of this process was the control of the alcohol stereochemistry with a sodium borohydride reduction. Since this process was described in a World patent application[7] and used a different protection scheme for the nitrogen, a variation of this synthesis starting from *N*-BOC-(3-fluorophenyl)alanine **3** was sought.

(1) Kath, J. C.; Brown, M. F.; Poss, C. S. U.S. Patent 2003/0018033, 2003.
(2) Huff, J. R. *J. Med. Chem.* **1991**, *38*, 2305.
(3) Greenlee, W. J. *J. Med. Res. Rev.* **1990**, *10*, 173.
(4) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921. Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828. Wuts, P. G. M.; Putt, S. R.; Ritter, A. R. *J. Org. Chem.* **1988**, *53*, 4503. Chakravarty, P. K.; de Laszlo, S. E.; Sarnella, C. S.; Springer, J. P.; Schuda, P. F. *Tetrahedron Lett.* **1989**, *30*, 415. Bradbury, R. H.; Revill, J. M.; Rivett, J. E.; Waterson, D. *Tetrahedron Lett.* **1989**, *30*, 3845. Herold, P.; Duthaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, *54*, 1178. Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. Radunz, H.-E.; Eirmann, V.; Schneider, G.; Riethmuller, A. *Tetrahedron* **1991**, *47*, 1887. Shiozaki, M.; Kobayashi, Y. *Tetrahedron* **1991**, *47*, 2785. DeCampo, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. Plata, D. J. Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1991**, *32*, 3623. Kotsuki, H.; Miyazaki, A.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4503. Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411. Armstrong, J. D., III; Hartner, F. W.; DeCamp, A. E.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1992**, *33*, 6599. Sakurai, M.; Saito, F.; Ohata, Y.; Yabe, Y.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1562. Sakurai, M.; Hata, T.; Yabe, Y. *Tetrahedron Lett.* **1993**, *34*, 5939. Meunier, N.; Veith, U.; Jager, V. *J. Chem. Soc., Chem. Commun.* **1996**, 331. Aguilar, N.; Mayano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3560. Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. Rueger, H.; Stutz, S.; Goschke, R.; Spindler, F.; Maibaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085.
(5) Jasys, V. J.; Urban, F. J. *Tetrahedron: Asymmetry* **2001**, *12*, 361.
(6) Diederich, A. M.; Ryckman, D. M. *Tetrahedron Lett.* **1993**, *34*, 6169.
(7) Ryckman, D. M.; Suter, S. R. World Patent Application WO 94/27955, 1994.

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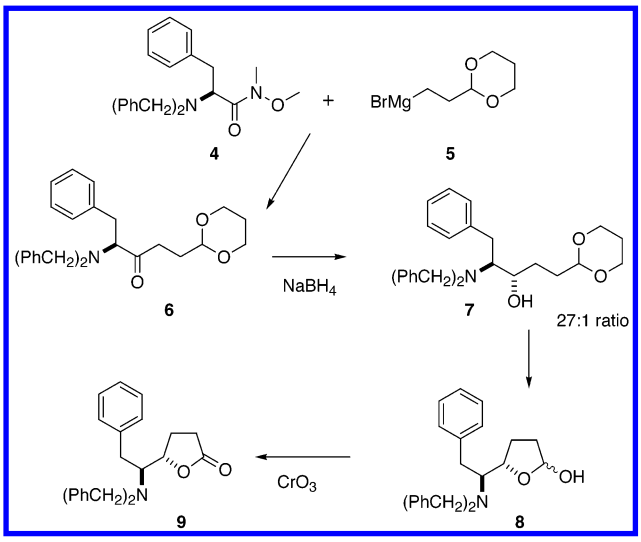
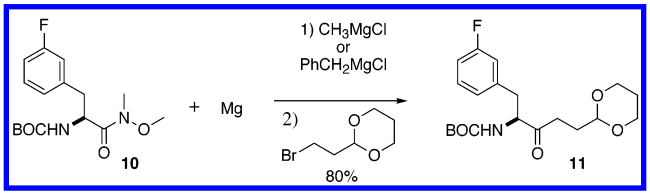
Scheme 1

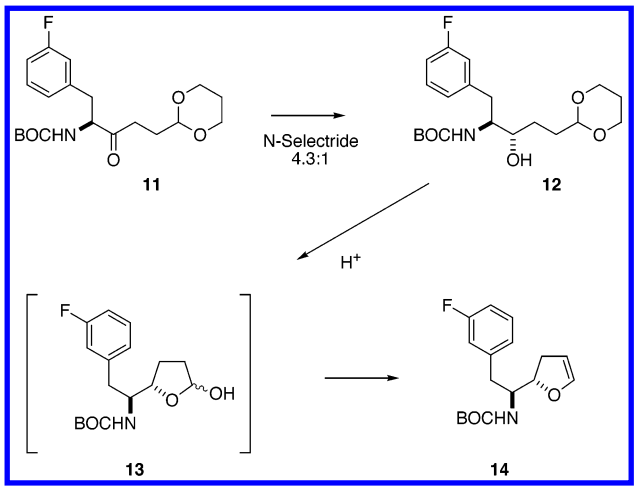


Scheme 2



The *N*-methyl-*N*-methoxy amide **10** (Weinreb amide) of *N*-BOC-(*S*)-(3-fluorophenyl)alanine **3** was prepared in 92% yield by a mixed anhydride procedure with isobutyl chloroformate and *N*-methylmorpholine in methylene chloride at − 5 °C. Use of carbonyl diimidazole in methylene chloride without additional base at room temperature to activate amino acid **3** resulted in Weinreb amide **10** of 90% ee. Initial attempts to combine amide **10** with preformed Grignard reagent **5** in tetrahydrofuran (THF) gave, at most, traces of the desired ketone **11**, but switching to a Barbier-type procedure was more successful. A mixture of Weinreb amide **10** and magnesium metal turnings in THF was treated with 2-(2-bromoethyl)-1,3-dioxane to provide ketone **11** in 50% yield. A 5-fold excess of both magnesium and alkyl bromide was required to react with all the starting material. A further optimized procedure utilized deprotonation of the Weinreb amide **10** N−H with methylmagnesium bromide in the presence of magnesium metal in THF followed by addition of 2-(2-bromoethyl)-1,3-dioxane under Barbier conditions with the reaction temperature maintained below 28 °C (Scheme 2).[8] The addition of methylmagnesium bromide was monitored by HPLC until traces of the methyl ketone were observed as an endpoint. At a toller running this chemistry, benzylmagnesium chloride was used in the deprotonation. This eliminated methane emissions, and no benzyl ketone was observed with excess benzylmagnesium chloride. With either Grignard for deprotonation, a yield of 80% was achieved in the lab, while 60% was more typical on a pilot plant scale. The different yields are probably due to the properties of this acetal-containing Grignard reagent. The six-membered dioxane containing Grignard used in our process has been reported to have more thermal stability then the corresponding five-membered dioxolane analogue,[9] but

Scheme 3



both share the potential for thermal decomposition with cyclopropane ring formation[10] as well as for Wurtz coupling.[11] In the lab procedure, the Barbier−Grignard reaction was initiated at about 15 °C and the remainder of the bromide was added keeping the reaction temperature below 28 °C. On one occasion when the reaction was being run in a 22 L flask, the Grignard would not initiate and had to be heated to a higher temperature. It was determined with reaction calorimetry and in situ IR that initiation at 35 °C was more reliable for large scale use. The rate of addition of the bromide was faster on a pilot plant scale, and the reaction temperature during addition was 55 °C to shorten reaction times. Full optimization of the pilot plant procedure for this process has not been carried out. On a lab scale, 2.6 equiv of magnesium were charged to the reaction flask and 2 equiv of 2-(2-bromoethyl)-1,3-dioxane were added as described above. After stirring for several hours or overnight, more bromide was added if starting Weinreb amide remained. Any excess magnesium was reacted during the quench of the reaction. On a pilot plant scale, 2.6 equiv of magnesium were used with 2.7 equiv of 2-(2-bromoethyl)-1,3-dioxane. With this procedure, little or no magnesium metal was left in the reactor to generate hydrogen gas during the quench. More than 200 kg of ketone **11** have been prepared in this manner.

Originally, the sequence of ketone **11** reduction followed by acetal hydrolysis of **12** and oxidation of the lactol **13** to lactone **1** was looked at as in the Diederich and Ryckman process (Scheme 3).[6] This was found to suffer from two serious problems. Unlike the sodium borohydride reduction of α-(*N*,*N*-dibenzylamino) ketones which provided the desired (*S*,*S*)-diastereomer very selectively, *N*-BOC-aminoketone **11** was not reduced diastereoselectively by a variety of hydride reagents. The best result was seen with *N*-Selectride at −78 °C with a 4.3:1 ratio of diastereomers observed favoring the desired (*S*,*S*)-isomer. Other reagents

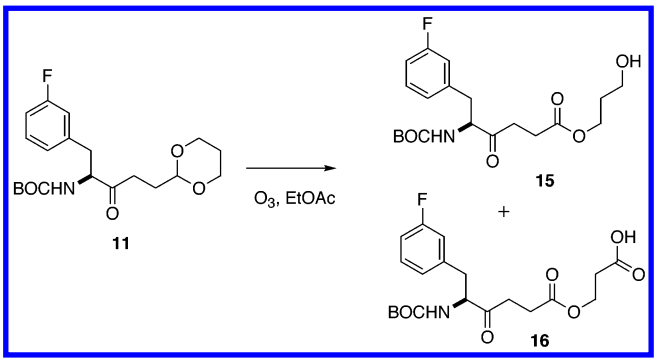
(8) A similar pre-deprotonation protocol has been recently reported in the synthesis of α-(*N*-BOC-amino)ketones from α-(*N*-BOC-amino)Weinreb amides. Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D. *Tetrahedron Lett.* **2002**, *43*, 8223.

(9) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560.

(10) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105. Greiner, A. *Tetrahedron Lett.* **1989**, *30*, 3547.

(11) Bal, S. B.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

Scheme 4



tested were the following: *L*-Selectride (1.3:1); *K*-Selectride (2:1); sodium borohydride (1:3.1); and DIBALH (1: 3.35) (ratio of (*S*,*S*):(*R*,*S*)). Second, the acidic hydrolysis of amino alcohol acetal **12** did not yield lactol **13** cleanly. Some reaction conditions tried included acetic acid, neat and in various cosolvents, pyridinium *p*-toluenesulfonate in aqueous acetone, aqueous hydrochloric acid in THF, and palladium dichloride in acetone among others. The major product in the acidic hydrolysis attempts was dihydrofuran **14** with only traces of the desired lactol **13**. An authentic sample of lactol **13** was prepared by DIBALH reduction of lactone **1** in toluene at − 78 °C.

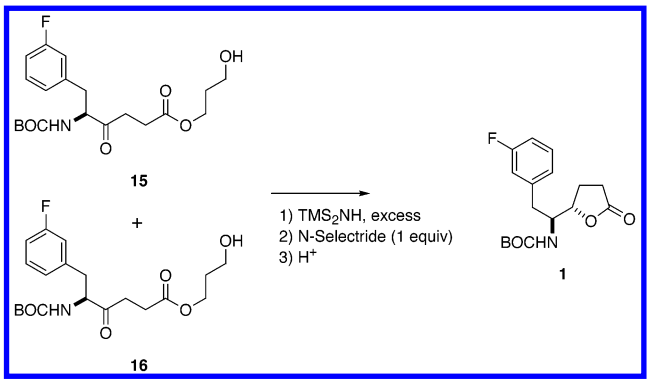
The ketoester corresponding to **11** with an ethyl ester in place of the acetal group could be reduced with *N*-Selectride in high diastereoselectivity (98% de) and yield (96%).[12] Based on this result, the opening of the acetal in **11** by oxidation to a carboxylate group was examined. After trying some oxidative acetal openings such as sodium perborate with acetic anhydride or Oxone supported on wet alumina,[13] we settled on the use of ozone as described by Deslongchamps.[14] Ketone **11** in ethyl acetate solution was treated with ozone at −15 °C until all of the starting acetal had reacted. At a small scale, the desired propane diol ester **15** was seen to form cleanly early in the reaction, but a new more polar compound was observed at low levels as the reaction neared completion. As the ozonolysis was scaled up, the level of the more polar compound increased to greater than 10%. This was isolated and shown to be the overoxidation product **16** (Scheme 4). One reason this was more prevalent on a larger scale was that the ozone/oxygen mixture was 3% in the lab and 5% in the pilot plant at a toller. Once the acetal has reacted, the rate of oxidation of the primary alcohol in **15** is rapid. The mixture of esters **15** and **16** could be reduced with 2 equiv of *N*-Selectride in THF at −78 °C with high diastereoselectivity (24:1) to provide lactone **1** after an oxidative workup with sodium perborate to quench the boron reagent and acid treatment to cyclize the hydroxycarboxylate.

(12) Unpublished results from C. P. Mason, Pfizer Sandwich, on an analogue provided this lead. For work on related α-(*N*-BOC-amino)ketones, see: Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045. Vabeno, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186.

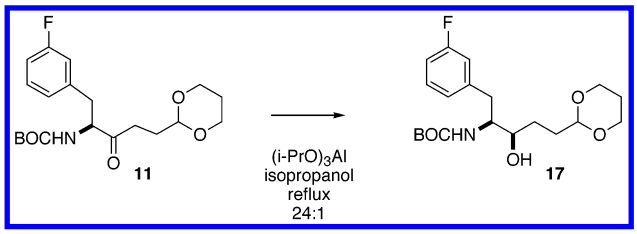
(13) Bhat, S.; Ramesha, A. R.; Chandrasekaran, S. *Synlett* **1994**, 329. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett* **1999**, 777.

(14) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651. This procedure has been used recently by Bailey. Bailey, W. F.; Reed, D. P.; Clark, D. R.; Kapur, G. N. *Org. Lett.* **2001**, *3*, 1865.

Scheme 5



Scheme 6



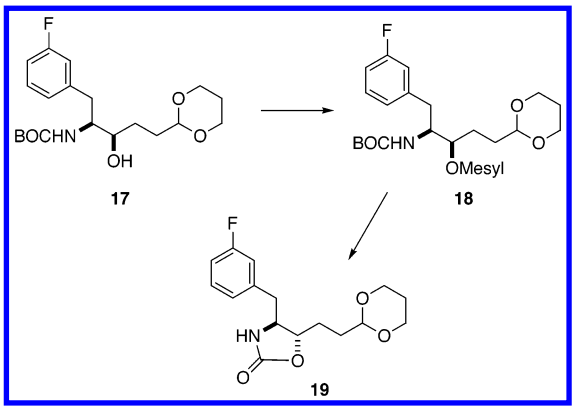
Before this chemistry was scaled up, a modified procedure was developed to protect the alcohol in **15** and carboxylate in **16** by pretreatment with hexamethyldisilazane in THF (Scheme 5). With this procedure, only 1 equiv of reducing agent was needed. The diastereoselectivity for this reduction was a 46:1 ratio favoring the desired (*S*,*S*)-isomer. This process was carried out by a toller to provide 9 kg of lactone **1** starting from 25 kg of ketone **11**.

At this point in the project, a useable bulk process was achieved; however, it had several drawbacks. We did not have in-house ozone capacity at the time of the work. Also, the *N*-Selectride reaction while very selective required low temperatures, an expensive reagent, and an oxidative workup to quench the reagent.

In considering other transformations utilizing ketone **11**, a patent application on the reduction of α-keto-*β*-aminocarboxylate esters was of interest.[15] In this work, a classical Meerwein−Pondorf−Verley reduction was used to prepare optically active erythro-3-amino-2-hydroxybutyric acid esters. While the diastereoselectivity was the opposite of the one required for lactone **1**, the simple conditions and reported high stereocontrol were attractive. When ketone **11** was reduced with a slight excess of aluminum triisopropoxide in 2-propanol at reflux, the result was a 24:1 ratio of diastereomers favoring the undesired (*S*,*R*)-diastereomer **17** (Scheme 6). While this would require an inversion of the alcohol center, the simplicity and ease of operation encouraged further study. It was determined that the initial product ratio of diastereomers did not equilibrate under the reaction conditions and that a side reaction in which the new alcohol moiety reacted with the BOC-group to form an oxazolidinone was less than 4%. Alcohol **17** was isolated by cooling the reaction mixture from reflux to room temperature, diluting with 2-propanol and filtering or diluting with 1 N HCl before filtering. The aqueous workup helped to improve the yield

(15) Satoh, H.; Turk, G. H. European Patent Application EP934923A1, 1999.

Scheme 7



and remove aluminum salts, while the alcohol procedure removed any color from the product albeit at some yield loss (88% versus 77%). In either procedure, most of the minor (*S*,*S*)-diastereomer is removed in the crystallization. In practice, the aqueous procedure was preferred and the alcohol contained less than 1.5% of the (*S*,*S*)-diastereomer.

For the inversion of the alcohol center in alcohol **17**, a precedent in the literature was followed.[16] Alcohol **17** was converted to mesylate **18** with methanesulfonyl chloride in pyridine at room temperature, and mesylate **18** was isolated in 94% yield by addition of water to cause precipitation. The crude, dried mesylate was redissolved in pyridine and heated to provide oxazolidinone **19** in 95% yield (Scheme 7). Alternatively, the mesylate was formed in THF with triethylamine and mesyl chloride between 23 and 30 °C. After washing the THF solution of mesylate **18** with brine, the solution was concentrated to remove water. Additional THF and triethylamine were added, and the mixture was heated at reflux to cyclize to **19** without isolation of the mesylate. The yield was about 80% overall for the in situ procedure, but it involved less handling. Oxazolidinone **19** was isolated as an oil after an extractive workup.

From oxazolidinone **19**, the conversion to lactone **1** could be carried out via an ozonolysis procedure. However, our examination of other acetal opening reactions to avoid ozone had led us to a reaction described by Yamauchi for the conversion of acetals to nitriles.[17] Acetal **19** was treated in ethanol with hydroxylamine hydrochloride and catalytic *p*-toluenesulfonic acid at reflux. This caused conversion of acetal **19** to nitrile **20** in 90% yield. Neither the aldehyde nor the oxime was observed as an intermediate in the reaction mixture. A second, minor product, a small amount of ester **21**, was seen. A toller found that adding hydroxylamine hydrochloride as an aqueous solution suppressed the formation of ester **21**. While nitrile **20** could be isolated as a solid, the crude reaction product was taken directly into the hydrolysis to improve the yield for the overall conversion. To complete the lactone process, the mixture of nitrile **20** and ester **21** was hydrolyzed in aqueous sodium hydroxide. The basic aqueous solution was treated with di-*tert*-butyl dicarbonate in THF under Shotten−Baumann conditions. A simple extractive workup and acid treatment provided lactone **1** as a crystalline solid (Scheme 8).

In conclusion, we have described the preparation of lactone **1** by two different processes that have been scaled up. The preferred method was based on the classical Meerwein−Pondorf−Verley reduction and the conversion of acetal **19** to nitrile **20** with hydroxylamine hydrochloride under acidic conditions in ethanol. This process has been used to prepare about 50 kg of lactone **1**.

Experimental Section

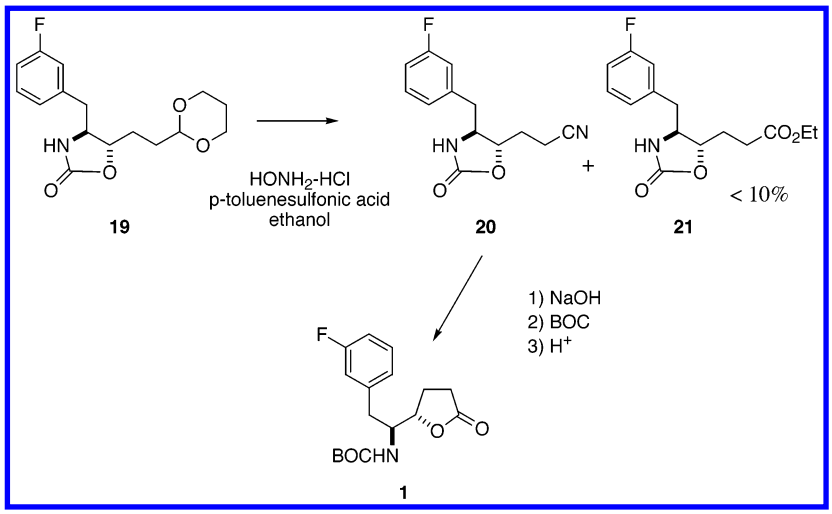
Melting points were determined on a Thomas−Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Varian Unity 400 (400 MHz) spectrometer in deuteriochloroform or dimethyl sulfoxide-d_6. Infrared spectra were taken in KBr by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Mass spectra were determined with a Finnigan 4510 mass spectrometer using fast atom bombardment (FAB). Elemental analyses were performed by Quantitative Technologies Inc. The reactions were monitored by TLC on silica gel plates, and isolated compounds were analyzed by HPLC. The HPLC assays were done on a Waters Novapack C18 column with a gradient elution consisting of water with 700 μL of 85% *o*-phosphoric acid (A) and acetonitrile (B) with detection at 210 nm. Starting and ending gradients are given below along with retention times.

***N′*-Methoxy-*N′*-methyl (*S*)-*N*-BOC-(3-fluorophenyl)-alanine Amide 10.** In a 1 L 4N-flask equipped with an addition funnel, a low temperature thermometer, an N_2 inlet, and a mechanical stirrer, *N*-BOC-(3-fluorophenyl)alanine **3** (56.6 g, 0.2 mol) was dissolved in methylene chloride (300 mL). *N*-Methylmorpholine (23.05 mL, 0.21 mol) was added in a slow stream with a slight exotherm of 18−24 °C. The solution was cooled to −25 °C, and isobutyl chloroformate (25.27 mL, 0.195 mol) was added over a 2−3 min while keeping the temperature between −25 and −20 °C. A precipitate formed as the reaction mixture was stirred at −20 to −10 °C for 1 h. In a separate flask, a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (21.45 g, 0.22 mol) in methylene chloride (200 mL) was treated with *N*-methylmorpholine (24.15 mL, 0.22 mol) at room temperature. The reaction remained a slurry throughout as *N*-methylmorpholine hydrochloride formed. After 1 h, the hydroxylamine suspension was added over 30 min to the mixed anhydride with the temperature rising to 5 °C. The mixture was stirred at room temperature over the weekend. (Reaction was probably done upon addition.)

The reaction was quenched by the addition of a solution of citric acid (50 g) in water (200 mL). The organic layer was separated and washed with water, saturated sodium bicarbonate solution, and brine. The organic layer was dried over magnesium sulfate, filtered, and evaporated to an oil which was pumped at high vacuum to remove residual solvents. The crude yield was 61.7 g, 97 wt %, and 90−92% corrected for HPLC purity assay. The ^{1}H NMR showed the presence of an impurity which was thought to be the *N*,*O*-dimethylhydroxylamine *sec*-butyl carbamate. This was suitable for use in the next step without purification. $[\alpha]_D$:

(16) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1988**, *27*, 1241. Beneditti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071.
(17) Yamauchi, M. *Chem. Pharm. Bull.* **1993**, *41*, 2042.

Scheme 8



+21.8 (c = 1.0, CH_2Cl_2). HPLC: initial eluent, 55% A−45% B; final, 10% A−90% B. R_t: **3**, 2 min; **10**, 2.5 min. Chiral HPLC: 96.6% ee. (Starting BOC-AA was 96.6% ee.) Column: Diacel Chiralcel OD. Mobile phase: 90:10 hexanes/2-propanol. Flow rate: 1.5 mL/min. Detection: 210 nm. R_t: **10**, 3.5 min; *ent*-**10**, 3.0 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (q, 1), 6.93−6.85 (m, 3), 5.24 (m, 1), 4.91 (m, 1), 3.66 (s, 3), 3.15 (s, 3), 3.02 (abx, 1), 2.84 (abx, 1), 1.36 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): 172.1, 164.1, 155.3, 129.9, 125.3, 116.6, 113.9, 79.9, 61.8, 51.6, 38.7, 32.3, 28.5. LCMS exact mass measurement: calcd for $C_{16}H_{23}N_2O_4F$+Na+, 349.1540; measured, 349.1548.

[4-[1,3]Dioxan-2-yl-(1*S*)-(3-fluorobenzyl)-2-oxo-butyl]-carbamic Acid *tert*-Butyl Ester 11. *N*′-Methoxy-*N*′-methyl (*S*)-N-BOC-(3-fluorophenyl)alanine amide **10** (61.4 g, 0.188 mol) was dissolved in THF (300 mL) in a 1 L flask under nitrogen. Magnesium turnings (11.76 g, 0.484 mol) were added, and the mixture was cooled to −10 °C. Methylmagnesium chloride (62.6 mL, 3 M in THF, 0.188 mol) was added dropwise over 25 min with the temperature below −5 °C. The reaction was then stirred for about 10 min until the gas evolution stopped (methane) and the temperature was 0 °C. The reaction was allowed to warm to about 13 °C, and 2-(2-bromoethyl)-1,3-dioxane (5 mL out of 45.34 mL, 0.285 mol, 1.75 equiv) was added to initiate the Grignard reaction. The exotherm was controlled to <28 °C by controlled addition of the remaining bromide. The reaction was then stirred overnight at room temperature. If starting amide **10** remained in the reaction, additional bromide was added based on the amount seen by HPLC. As much as 2.6 equiv of bromide and magnesium have been required to fully consume the Weinreb amide starting material at lab scale.

The reaction was quenched by addition of a solution of ammonium chloride (165 g) in water (1 L), and ethyl acetate (400 mL) was added. The layers were stirred for 10 min and separated. The aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layers were washed with water (2 × 400 mL) and brine. The solution was dried with magnesium sulfate, filtered, and evaporated to a waxy, yellow solid. The solid was stirred with diisopropyl ether (IPE) (150 mL) for 30 min, and then hexanes (200 mL) were added and the slurry was stirred for 2 h. The solids were collected and washed with hexanes (2 × 100 mL). After drying, the solids weighed 49.66 g, 76% yield, based on starting Weinreb amide or 65% based on starting BOC-amino acid. Mp 107−108.5 °C. $[\alpha]_D$: − 36.8 (c = 1.0, MeOH). HPLC: initial eluent, 60% A−40% B; final, 10% A−90% B. R_t: **10**, 3.8 min; **11**, 5.9 min. Chiral HPLC: 99.82% product; 0.029% enantiomer; 0.15% Weinreb amide. Column: Diacel Chiralcel OD. Mobile phase: 90:10 hexanes/2-propanol. Flow rate: 1.5 mL/min. Detection: 210 nm. R_t: *ent*-**11**, 7.8 min; **11**, 6.9 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (m, 1), 6.85 (m, 3), 5.18 (d, 1), 4.52 (m, 2), 4.01 (m, 2), 3.68 (m, 2), 3.10 (m, 1), 2.87 (m, 1), 2.56 (m, 2), 2.00 (m, 1), 1.85 (m, 2), 1.37 (m, 10). ^{13}C NMR ($CDCl_3$, 100 MHz): 208.2, 164.2, 155.3, 139.1, 130.1, 125.2, 116.5, 114.0, 100.7, 80.0, 67.0, 60.2, 37.4, 34.4, 29.0, 28.5, 25.9. Anal. Calcd for $C_{20}H_{28}NO_5F$: C, 62.98; H, 7.398; N, 3.67. Found: C, 62.77; H, 7.52; N, 3.67.

[4-[1,3]Dioxan-2-yl-(1*S*)-(3-fluorobenzyl)-(2*R*)-hydroxybutyl]carbamic Acid *tert*-Butyl Ester 17. [4-[1,3]-Dioxan-2-yl-(1*S*)-(3-fluorobenzyl)-2-oxo-butyl]carbamic acid *tert*-butyl ester **11** (7.5 g, 19.7 mmol) and aluminum triisopropoxide (4.4 g, 21.6 mmol) were added to 2-propanol (60 mL), and the mixture was heated to reflux for 0.5 h. The reaction was cooled to room temperature with an ice water bath. At this point, two different workups were possible.

(A) The reaction was diluted first with 1 N HCl (120 mL), and then water was added to a ca. 400 mL volume. After stirring for 1 h, the solids were collected, washed with water, and dried in vacuo. This provided the desired alcohol, 6.63 g, 88% yield. The material was slightly colored but suitable for the next reaction.

(B) The cooled reaction mixture was diluted with 2-propanol (60 mL) and stirred for 1 h. The solids were collected and washed with 2-propanol (3 × 15 mL) and hexanes and air-dried. The yield was 5.8 g, 77% of white solids with only trace impurities. Mp 180.5−181.5 °C. $[\alpha]_D$: − 16.1 (c = 1.0, CH_2Cl_2). HPLC: initial eluent, 60% A−40% B; final,

10% A−90% B. R_t: **11**, 5.9 min; **17**, 3.1 min; (*R*,*S*)-diastereomer, 3.6 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (m, 2), 6.98 (d, 1), 6.94−6.86 (m, 2), 4.60 (m, 2), 4.15 (m, 2), 3.78 (m, 3), 3.61 (s, 1), 3.46 (s, 1), 2.91 (m, 1), 2.75 (m, 1), 2.16 (m, 1), 1.84−1.55 (m, 4), 1.34 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): 164.2, 156.0, 129.9, 125.3, 116.5, 113.2, 102.1, 79.6, 73.7, 67.2, 56.3, 35.6, 32.1, 28.5, 27.9, 25.8.

Anal. Calcd for $C_{20}H_{30}NO_5F$: C, 62.643; H, 7.885; N, 3.65. Found: C, 62.60; H, 8.00; N, 3.64.

Methanesulfonic Acid (2*S*)-*tert*-Butoxycarbonylamino-1-(2-[1,3]dioxan-2-yl-ethyl)-(3*R*)-(3-fluorophenyl)propyl Ester 18. [4-[1,3]Dioxan-2-yl-(1*S*)-(3-fluorobenzyl)-(2*R*)-hydroxybutyl]carbamic acid *tert*-butyl ester **17** (30 g, 78.3 mmol) was added to pyridine (100 mL) under nitrogen. Methanesulfonyl chloride (6.67 mL, 86 mmol) was added dropwise over 35 min with a mild exotherm from 20 to 27 °C. The reaction mixture was stirred for 2.5 h at which time TLC showed the conversion was complete. The reaction was cooled to 15 °C in an ice water bath, and water (250 mL) was added slowly with a slight initial exotherm. The resulting slurry was stirred at 15 °C for 20 min, and the solids were collected and washed with water. The solids were air-dried and then slurried in isopropyl ether (275 mL) for 5 h. The product was filtered and washed with IPE and dried. The yield was 34 g, 94%. Mp 121−22 °C. $[\alpha]_D$: − 4.2 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (m, 1), 6.98 (d, 1), 6.91 (m, 2), 4.86 (s, 1), 4.80 (d, 1), 4.10 (m, 3), 3.75 (t, 1), 3.07 (s, 3), 2.95 (dd, 1), 2.64 (m, 1), 2.05 (m, 1), 1.87−1.68 (m, 4), 1.32 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): 164.2, 161.8, 155.5, 140.1, 130.1, 125.0, 116.3, 113.7, 101.1, 84.4, 79.9, 67.1, 54.0, 38.9, 35.5, 31.0, 28.4, 25.9, 25.5. Anal. Calcd for $C_{21}H_{32}NO_7FS$: C, 54.647; H, 6.987; N, 3.035. Found: C, 54.32; H, 7.08; N, 2.96.

5*S*-(2-[1,3]Dioxan-2-yl-ethyl)-(4*S*)-(3-fluorobenzyl)oxazolidin-2-one 19. Methanesulfonic acid (2*S*)-*tert*-butoxycarbonylamino-1-(2-[1,3]dioxan-2-yl-ethyl)-(3*R*)-(3-fluorophenyl)propyl ester **18** (29 g, 62.0 mmol) was dissolved in dry pyridine (50 mL) under nitrogen, and the mixture was heated in an oil bath to 80 °C. After 2 h, the reaction solution was cooled to rt, and ethyl acetate and water were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 3 N HCl (2 × 300 mL), water, and brine. The solution was dried over sodium sulfate. The solution was filtered and evaporated in vacuo to provide the desired product as an oil in quantitative yield, 20.1 g. This was suitable for use in the next step. $[\alpha]_D$: − 47.7 (c = 1.0, MeOH). HPLC: initial eluent, 70% A−30% B; final, 10% A−90% B. R_t: **19**, 5.1 min; (*R*,*S*)-diastereomer, 5.5 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (m,1), 6.91 (m, 2), 6.84 (d, 1), 6.60 (s, 1), 4.45 (s, 1), 4.26 (s, 1), 3.98 (m, 2), 3.67 (m, 3), 2.78 (m, 2), 1.95 (m, 1), 1.71−1.53 (m, 4), 1.28 (d, 1). ^{13}C NMR ($CDCl_3$, 100 MHz): 164.3, 161.9, 159.4, 138.7, 130.6, 125.2, 116.3, 114.2, 101.3, 81.4, 67.0, 59.0, 41.2, 30.3, 29.0, 25.9. LCMS exact mass measurement: calcd for $C_{16}H_{20}NO_4F$+Na+, 332.1274; measured, 332.1262.

3-[(4*S*)-(3-Fluorobenzyl)-2-oxo-oxazolidin-(5*S*)-yl]propionitrile 20. (5*S*)-(2-[1,3]Dioxan-2-yl-ethyl)-(4*S*)-(3-fluorobenzyl)oxazolidin-2-one **19** (19.2 g, 62.13 mmol) was combined with hydroxylamine hydrochloride (5.61 g, 80.77 mmol) and *p*-toluenesulfonic acid (1.18 g, 6.43 mmol) in ethanol (200 mL) and heated to reflux overnight. The reaction was concentrated in vacuo, and the resulting oil was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with water and brine and concentrated to an oil in vacuo. The oil was stirred with IPE (80 mL) for 2 h during which time a solid formed. The suspension was diluted with an equal volume of hexanes. The solids were collected by filtration, washed with hexanes, and dried in vacuo to yield the desired nitrile, 13.0 g, 90%. mp 68.5−70 °C. $[\alpha]_D$: − 67.3 (c = 1.0, MeOH). HPLC: initial eluent, 70% A−30% B; final, 10% A−90% B. R_t: **19**, 5.1 min; **20**, 3.3 min; **21**, 6.8 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 1), 6.97 (m, 2), 6.91 (d, 1), 6.41 (s, 1), 4.36 (m, 1), 3.71 (m, 1), 2.95−2.82 (m, 2), 2.46 (t, 2), 1.93 (m, 1), 1.76 (m, 1). ^{13}C NMR ($CDCl_3$, 100 MHz): 164.5, 162.0, 158.4, 137.9, 131.0, 125.1, 118.7, 116.3, 114.7, 79.5, 58.8, 41.1, 30.7, 13.6. LCMS exact mass measurement: calcd for $C_{13}H_{13}N_2O_2F$+Na+, 249.1039; Measured, 249.1027.

[(2*S*)-(3-Fluorophenyl)-(1*S*)-(5-oxotetrahydrofuran-2-yl)ethyl]carbamic Acid *tert*-Butyl Ester 1. 3-[(4*S*)-(3-Fluorobenzyl)-2-oxo-oxazolidin-(5*S*)-yl]propionitrile **20** (10.7 g, 43.15 mmol) was dissolved in 50% aqueous ethanol (100 mL) with sodium hydroxide (6.9 g, 172 mmol), and the solution was heated to reflux overnight. The reaction was cooled to rt. The solution was concentrated in vacuo, more water was added, and the solution was concentrated again to remove ethanol. The final oil was diluted to 75 mL with water. The aqueous solution was cooled in an ice bath, and concentrated HCl was added to adjust the pH to 10. Tetrahydrofuran (50 mL) was added to the reaction, and di-*tert*-butyl dicarbonate (12.22 g, 56 mmol) was added. The pH was monitored, and additional sodium hydroxide pellets were added to maintain a pH > 9.0. After stirring overnight, the THF was evaporated in vacuo and the aqueous solution was extracted with ethyl acetate twice. This was found to contain excess di-*tert*-butyl dicarbonate. The aqueous layer was acidified with acetic acid (10 mL) and extracted twice with ethyl acetate. The combined ethyl acetate layers were evaporated, and the solid residue was dissolved in toluene (125 mL) and acetic acid (5 mL) and heated to reflux for 3 h. This was cooled and diluted with ethyl acetate (125 mL). Water and excess sodium bicarbonate were added to neutralize the acetic acid. The organic layer was evaporated in vacuo. The desired lactone was isolated as a solid by slurring in a mixture of isopropyl ether and hexanes (1:1); 12.58 g, 90.3% yield. Mp 108−108.5 °C. $[\alpha]_D$: − 26.1 (c = 1.0, MeOH). HPLC: initial eluent, 60% A−40% B; final, 10% A−90% B. R_t: **1**, 3.4 min; **20**, 0.9 min; (*R*,*S*)-diastereomer, 3.1 min. HPLC: 99.8% desired diastereomer. Chiral HPLC: Chiralpak AS. Mobile phase: 1000:30 hexane/ethanol. Flow rate: 1.5 mL/min. Detection: 210 nm. R_t: **1**, 12.5 min; *ent*-**1**, 9.8 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (m, 1), 6.98 (d, 1), 6.90 (m, 2), 4.82 (d, 1), 4.46 (t, 1), 3.97 (q, 1), 2.88 (m, 2), 2.49 (m, 2), 2.11 (m, 2), 1.34 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): 177.4, 164.3, 161.9, 156.1, 140.0, 130.3, 125.2, 116.4, 113.9, 80.4, 54.1, 39.3, 28.9, 28.4, 24.3. Anal. Calcd for $C_{17}H_{22}NO_4F$: C, 63.14; H, 6.86; N, 4.33; F, 5.88. Found: C, 62.98; H, 6.85; N, 4.14; F, 5.95.

(5*S*)-*tert*-Butoxycarbonylamino-6-(3-fluorophenyl)-4-oxohexanoic Acid 3-Hydroxypropyl Ester 15. [4-[1,3]-Dioxan-2-yl-(1*S*)-(3-fluorobenzyl)-2-oxo-butyl]carbamic acid *tert*-butyl ester **11** (10 g, 0.026 mol) was dissolved in ethyl acetate (100 mL) and cooled to −15 °C. Ozone was bubbled through the solution for 55 min at which time the starting material was gone according to TLC [model G1-1 PCI O_3 generator; run at 95% O_3 capacity (where 100% equals a 3% ozone stream in oxygen), 18 psi with air flow at 6SCFH]. The solution was purged with O_2 for several minutes, and then water (50 mL) was added followed by sodium bisulfate (2.5 g) and the biphasic mixture was stirred for 30 min at which time it was negative to starch iodide paper. The organic layer was separated, washed with water (2×) and with brine, and dried over sodium sulfate for 3 h. The solution was filtered and evaporated to a yellow oil. This was evaporated with methylene chloride several times and used as is for the next reaction. A sample was isolated by chromatography. Mp 79−80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 1), 6.97 (m, 3), 5.16 (d, 1), 4.55 (q, 1), 4.27 (t, 2), 3.71 (t, 2), 3.18 (abx, 1), 2.94 (abx, 1), 2.81 (m, 2), 2.63 (m, 2), 2.15 (bs, 1), 1.89 (t, 2), 1.43 (s, 9).

A smaller scale ozonolysis was run as above until the initial product was oxidized to the more polar material. The reaction was worked up as described above to provide a sample of the carboxylic acid **16** as a white solid. Mp 101.5−103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (m, 1), 6.97 (m, 3), 5.17 (d, 1), 4.58 (q, 1), 4.38 (t, 2), 3.19 (abx, 1), 2.93 (abx, 1), 2.82 (m, 2), 2.72 (t, 2), 2.64 (t, 2), 1.43 (s, 9). Mass spectrum: *m*/*e* 411 (M^+).

[(2*S*)-(3-Fluorophenyl)-(1*S*)-(5-oxotetrahydrofuran-2-yl)ethyl]carbamic Acid *tert*-Butyl Ester 1. (5*S*)-*tert*-Butoxycarbonylamino-6-(3-fluorophenyl)-4-oxohexanoic acid 3-hydroxypropyl ester **15** (10.1 g, 0.026 mol) was dissolved in tetrahydrofuran (100 mL) and treated with hexamethyldisilazane (5.8 mL, 0.027 mol) dropwise over 4 min. The reaction was heated to a gentle reflux while the N_2 outflow was monitored for ammonia with a moist pH paper. After 2.5 h, the ammonia was negligible and the reflux was increased for 30 min to remove excess reagent. The reaction was cooled to −78 °C, and *N*-Selectride (31.5 mL, 0.0315 mol) was added dropwise over 35 min. After 1 h at − 78 °C, acetic acid (10 mL) in THF (30 mL) was added dropwise. The reaction was allowed to warm to −10 °C, and ethyl acetate (300 mL) and water (300 mL) were added. This was stirred for 10 min, and the layers were separated. The ethyl acetate layer was washed twice with water. The ethyl acetate solution was stirred with aqueous sodium perborate (3 equiv relative to the *N*-Selectride) for several hours. The layers were separated, and the organic layer was washed with water and with brine, dried over magnesium sulfate, and concentrated to an oil in vacuo. The crude oil was dissolved in toluene (100 mL) with acetic acid (10 mL), and the solution was refluxed overnight.

The toluene solution was cooled to room temperature, and ethyl acetate (100 mL), water (100 mL), and 6 N HCl (15 mL) were added; the mixture was stirred for 30 min. The organics were separated and washed with water (2×), saturated sodium bicarbonate (2×), water, and brine. The solution was dried over magnesium sulfate and evaporated to an oil. The oil was dissolved in a 1:1 mixture of ethyl acetate and hexanes and passed through a silica gel pad with the same solvent mixture. The product containing fractions were combined (3−6 of 75−100 mL fractions) and evaporated to an oil which started to crystallize. IPE (30 mL) was added, the slurry was stirred for 10 min, and hexanes (30 mL) were added. After stirring for an additional 10 min, the solids were collected and washed with hexanes to provide the lactone as a white solid; 5 g, 59% yield. This material was analytically pure by CHN assay and NMR. It was identical with that described above.

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