A New Magnesium-Catalyzed Doubly Diastereoselective *anti*-Aldol Reaction Leads to a Highly Efficient Process for the Total Synthesis of Lactacystin in Quantity

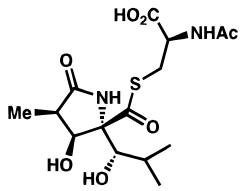
E. J. Corey,* Weidong Li, and Gregory A. Reichard

Contribution from the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

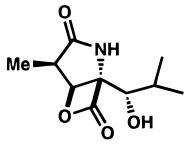
Received October 2, 1997

Abstract: A new process is described for metal-catalyzed doubly diastereoselective Mukaiyama aldol coupling of a chiral tertiary α-amino aldehyde and an achiral silyl enol ether to form selectively an *anti*-aldol product. The metal requirement is strict, since of several salts tested only MgI_2 functions as an effective catalyst. The MgI_2-catalyzed aldol greatly facilitates the total synthesis of lactacystin (**1**) and the corresponding β-lactone (**2**), microbial products which are potent and selective inhibitors of proteasome function, cell cycle progression, and gene regulation. The method also allows the synthesis of analogues of **1** in which the 7β-methyl group of lactacystin is replaced by higher alkyl or aralkyl groups. Detailed experimental procedures are presented for the optimized synthesis of lactacystin on the scale required to meet the current needs of many hundreds of biological laboratories.

Lactacystin (**1**) is a microbial product which was obtained by Ōmura et al. as a result of the screening of several thousand microbial cultures for the capacity to induce differentiation of the neuro 2A (neuroblastoma) cell line.[1,2] It was originally thought that lactacystin might be a small molecular mimic of nerve growth factor.[3−6] Stimulated by the unusual structure of **1**, the remarkable biological activity, and the scarcity of natural material, several research groups undertook the total syntheses.[7−10] The first total synthesis of **1**, in these laboratories in 1992[7] (and a subsequent modified version[11]), made available **1** (and radiolabeled **1**) and was instrumental in research which demonstrated that the biological activity of lactacystin is due to potent, highly selective, and irreversible inhibition of proteasome-mediated peptidase activity.[12] Conclusive evidence was obtained that the β-lactone **2**[12,13] is the effective agent and that it acts by acylation of the amino terminal threonine residue of



Lactacystin, 1



2

a proteasome subunit. This result was confirmed by X-ray crystallographic studies at 2.4 Å resolution.[14,15] Proteasomes are large, hollow cylindrical protein structures (mass 700−900 kD, length roughly 150 Å, and diameter roughly 100 Å) composed of four stacked rings of seven protein subunits (Figure 1). They occur in prokaryotes and eukaryotes and serve as machines for the degradation of ubiquitin-conjugated proteins.[16] Proteasomes thus mediate the turnover of various proteins including misfolded or denatured proteins[17] and many other proteins including those involved in cell cycle progression[18] and the regulation of gene transcription.[19] In consequence, lactacystin and the β-lactone **2** have emerged as important new tools for the study of protein biochemistry and cell biology. Synthetic lactacystin has been in use in many hundreds of biological laboratories. The rapidly growing demand for lactacystin has provided an incentive for a more efficient and economical

(1) Ōmura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113.
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S0002-7863(97)03444-6 CCC: $15.00
Published on Web 02/28/1998

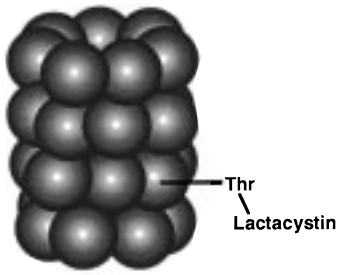
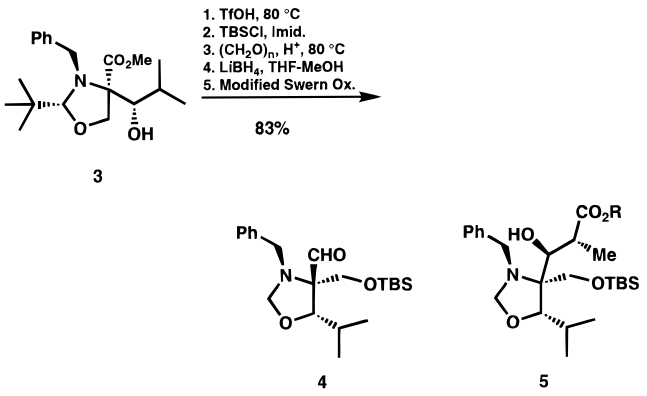


Figure 1.

process for its synthesis. In this paper we describe a type of metal-catalyzed, stereocontrolled aldol reaction which has been successfully applied to lactacystin synthesis. This new advance and other improvements in the originally described synthesis,[7] which are detailed herein, greatly simplify the preparation of multigram or larger amounts of lactacystin.

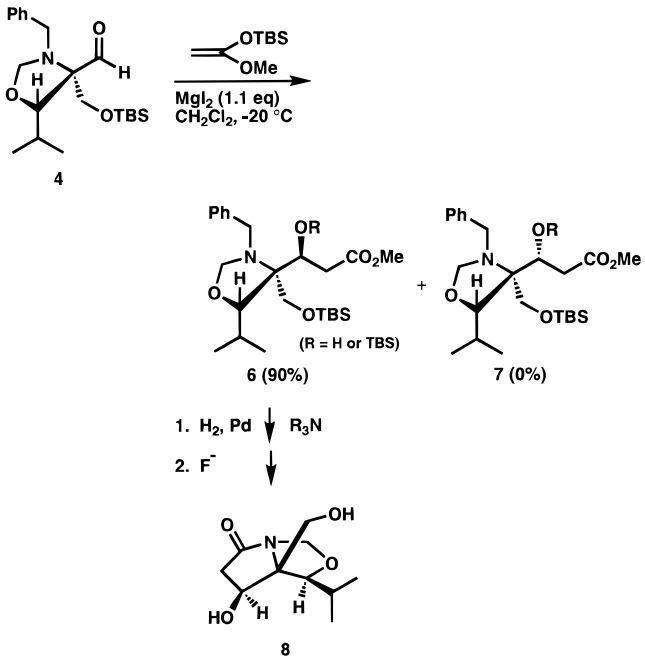
Our first synthesis of **1** utilized as an early intermediate the crystalline aldol **3** which is available in quantity from (*S*)-serine methyl ester hydrochloride in three steps (without chromatography).[7] In the next stage of the process **3** was converted as shown to the aldehyde **4** which serves as a component in a second critical aldol coupling with a propionate ester enolate (or equivalent) to produce an *anti*-aldol product, **5**. On a larger



scale (ca. 70 g) the synthesis of **4** from **3** has been improved so that it can be carried out simply and in excellent overall yield (for details, see the Experimental Section). In the Swern oxidation step leading to the aldehyde **4**, it was advantageous to conduct the reaction by the addition of cold, preformed Swern reagent (from DMSO and oxalyl chloride in CH_2Cl_2 at −78 °C) to a mixture of the primary alcohol precursor and triethylamine in CH_2Cl_2 solution at −78 °C. The normal mode of Swern oxidation produced a number of byproducts. However, the initially developed[7] aldol process to form **5**, R = 2,6-dimethylphenyl, using the Pirrung−Heathcock procedure,[20] was much less satisfactory because the best formyl face selectivity that could be obtained was ca. 2:1, and after a cumbersome chromatographic separation the yield of **5**, R = 2,6-dimethylphenyl, was at best 50%. Although improved formyl face selectivity and good anti diastereoselectivity could be realized using M. Braun's chiral controller and the Cp_2ZrCl enolate,[11,21]this aldol process was also not satisfactory for the production of **5** on a larger scale since a 4-fold excess of the chiral enolate component was required for complete conversion and since the next reaction with the bulky Braun ester was too slow to be practical. In addition, a cumbersome silica gel column chromatography was required to obtain pure aldol **5**.[11]

(20) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.
(21) Braun, M.; Sacha, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *10*, 1318.

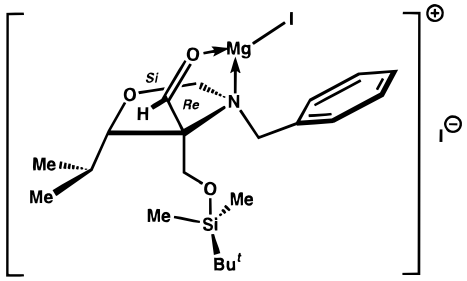
Because of the problems enumerated above with the aldol step **4** → **5**, we turned to the possibility of using metal chelation between the basic *N*-benzyl nitrogen and the formyl oxygen of **4** to activate a Mukaiyama-type aldol process and to enhance formyl face selectivity. To the best of our knowledge, no efficient double-face selective, Mukaiyama aldol reactions of an achiral silyl enol ether have previously been reported.[22,23] M. T. Reetz et al. have investigated a single case of a Mukaiyama aldol reaction, that of chiral *N*,*N*-dibenzylalanal with $TiCl_4$ and the trimethylsilyl enol ether of phenyl acetate, and observed a poor yield of aldol adduct (25%) with 95:5 monodiastereoselectivity.[24,25] Nonetheless, we investigated extensively the reaction of **4** with $TiCl_4$ and other Lewis acids with the *tert*-butyldimethylsilyl (TBS) enol ether of ethyl acetate to ascertain feasibility of a chelate-controlled aldol reaction. The use of $TiCl_4$ as catalyst in CH_2Cl_2 at −78 °C resulted in slow decomposition of the aldehyde **4** without formation of any aldol product, as determined by thin-layer chromatographic (TLC) analysis. Interestingly, experiments with the bicoordinate Lewis acids $SnCl_4$, $ZnCl_2$, and $Cu(OTf)_2$ in CH_2Cl_2 in the aldol reaction of **4** with ethyl acetate enol *tert*-butyldimethylsilyl ether led neither to substrate decomposition nor to reaction even at 0 and 23 °C. These results, especially with cupric triflate, seemed to indicate that the benzyl-protected nitrogen of **4** was probably too sterically hindered to coordinate to the metal. For this reason (among others), MgI_2 was tried as catalyst. It was extremely gratifying that this experiment produced the desired aldol adduct **6** in 90% yield with *complete* diastereoselectivity. None of the isomeric aldol product **7** could be detected by ^1H NMR or TLC analysis of the crude reaction product. The stereochemistry of the aldol adduct **6** was proved by two-step conversion to the crystalline dihydroxy γ-lactam **8**, the structure of which was



shown by X-ray diffraction analysis.[26] The use of $MgBr_2$ as

(22) (a) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
(23) For a general review of functional group mediated diastereoselective reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(24) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
(25) See also: Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.

catalyst in the aldol reaction of **4** also produced **6**, but at a slower rate and in lower yield. We had observed earlier the superiority of MgI_2 over $MgBr_2$ in catalytic enantioselective Diels−Alder reactions with a chiral bisoxazoline as ligand,[27] which can reasonably be attributed to the more facile dissociation of I^- from species such as L_2MgI_2.[28] The preferred stereochemical course of the transformation **4** → **6** had been predicted from the expectation that the reaction would occur via a chelate of IMg^+ with the formyl oxygen and the α-*tert*-amino group (**9**)[28]

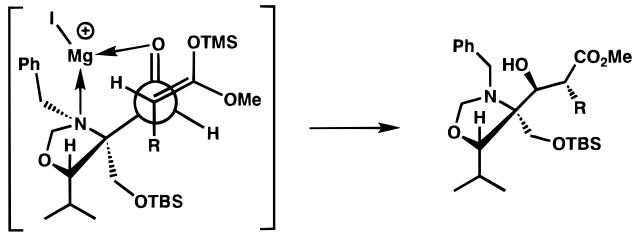


9

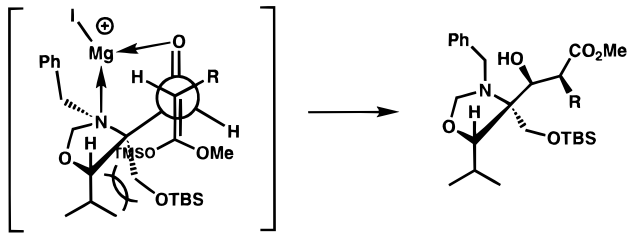
by attack of the nucleophilic silyl enol ether on the *si* face of the formyl carbon. The *re* face of the formyl group in **9** is sufficiently screened by the *N*-benzyl and OTBS groups to favor highly selective formation of aldol product **6**.

The corresponding aldol reaction of aldehyde **4** with the (*E*)-trimethylsilyl enol ether of methyl propionate and MgI_2 proceeded with high *si*/*re* formyl face selectivity (ca. 40:1) and also with very good double diastereoselectivity. Thus, with a 10:1 mixture of (*E*)- and (*Z*)-trimethylsilyl enol ethers of methyl propionate the desired major aldol product **10** was obtained in 9:1 predominance over the diastereomer **11**. Possibly the ratio of **10** to **11** would be even higher starting with pure (*E*)-silyl enol ether. The aldol products **10** and **11**, which were readily separated by flash chromatography on silica gel, were isolated in yields of 77% and 8%, respectively. A very small amount (ca. 2%) of the double diastereomer of **10**, the (2*S*,3*R*)-aldol **12**, was also isolated. The stereochemistry of the major aldol product **10** was established by subsequent conversion to lactacystin (as well as to known synthetic intermediates in the process; see Scheme 1).

The specific effectiveness of MgI_2 for the doubly diastereoselective conversion of **5** to the *anti*-aldol product **10** using an *achiral* silyl enol ether is noteworthy and novel. A variety of other types of anti-selective aldol reactions can be found in the work of Heathcock,[29] Gennari,[30] Paterson,[31] and Evans.[32] We believe that the preferential formation of **10** can be explained most simply on the basis of the IMg^+ chelate structure **9** which allows a low-energy pathway via the transition-state assembly depicted in **13**. This arrangement involves a synclinal relationship between the formyl CO and enol ether C=C about the bond which is being formed in the aldol process. Structure **13** involves considerably less steric repulsion than alternative geometries for attachment of the silyl enol ether to the IMg^+ chelate, such as the antiperiplanar arrangement shown in **14**.



13 *(synclinal)* **10** *(anti aldol)*



14 *(antiperiplanar)* **11** *(syn aldol)*

Mukaiyama-like aldol reactions via an "open transition state" (i.e., not six-membered pericyclic processes) have generally been considered to occur preferentially via antiperiplanar geometry.[29] Clearly, the antiperiplanar pathway via **14**, which would lead to a *syn*-aldol product, is disfavored because of the steric repulsions which are shown.

The effectiveness of the doubly diastereoselective aldol reaction was undiminished with increasing scale. In one experiment conducted in a 1 L flask, 23 g of the aldehyde **4** was converted to 21.8 g of the *anti*-aldol product **10**. The rest of the sequence for producing synthetic lactacystin could also be performed readily and efficiently on a larger scale, after careful experimentation to optimize procedures. Scheme 1 summarizes the conditions and yields for the remaining eight steps of the synthesis of **1** via the β-lactone precursor **2**. In the conversion of **15** to **16**, the modified Swern oxidation procedure described for the preparation of aldehyde **4** gave much better results than the conventional Swern procedure. The modified Swern oxidation was conducted by adding the preformed Swern reagent to a solution of **15** and Et_3N in CH_2Cl_2, all at −78 °C. Under these conditions the reaction was both position selective for the primary alcohol and very clean. It is apparent that the synthesis of **1** described herein can be used without difficulty to prepare centigram or kilogram amounts of lactacystin or the β-lactone **2**.

Doubly diastereoselective MgI_2-catalyzed Mukaiyama aldol reactions were also achievable with the trimethylsilyl enol ethers of methyl butyrate, methyl valerate, methyl isobutyrate, and methyl hydrocinnamate to form the *anti*-aldols **17a**−**17d** in the indicated yields. These intermediates were then transformed

(26) (a) Crystal structure data for **8**: $C_{10}H_{17}NO_4$, orthorhombic, $P2_12_12_1$, a = 6.6289(2) Å, b = 8.5550(2) Å, c = 19.5992(3) Å; α = β = γ = 90°, Z = 4, $R_1[I > 2\sigma(I)]$ = 0.0449. (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, U.K.

(27) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807.

(28) The IMg^+ chelate **9** can be expected to be much more reactive than the corresponding MgI_2 chelate; see: Hayashi, Y.; Jeffrey, J. R.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502. However, both chelates would lead to the observed preference for aldol product **6** over **7**.

(29) (a) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. (b) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213.

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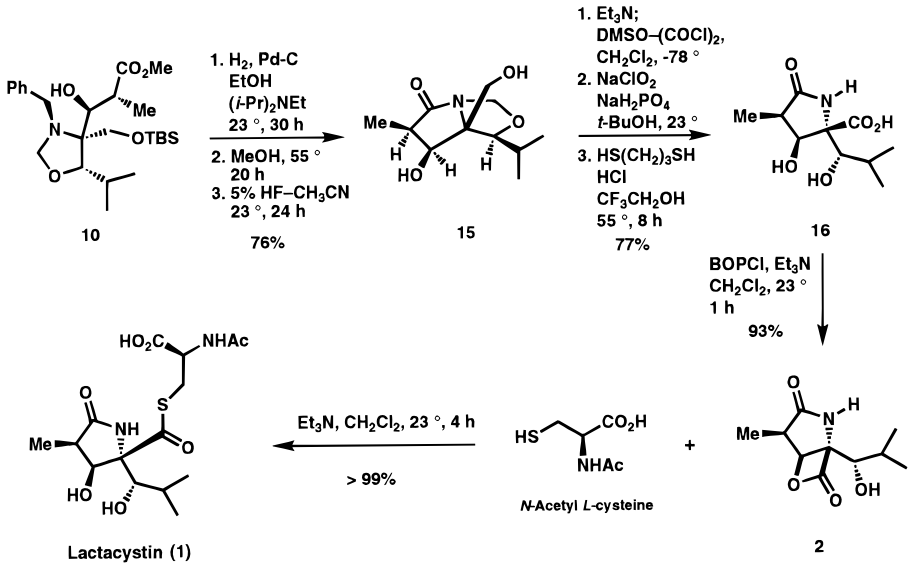
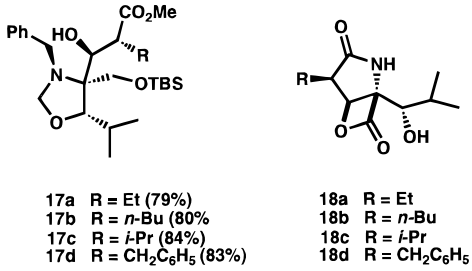
(32) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 9598.

Scheme 1



by a sequence analogous to that outlined in Scheme 1 to the corresponding lactacystin β-lactone analogues **18a**−**18d**, all of



17a R = Et (79%)
17b R = *n*-Bu (80%
17c R = *i*-Pr (84%)
17d R = $CH_2C_6H_5$ (83%)

18a R = Et
18b R = *n*-Bu
18c R = *i*-Pr
18d R = $CH_2C_6H_5$

which showed good biological activity. The 7-ethyl analogue of lactacystin has been found to be even more effective than lactacystin in blocking the progression of the malaria parasite *Plasmodium berghei* to the infective exoerythrocytic and erythocytic states.[33]

Experimental Section

General Procedures. All anhydrous solvents (THF, CH_2Cl_2, Et_2O, CH_3CN, benzene) were dried by standard techniques and freshly distilled before use. All reactions were carried out under N_2 and monitored by thin-layer chromatography (TLC). All organic extracts were washed with brine before being dried over $MgSO_4$. All oily products were purified by flash silica gel chromatography (SGC) eluting with a solvent mixture of hexane and ethyl acetate. Melting points (mp) were determined using a Fisher-Johns hot stage apparatus and are uncorrected. Specific optical rotations ([α]) were measured using a Perkin-Elmer 241 polarimeter at 23 °C with a sodium lamp (D line, 589 nm). FTIR spectra were recorded on a Nicolet 5 ZDX FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM series instrument. Mass spectral analyses and high-resolution mass spectral analyses (HRMS) were measured on a JEOL model AX-505 or SX-102 spectrometer by means of EI, CI, or FAB.

Conversion of β-Hydroxy Ester 3 to *N*-Benzyl Amino Aldehyde 4. To a stirred solution of crystalline β-hydroxy ester **3** (73.0 g, 208.9 mmol) in 95% methanol−water (480 mL) was added dropwise trifluoromethanesulfonic acid (73.0 mL, 835.6 mmol, 4.0 equiv) at 23 °C (cooling with a water bath). The resulting solution was heated to 80−85 °C in an open flask by an oil bath with efficient stirring, and the methanol was removed by gradual distillation over 6.5 h. The reaction mixture was poured into a mixture of half-saturated aqueous $NaHCO_3$ solution (650 mL) and 20% aqueous K_2CO_3 solution (50 mL) carefully and diluted with EtOAc−ether (v/v 2:1, 2000 mL). The organic layer was washed with water (3 × 500 mL) and brine (500 mL) and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded *N*-benzyl-(*S*)-α-(hydroxymethyl)-(*S*)-β-hydroxyleucine methyl ester as a colorless oil, which was used without further purification after azeotropic drying with anhydrous benzene (2 × 250 mL). To a stirred solution of this product in DMF (260 mL) were added imidazole (21.3 g, 313.2 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl chloride (34.5 g, 228.9 mmol, 1.1 equiv). After 25 h of stirring at 23 °C, the reaction mixture was diluted with ethyl acetate−ether (v/v 2:1, 2000 mL), washed with 0.5 M aqueous citric acid solution (4 × 120 mL), water (5 × 400 mL), and brine (500 mL), and dried. After evaporation of the solvent, the resulting oil was dried by azeotropic distillation with benzene (2 × 500 mL) to give a colorless oil, which without further purification was taken up into anhydrous benzene (520 mL) and treated with powdered paraformaldehyde (60.0 g, 2.0 mol, 10 equiv) and *p*-TsOH·H_2O (1.90 g, 10.0 mmol, 5 mol %). The resulting suspension was heated to 80 °C for 0.5 h with efficient stirring, cooled to room temperature, and filtered through a pad of silica gel. The resulting filtrate was diluted with ether (2000 mL), washed with 5% aqueous $NaHCO_3$ solution (250 mL), water (3 × 400 mL), and brine (500 mL), and dried ($MgSO_4$) overnight. Evaporation of the solvent under reduced pressure afforded the 1,3-oxazolidine derivative of *N*-benzyl-(*S*)-α-(((*tert*-butyldimethylsilyl)oxy)methyl)-(*S*)-β-hydroxyleucine methyl ester as a colorless oil, which was dried by azeotropic distillation with benzene (2 × 500 mL) and taken up into THF (800 mL). This solution was treated with a 2 M lithium borohydride solution of THF (Aldrich, 200 mL, 400 mmol, 2.0 equiv) with stirring at 23 °C and then with methanol (50 mL) (cooling with a water bath to 25 °C). After 15 h of stirring, more lithium borohydride (2 M in THF, 200 mL, 400 mmol) was added followed by more methanol (25 mL). After additional stirring for 5 h, the reaction mixture was treated with water (500 mL) and diluted with ethyl acetate−ether (v/v 2:1, 3000 mL). The organic layer was washed with water (3 × 500 mL) and brine (500 mL) and dried. After evaporation of the solvent in vacuo, the primary alcohol corresponding to aldehyde **4** was obtained as a colorless oil (ca. 76 g), which was dried by azeotropic distillation with benzene (3 × 300 mL). A solution of this product in CH_2Cl_2 (1000 mL) at −78 °C was treated with triethylamine (291.3 mL, 2.09 mol, 10 equiv) and then with a cold (−78 °C) CH_2Cl_2 solution (850 mL) of Swern reagent prepared from oxalyl chloride (54.8 mL, 0.63 mol, 3.0 equiv) and DMSO (59.7 mL, 0.84 mol, 4.0 equiv) at −78 °C over 10 min. The resulting reaction mixture was stirred for 2 h and allowed to warm slowly to 0 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (600 mL) and with ether−EtOAc (v/v 4:1, 2000 mL). The organic phase was

(33) Gantt, S. M.; Myung, J. M.; Briones, M. R. S.; Li, W. D.; Corey, E. J.; Omura, S.; Nussenzweig, V.; Sinnis, P. *J. Clin. Invest.*, submitted for publication.

washed with water and brine and dried. The crude oil was purified by flash SGC (eluting with 5% EtOAc in hexane) to give aldehyde **4** (65.5 g, 83%) as a waxy solid, mp 42 °C; R_f 0.60 (Hex−EtOAc 4:1); $[\alpha]^{23}_D$ −26.4° (*c* 1.18, CH_2Cl_2); FTIR (film) ν_{max} 2957, 2929, 2857, 1726, 1472, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3 H, CH_3Si), 0.13 (s, 3 H, CH_3Si), 0.80 (d, 3 H, J = 6.6 Hz, $(CH_3)_2CH$), 1.02 (s, 9 H, $C(CH_3)_3$), 1.05 (d, 3 H, J = 6.6 Hz, $(CH_3)_2CH$), 2.07 (m, 1 H, $CH(CH_3)_2$), 3.76 (d, 1 H, J = 9.6 Hz, OCHCH), 3.84 (d, 1 H, J = 13.6 Hz, CH_2Ph), 3.93 (d, 1 H, J = 13.6 Hz, CH_2Ph), 3.98 (d, 1 H, J = 11.5 Hz, CH_2OSi), 4.11 (d, 1 H, J = 11.5 Hz, CH_2OSi), 4.48 (s, 1 H, NCH_2O), 4.50 (s, 1 H, NCH_2O), 7.28−7.34 (m, 5 H, Ph-H), 9.42 (s, 1 H, CHO) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.9, −5.7, 18.0, 19.3, 20.2, 25.7, 28.7, 50.9, 60.2, 71.8, 86.1, 87.1, 127.3, 128.2, 128.4, 138.6, 200.8 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{21}H_{35}NO_3Si]^+$ 378.2464, found for $[M + H]^+$ 378.2455. Data for the primary alcohol corresponding to aldehyde **4**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H, CH_3Si), 0.99 (s, 9 H, *t*-BuSi), 1.07 (d, 3 H, J = 6.6 Hz, $(CH_3)_2$-CH), 1.11 (d, 3 H, J = 6.6 Hz, $(CH_3)_2CH$), 2.06 (br m, 1 H, $CH(CH_3)_2$), 3.12 (br s, OH), 3.67 (br d, 1 H, J = 11.3 Hz, CH_2OH), 3.73 (d, 1 H, J = 9.1 Hz, OCHCH), 3.76 (d, 1 H, J = 11.3 Hz, CH_2OH), 3.82 (d, 1 H, J = 13.4 Hz, CH_2Ar), 3.87 (ABq, 2 H, J = 10.8 Hz, CH_2OSi), 4.10 (d, 1 H, J = 13.4 Hz, CH_2Ar), 4.40 (s, 1 H, NCH_2O), 4.43 (s, 1 H, NCH_2O), 7.20−7.45 (m, 5 H, ArH) ppm; FABMS (NBA + NaI) *m*/*z* 402 $[M + Na]^+$ (14%), 380 $[M + H]^+$ (65%), 348 $[M - CH_2OH]^+$ (100%); HRMS (CI, NH_3) *m*/*z* calcd for $[C_{21}H_{38}NO_3Si]^+$ 380.2621, found for $[M + H]^+$ 380.2634.

Conversion of Aldehyde 4 to Aldol 10 by MgI_2-Mediated Mukaiyama Aldol. To a stirred suspension of anhydrous MgI_2 (from Aldrich, 97%, 18.6 g, 66.9 mmol, 1.1 equiv) in CH_2Cl_2 (550 mL) was added a solution of aldehyde **4** (23.0 g, 60.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture was stirred for 20 min at that temperature and cooled to −10 °C, whereupon the trimethylsilyl enol ether of methyl propionate (14.6 g, 91.3 mmol)[34] was added dropwise down the side of the flask over 15 min. The resulting reaction mixture was allowed to warm gradually to 0 °C over 30 min and stirred at 0 °C for an additional 1.5 h. The reaction mixture was diluted with a mixture of half-saturated aqueous $NaHCO_3$ (200 mL) in ether (800 mL). The organic phase was washed successively with 5 wt % aqueous $Na_2S_2O_3$, water, and brine (150 mL each) and then dried over $MgSO_4$. After evaporation of the solvent in vacuo, the resulting residual oil was taken up into methanol (500 mL) and treated with K_2CO_3 (3.5 g, 25.4 mmol) at 23 °C with stirring for 20 h (to effect the conversion of trimethylsilyl ether adduct to the corresponding free aldol). The reaction mixture was concentrated down to half of the original volume and poured into a mixture of ether−water (1000 mL/200 mL). The organic phase was washed with water and brine (200 mL each) and dried. Evaporation of the solvent under reduced pressure gave crude **10**, which was purified by flash silica gel chromatography (2 kg) eluting with a solvent mixture of ethyl acetate in hexane (4−8%) to afford *anti*-aldol **10** (21.8 g, 77%) as a colorless oil along with *syn*-aldol **11** (8%) and *re* facial *anti*-aldol **12** (2%). Data for **10**: R_f 0.4 (Hex−EtOAc 10:1); $[\alpha]^{23}_D$ −2.0° (*c* 1.0, $CHCl_3$); FTIR (film) ν_{max} 3453, 1713, 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3 H, CH_3Si), 0.12 (s, 3 H, CH_3Si), 0.92 (s, 9 H, *t*-BuSi), 1.01 (t, 6 H, J = 6.3 Hz, $(CH_3)_2CH$), 1.36 (d, 3 H, J = 7.1 Hz, CH_3CH), 2.13 (m, 1 H, $CH(CH_3)_2$), 2.86 (m, 1 H, $CHCH_3$), 3.62 (s, 3 H, CH_3OCO), 3.69 (d, 1 H, J = 4.4 Hz, OCH), 3.90 (d, 1 H, J = 13.2 Hz, CH_2Ph), 4.01 (br m, 1 H, CHOH), 4.07 (s, 2 H, CH_2OSi), 4.11 (d, 1 H, J = 5.6 Hz, HOCH), 4.17 (d, 1 H, J = 13.2 Hz, CH_2Ph), 4.26 (d, 1 H, J = 2.3 Hz, NCH_2O), 4.29 (d, 1 H, J = 2.3 Hz, NCH_2O), 7.16−7.30 (m, 5 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.8, −5.7, 17.2, 18.1, 19.5, 21.7, 25.9(3C), 28.7, 39.7, 51.7, 52.4, 70.0, 69.6, 75.6, 85.5, 86.5, 127.0, 127.9, 128.3, 128.4, 139.4, 177.1 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{25}H_{43}NO_5SiNa]^+$ 488.2808, found for $[M + Na]^+$ 488.2805. Data for **11**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6 H, CH_3Si), 0.93 (s, 9 H, *t*-BuSi), 1.03 (d, 3 H, J = 6.8 Hz, CH_3), 1.06 (d, 3 H, J = 6.8 Hz, CH_3), 1.33 (d, 3 H, J = 7.0 Hz, CH_3CH), 2.12 (m, 1 H, $CHMe_2$), 2.82 (m, 1 H, $CHCH_3$), 3.65 (s, 3 H, OCH_3), 3.75 (d, 1 H, J = 13.1 Hz, CH_2Ph), 3.91 (m, 2 H), 4.08 (m, 2 H), 4.16 (br d, 1 H, J = 6.7 Hz, CHOH), 4.27 (br m, 2 H, NCH_2O), 7.18−7.35 (m, 5 H, ArH) ppm. Data for **12**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 and 0.14 (each s, 3 H, CH_3Si), 0.93 (s, 9 H, *t*-BuSi), 1.03 (t, 6 H, J = 6.7 Hz, $(CH_3)_2CH$), 1.36 (d, 3 H, J = 7.2 Hz, CH_3CH), 2.06 (m, 1 H, $CHMe_2$), 3.03 (m, 1 H, $CHCH_3$), 3.61 (s, 3 H, OCH_3), 3.70 (d, 1 H, J = 7.2 Hz, O−CH), 3.88 and 4.15 (each d, 1 H, J = 13.7 Hz, CH_2Ph), 4.02 (ABq, 2 H, J = 10.8; 5.4 Hz, CH_2OTBS), 3.85 (br d, 1 H, J = 3.6 Hz, CHOH), 4.30 (br s, OH), 4.26 and 4.33 (each d, 1 H, J = 2.4 Hz, NCH_2O), 7.15−7.35 (m, 5 H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.8, −5.7, 17.9, 18.1, 20.1, 21.3, 25.9(3C), 28.4, 39.8, 51.7, 52.3, 61.8, 69.6, 74.7, 85.4, 86.8, 127.0, 127.9, 128.2(2C), 139.9, 177.2 ppm.

Conversion of Aldol 10 to Dihydroxy-γ-lactam 15. To a solution of aldol **10** (20.0 g, 43.0 mmol) and 0.1 mL of *i*-Pr_2NEt in ethanol (250 mL) was added 10% Pd−C (2.40 g). The resulting mixture was degassed and hydrogenated under balloon pressure for 22 h at 23 °C. The reaction mixture was filtered through a pad of Celite, and the resulting filtrate was concentrated in vacuo. The oily residue was taken up in methanol (100 mL) and heated to 50 °C for 24 h. After evaporation of the solvent in vacuo, the resulting crude (((*tert*-butyldimethylsilyl)oxy)methyl)hydroxy-γ-lactam intermediate was dissolved in CH_3CN (300 mL) and treated with a solution of 48% HF (15.5 mL). After 24 h of stirring at 23 °C, the reaction mixture was diluted with EtOAc (800 mL), loaded onto a pad of silica gel (1500 g), and eluted with 10% (v/v) methanol in EtOAc (3000 mL). After evaporation of the solvent under reduced pressure, the resulting solid residue was recrystallized from 50% EtOAc in hexane to give dihydroxy-γ-lactam **15** (7.5 g, 76%) as colorless crystals: mp 160 °C dec; R_f 0.38 (EtOAc); $[\alpha]^{23}_D$ +44.2° (*c* 0.95, CH_2Cl_2); FTIR (film) ν_{max} 3367, 1695, 1060, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, 3 H, J = 6.7 Hz, $(CH_3)_2CH$), 1.06 (d, 3 H, J = 6.7 Hz, $(CH_3)_2$-CH), 1.32 (d, 3 H, J = 7.8 Hz, CH_3CH), 1.72 (m, 1 H, $CH(CH_3)_2$), 2.14 (dd, 1 H, J = 4.2; 8.5 Hz, $HOCH_2$), 2.96 (dq, 1 H, J = 9.5; 7.8 Hz, $CHCH_3$), 3.00 (d, 1H, J = 10.4 Hz, OCHCH), 3.08 (d, 1 H, J = 11.0 Hz, HOCH), 3.75 (dd, 1 H, J = 4.2; 11.8 Hz, CH_2OH), 4.02 (dd, 1 H, J = 8.5; 11.8 Hz, CH_2OH), 4.43 (t, 1 H, J = 10.2 Hz, CHOH), 4.65 (d, 1 H, J = 5.0 Hz, NCH_2O), 5.18 (d, 1 H, NCH_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 18.3, 20.7, 27.8, 45.6, 58.6, 71.8, 73.7, 75.4, 89.5, 179.8 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{11}H_{19}NO_4Na]^+$ 252.1212, found for $[M + Na]^+$ 252.1228.

Conversion of Dihydroxy-γ-lactam 15 to Dihydroxy Acid 16. A solution of dihydroxy-γ-lactam **15** (7.5 g, 32.7 mmol) in CH_2Cl_2 (420 mL) was cooled to −78 °C and treated with Et_3N (45.0 mL, 322.8 mmol) and a CH_2Cl_2 solution of Swern reagent prepared from oxalyl chloride (5.7 mL, 65.2 mmol, 2 equiv) and DMSO (7.0 mL, 98.0 mmol, 3 equiv) at −78 °C over 10 min. The reaction mixture was stirred for 2 h at −78 °C and poured into a mixture of CH_2Cl_2 (1200 mL) and saturated aqueous $NaHCO_3$ (500 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (800 mL). The combined organic phases were dried and concentrated in vacuo to give the crude hydroxy-γ-lactam aldehyde intermediate as a colorless oil, which without purification was taken up into *t*-BuOH (350 mL) and 2-methyl-2-butene (200 mL). The resulting mixture was treated with a freshly prepared solution of $NaClO_2$ (30.0 g, 331.5 mmol, 10 equiv) in 20% aqueous NaH_2PO_4 (200 mL) at 23 °C. After 1 h of vigorous stirring at 23 °C, the reaction mixture was poured into EtOAc (1500 mL), and the aqueous phase was extracted with EtOAc (1000 mL). The combined organic phases were dried and concentrated in vacuo. The oily residue was taken up into EtOAc (500 mL) and washed with 8% aqueous NaH_2PO_4 (50 mL), and the aqueous phase was extracted with EtOAc (2 × 500 mL). The combined organic phases were dried and concentrated in vacuo to yield the crude hydroxy carboxylic acid as a colorless film, which without purification was treated with 1,3-propanedithiol (11.8 mL, 116.0 mmol, 3.6 equiv) and a saturated solution of HCl (gas) (ca. 1−2 wt %) in CF_3CH_2OH (300 mL) at 23 °C. The reaction vessel was sealed with a polypropylene cap and heated to 50−55 °C for 7.5 h. The reaction mixture was cooled and concentrated in vacuo. The resulting solid residue was triturated with 20% CH_2Cl_2 in hexane (5 × 200 mL) and dried under high vacuum to afford dihydroxy acid **16** (6.0 g, 77%, three steps) as a white powder: mp 240 °C dec; R_f 0.45 ($CHCl_3$−MeOH−HOAc 10:10:1); $[\alpha]^{23}_D$ +44.5 (*c* 0.90, DMSO); FTIR (film) ν_{max} 3600−2800 (br), 1695, 1687 cm

(34) Prepared according to Kita, Y.; Segowa, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1099.

$^{-1}$; ^{1}H NMR (300 MHz, pyridine-d_5) δ 1.29 (d, 3 H, J = 6.8 Hz, (CH_3)$_2$CH), 1.33 (d, 3 H, J = 6.6 Hz, (CH_3)$_2$CH), 1.57 (d, 3 H, J = 7.5 Hz, CH_3CH), 2.37 (m, 1 H, CH(CH$_3$)$_2$), 3.73 (m, 1 H, CHCH$_3$), 4.76 (d, 1 H, J = 6.3 Hz, CHOH), 5.26 (d, 1 H, J = 5.9 Hz, CHOH), 9.40 (s, 1 H, NHCO) ppm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.79 (d, 3 H, J = 6.8 Hz, (CH_3)$_2$CH), 0.85 (d, 3 H, J = 6.8 Hz, (CH_3)$_2$CH), 0.87 (d, 3 H, J = 7.8 Hz, CH_3CH), 1.57 (m, 1 H, CH(CH$_3$)$_2$), 2.67 (m, 1 H, CHCH$_3$), 3.72 (d, 1 H, J = 6.2 Hz, OCHCH), 4.23 (d, 1 H, J = 5.8 Hz, CHOH), 4.88 (br s, 1 H, OH), 5.28 (br s, 1 H, OH), 7.66 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 8.7, 19.0, 20.2, 30.4, 40.4, 74.4, 77.7, 105.4, 172.6, 178.3 ppm; HRMS (FAB, NBA + NaI) m/z calcd for [C$_{10}$H$_{18}$NO$_5$]$^+$ 232.1185, found for [M + H]$^+$ 232.1186.

Conversion of Dihydroxy Acid 16 to β-Lactone 2. A suspension of dihydroxy acid **16** (800.0 mg, 3.46 mmol) in CH_2Cl_2 (50 mL) was treated with Et_3N (1.44 mL, 10.3 mmol, 3 equiv) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 1.32 g, 5.2 mmol, 1.5 equiv) at 23 °C. After 0.5 h of stirring at 23 °C, the resulting reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was loaded onto a pad of silica gel (15 g) and eluted with EtOAc (150 mL). The eluent was concentrated in vacuo, and the solid residue was recrystallized from EtOAc to give β-lactone **2** (690.0 mg, 93%) as colorless crystals: mp 185 °C dec; R_f 0.10 (EtOAc); $[\alpha]^{23}_D$ −93.9° (*c* 0.53, CH_3CN); FTIR (CH_2Cl_2) ν_{max} 3687, 3602, 3410, 1840, 1731, 1640 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-d_5) δ 0.98 (d, 3 H, J = 6.8 Hz, (CH_3)$_2$CH), 1.10 (d, 3 H, J = 6.8 Hz, (CH_3)$_2$CH), 1.45 (d, 3 H, J = 7.5 Hz, CH_3CH), 2.09 (m, 1 H, CH(CH$_3$)$_2$), 3.03 (dq, 1 H, J = 6.1; 7.4 Hz, CHCH$_3$), 4.33 (dd, 1 H, J = 3.6; 6.7 Hz, OCHCH), 5.68 (d, 1 H, J = 6.1 Hz, CHOCO), 7.85 (d, 1 H, J = 6.8 Hz, OH), 10.50 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, pyridine-d_5) δ 8.8, 16.5, 20.4, 29.8, 38.9, 70.6, 77.0, 80.5, 172.4, 177.4 ppm; HRMS (CI, NH_3) m/z calcd for [C$_{10}$H$_{19}$N$_2$O$_4$]$^+$ 231.1344, found for [M + NH$_4$]$^+$ 231.1354.

Conversion of β-Lactone 2 to Lactacystin (1) by Coupling with *N*-Acetyl-L-cysteine. A suspension of β-lactone **2** (500.0 mg, 2.35 mmol) in CH_2Cl_2 was treated with *N*-acetyl-L-cysteine (383.0 mg, 2.33 mmol, 1.0 equiv) and Et_3N (0.98 mL, 7.05 mmol, 3.0 equiv) at 23 °C under N_2. The resulting reaction mixture was stirred for 4 h at 23 °C and concentrated in vacuo. The solid residue was dissolved in dry pyridine (10 mL) and evaporated under reduced pressure. The azeotropic distillation with pyridine was repeated again (to effect the complete removal of Et_3N). Regeneration of the free acid by azeotropic distillation with a mixture of THF−HOAc (v/v 5:1, 2 × 10 mL) was followed by trituration with a mixture of EtOAc−HOAc (v/v 20:1, 2 × 20 mL) to afford lactacystin (880.0 mg, >99%) as a colorless powder: mp 233−235 °C dec; R_f 0.33 (THF−EtOAc−HOAc 4:2:1); $[\alpha]^{23}_D$ +78.6 (*c* 0.49, MeOH); FTIR (neat) ν_{max} 3584, 3484, 3317, 3216, 1698, 1674, 1647, 1623, 1617, 1560 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-d_5) δ 1.18 (d, 3 H, J = 6.7 Hz, (CH_3)$_2$CH), 1.25 (d, 3 H, J = 6.7 Hz, (CH_3)$_2$CH), 1.57 (d, 3 H, J = 7.5 Hz, CH_3CH), 2.04 (s, 3 H, CH_3CON), 2.25 (m, 1 H, CH(CH$_3$)$_2$), 3.48 (dq, 1 H, J = 7.4; 7.4 Hz, CHCH$_3$), 3.84 (dd, 1 H, J = 6.7; 13.6 Hz, CH$_2$S), 4.05 (dd, 1 H, J = 4.8; 13.6 Hz, CH$_2$S), 4.60 (d, 1 H, J = 7.0 Hz, CHOH), 5.34 (d, 1 H, J = 7.0 Hz, CHOH), 5.42 (br q, 1 H, J = 7.0 Hz, CHCH$_2$S), 8.80 (d, 1 H, J = 8.2 Hz, NH), 9.90 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, pyridine-d_5) δ 10.2, 19.9, 21.5, 23.0, 31.4, 32.1, 41.9, 53.0, 75.9, 80.0, 81.4, 170.2, 173.7, 181.3, 203.0 ppm; HRMS (FAB, NBA + NaI) m/z calcd for [C$_{15}$H$_{24}$N$_2$O$_7$SNa]$^+$ 399.1202, found for [M + Na]$^+$ 3399.1198.

Mukaiyama aldol products **17a**−**17d** were prepared by applying the procedure described above with aldehyde **4** and the trimethylsilyl enol ethers of methyl butyrate, methyl valerate, methyl isobutyrate, and methyl hydrocinnamate, respectively. The corresponding β-lactone analogues **18a**−**18d** were prepared by a sequence analogous to that described above. The chemical yields and spectral data of the various intermediates are summarized below.

Aldol 17a: 79%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.11 and 0.12 (each s, 3 H, CH$_3$Si), 0.92 (s, 9 H, *t*-BuSi), 0.94 (t, 3 H, J = 7.3 Hz, CH_3-CH$_2$), 0.99 (d, 3 H, J = 6.7 Hz, (CH_3)$_2$CH), 1.03 (d, 3 H, J = 6.7 Hz, (CH_3)$_2$CH), 1.74 (m, 1 H, CH_2CH$_3$), 1.92 (m, 1 H, CH_2CH$_3$), 2.18 (sept, 1 H, J = 6.7 Hz, CH(CH$_3$)$_2$), 2.68 (m, 1 H, CH), 3.58 (s, 3 H, OCH$_3$), 3.63 (d, 1 H, J = 6.3 Hz, CHOH), 3.93 (d, 1 H, J = 13.1 Hz, CH$_2$Ph), 4.10 (br m, 3 H), 4.16 (d, 1 H, J = 13.1 Hz, CH$_2$Ph), 4.26 (dd, 2 H, J = 2.3; 4.7 Hz, NCH$_2$O), 7.16−7.35 (m, 5 H, ArH) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ −5.8, −5.7, 12.1, 18.1, 19.8, 21.5, 25.2, 25.9, 28.7, 46.7, 51.5, 52.9, 62.1, 69.7, 74.7, 85.8, 86.8, 127.0, 128.3, 139.6, 176.8 ppm; HRMS (FAB, NBA + NaI) m/z calcd for [C$_{25}$H$_{45}$NO$_5$SiNa]$^+$ 502.2965, found for [M + Na]$^+$ 502.2956.

Aldol 17b: 80%; $[\alpha]^{23}_D$ −135.5° (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.11 (s, 3 H, CH$_3$), 0.12 (s, 3 H, CH$_3$), 0.90 (t, 3 H, J = 7.3 Hz, CH$_3$), 0.91 (s, 9 H, *t*-BuSi), 0.99 (d, 3 H, J = 6.6 Hz, CH$_3$), 1.02 (d, 3 H, J = 6.6 Hz, CH$_3$), 1.16−1.40 (br m, 4 H, CH$_2$), 1.69 (m, 1H), 1.91 (m, 1 H), 2.17 (sept, 1 H, J = 6.6 Hz, CH), 2.73 (br m, 1 H, CH-CO$_2$Me), 3.58 (s, 3 H, OCH$_3$), 3.64 (d, 1 H, J = 6.2 Hz, CHOH), 3.93 (d, 1 H, J = 13.1 Hz, CH$_2$Ph), 4.16 (d, 1 H, J = 13.1 Hz, CH$_2$-Ph), 4.04−4.12 (br m, 3 H), 4.26 (d, 2 H, J = 2.7 Hz, NCH$_2$O), 7.16−7.35 (m, 5 H, ArH) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.8, −5.7, 14.0, 18.2, 19.7, 21.5, 22.6, 25.9, 28.7, 29.4, 29.8, 31.8, 45.1, 51.5, 52.9, 62.1, 69.7, 74.1, 74.9, 85.8, 86.7, 127.0, 127.8, 128.3, 128.6, 128.6, 139.6, 176.9 ppm; HRMS (FAB, NBA + NaI) m/z calcd for [C$_{28}$H$_{49}$-NO$_5$SiNa]$^+$ 530.3278, found for [M + Na]$^+$ 530.3275.

Aldol 17c: 84%; $[\alpha]^{23}_D$ +25.4° (*c* 0.40, EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.11 and 0.12 (2s, 3 H, CH$_3$Si), 0.92 (s, 9 H, *t*-BuSi), 0.93 (d, 3 H, J = 6.6 Hz, CH$_3$), 0.98 (d, 3 H, J = 6.6 Hz, CH$_3$), 1.02 (d, 3 H, J = 6.5 Hz, CH$_3$), 1.04 (d, 3 H, J = 6.5 Hz, CH$_3$), 2.23 (br m, 2 H, CH(CH$_3$)$_2$), 2.40 (dd, 1 H, J = 1.5; 9.4 Hz, CH(CH$_3$)$_2$), 3.50 (s, 3 H, OCH$_3$), 3.52 (d, 1 H, J = 7.5 Hz, OCH), 3.95 (d, 1 H, J = 12.7 Hz, CH$_2$Ph), 4.09 (d, 1 H, J = 10.5 Hz, CH$_2$OSi), 4.15 (d, 1 H, J = 10.5 Hz, CH$_2$OSi), 4.17 (d, 1 H, J = 12.7 Hz, CH$_2$Ph), 4.12 (br d, 1 H, J = 9.3 Hz, CHOH), 4.20 (d, 1 H, J = 2.5 Hz, NCH$_2$O), 4.30 (d, 1 H, J = 2.5 Hz, NCH$_2$O), 4.23 (br d, 1 H, J = 9.3 Hz, *H*OCH), 7.16−7.36 (m, 5 H, ArH) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.7, −5.7, 18.2, 20.4, 20.7, 21.0, 21.1, 25.9, 28.6, 29.6, 50.8, 51.2, 53.8, 62.0, 69.8, 73.2, 86.1, 87.2, 127.0, 128.2, 129.1, 139.8, 177.0 ppm; HRMS (FAB, NBA + NaI) m/z calcd for [C$_{27}$H$_{47}$NO$_5$SiNa]$^+$ 516.3121, found for [M + Na]$^+$ 516.3131.

Aldol 17d: 83%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.084 and 0.10 (each s, 3 H, CH$_3$Si), 0.62 (d, 3 H, J = 6.7 Hz, CH$_3$), 0.90 (s, 9 H, *t*-BuSi), 0.95 (d, 3 H, J = 6.7 Hz, CH$_3$), 2.12 (m, 1 H, CH), 2.96−3.14 (m, 2 H), 3.38 (d, 1 H, J = 7.4 Hz, CH−O), 3.46 (s, 3 H, OCH$_3$), 3.92 (d, 1 H, J = 13.0 Hz, CH$_2$Ph), 4.19 (d, 1 H, J = 13.0 Hz, CH$_2$-Ph), 4.03 (d, 1 H, J = 10.7 Hz, CH$_2$OTBS), 4.14 (d, 1 H, J = 10.7 Hz, CH$_2$OTBS), 4.25 (dd, 2 H, J = 2.5; 6.1 Hz, NCH$_2$O), 3.97 (br d, 1 H, J = 7.1 Hz, *H*OCH), 4.33 (br d, 1 H, J = 8.0 Hz, CHOH), 7.15−7.30 (m, 10 H, ArH) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ −5.8, −5.7, 18.1, 20.2, 20.5, 25.9(3C), 28.5, 37.5, 46.3, 51.6, 53.3, 61.8, 69.7, 74.0, 86.0, 87.2, 126.7, 126.9, 128.2, 128.3, 128.6, 128.7, 129.2, 138.5, 139.6, 176.5 ppm; HRMS (FAB, NBA + NaI) m/z calcd for [C$_{31}$H$_{47}$NO$_5$-SiNa]$^+$ 564.3121, found for [M + Na]$^+$ 564.3107.

γ-Lactam 15, Ethyl Analogue: 78%; $[\alpha]^{23}_D$ +60° (*c* 0.01, EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.04 (t, 6 H, J = 6.7 Hz, (CH_3)$_2$CH), 1.12 (t, 3 H, J = 7.3 Hz, CH_3CH$_2$), 1.74 (m, 2 H, CH$_2$), 1.84 (m, 1 H, CH_2CH$_3$), 2.44 (dd, 1 H, J = 4.0; 8.5 Hz, *H*OCH$_2$), 2.68 (br q, 1 H, J = 7.6 Hz, CH), 2.96 (d, 1 H, J = 10.3 Hz, CHOH), 3.34 (d, 1 H, J = 10.5 Hz, CHOH), 3.76 (dd, 1 H, J = 4.0; 11.8 Hz, CH_2OH), 4.01 (dd, 1 H, J = 8.5; 11.8 Hz, CH_2OH), 4.48 (t, 1 H, J = 9.8 Hz, CHOH), 4.62 (d, 1 H, J = 5.0 Hz, NCH$_2$O), 5.17 (d, 1 H, J = 5.0 Hz, NCH$_2$O) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 12.8, 18.5, 20.0, 20.8, 27.9, 52.0, 57.5, 59.1, 71.9, 73.3, 76.0, 89.3, 179.8 ppm; HRMS (CI, NH_3) m/z calcd for [C$_{12}$H$_{22}$NO$_4$]$^+$ 244.1549, found for [M + H]$^+$ 244.1552.

γ-Lactam 15, *n*-Butyl Analogue: 80%; $[\alpha]^{23}_D$ +14.0° (*c* 0.02, EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.89 (t, 3 H, J = 7.3 Hz, CH_3-CH$_2$), 1.00 (d, 3 H, J = 6.5 Hz, CH_3CH), 1.01 (d, 3 H, J = 6.5 Hz, CH$_3$), 1.32 (m, 2 H, CH$_2$), 1.48 (m, 2 H), 1.60−1.82 (br m, 3H), 2.71 (q, 1 H, J = 8.8 Hz, CH), 2.93 (d, 1 H, J = 10.3 Hz, CHOH), 3.32 (br s, 1 H, OH), 3.72 (dd, 1 H, J = 4.5; 11.8 Hz, CH_2OH), 3.96 (dd, 1 H, J = 7.6; 11.8 Hz, CH_2OH), 3.84 (d, 1 H, J = 9.6 Hz, *H*OCH$_2$), 4.44 (t, 1 H, J = 9.6 Hz, CHOH), 4.59 (d, 1 H, J = 5.0 Hz, NCH$_2$O), 5.09 (d, 1 H, J = 5.0 Hz, NCH$_2$O) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.9, 18.5, 20.8, 22.8, 26.2, 27.9, 30.3, 50.4, 58.9, 71.7, 73.2, 75.6, 89.2, 179.9 ppm; HRMS (CI, NH_3) m/z calcd for [C$_{14}$H$_{26}$NO$_4$]$^+$ 272.1862, found for [M + H]$^+$ 272.1870.

***tert*-Butyldimethylsilyl Ether of the *n*-Butyl Analogue of 15:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.082 and 0.090 (2s, 3 H, CH_3Si), 0.90 (s, 9 H, *t*-BuSi), 0.89 (t, 3 H, $J = 7.3$ Hz, CH_3), 1.00 (d, 3 H, $J = 6.4$ Hz, CH_3), 1.02 (d, 3 H, $J = 6.4$ Hz, CH_3), 1.32 (m, 2 H), 1.50 (br m, 2 H), 1.60−1.80 (br m, 3 H), 2.70 (q, 1 H, $J = 9.2$ Hz, CH), 2.90 (d, 1 H, $J = 10.4$ Hz, OH), 3.62 (d, 1 H, $J = 10.9$ Hz, OCH), 3.70 (d, 1 H, $J = 10.8$ Hz, CH_2OSi), 3.99 (d, 1 H, $J = 10.8$ Hz, CH_2OSi), 4.39 (t, 1 H, $J = 10.1$ Hz, C*H*OH), 4.54 (d, 1 H, $J = 5.0$ Hz, NCH_2O), 5.14 (d, 1 H, $J = 5.0$ Hz, NCH_2O) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.6, −5.3, 14.0, 18.4, 18.5, 20.8, 22.8, 25.9, 26.4, 27.9, 30.2, 50.4, 60.3, 72.0, 73.0, 75.7, 89.4, 179.2 ppm.

***γ*-Lactam 15, Isopropyl Analogue:** 82%; $[\alpha]^{23}_D$ +11.4° (*c* 0.1, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, 6 H, $J = 6.3$ Hz, $(CH_3)_2CH$), 1.09 and 1.12 (each d, 3 H, $J = 6.8$ Hz, CH_3), 1.75 (br m, 1 H, CH), 2.24 (m, 1 H, CH), 2.53 (dd, 1 H, $J = 6.6$; 8.8 Hz, CH), 2.86 (d, 1 H, $J = 10.2$ Hz, CHO*H*), 3.30 (br s, OH), 3.77 (d, 1 H, $J = 11.8$ Hz, CH_2OH), 3.99 (d, 1 H, $J = 11.8$ Hz, CH_2OH), 4.06 (d, 1 H, $J = 9.1$ Hz, C*H*OH), 4.52 (t, 1 H, $J = 9.1$ Hz, C*H*OH), 4.56 (d, 1 H, $J = 5.0$ Hz, NCH_2O), 5.13 (d, 1 H, $J = 5.0$ Hz, NCH_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 20.3, 20.9, 23.3, 26.1, 28.0, 55.3, 59.2, 71.9, 72.4, 76.0, 88.4, 179.9 ppm; HRMS (CI, NH_3) *m*/*z* calcd for $[C_{13}H_{24}NO_4]^+$ 258.1705, found for $[M + H]^+$ 258.1709.

***tert*-Butyldimethylsilyl Ether of the Isopropyl Analogue of 15:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.066 and 0.076 (each s, 3 H, CH_3Si), 0.875 (s, 9 H, *t*-BuSi), 0.99 and 1.00 (each d, 3 H, $J = 6.5$ Hz, CH_3), 1.08 and 1.10 (each d, 3 H, $J = 6.7$ Hz, CH_3), 1.70 (m, 1 H), 2.22 (sept, 1 H, $J = 6.7$ Hz, CH), 2.46 (dd, 1 H, $J = 7.4$; 8.8 Hz, CH), 2.82 (d, 1 H, $J = 10.3$ Hz, CHO*H*), 3.74 (d, 1 H, $J = 10.7$ Hz, CH_2OSi), 3.81 (d, 1 H, $J = 9.3$ Hz, C*H*OH), 4.00 (d, 1 H, $J = 10.7$ Hz, CH_2OSi), 4.46 (t, 1 H, $J = 9.2$ Hz, *H*OCH), 4.49 (d, 1 H, $J = 5.0$ Hz, NCH_2O), 5.14 (d, 1 H, $J = 5.0$ Hz, NCH_2O) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.7, −5.5, 18.3, 18.8, 20.4, 20.9, 23.3, 25.8, 26.0, 28.0, 55.4, 60.5, 72.0, 72.3, 76.0, 88.5, 179.1 ppm.

***γ*-Lactam 15, Benzyl Analogue:** 84%; $[\alpha]^{23}_D$ +50° (*c* 0.01, EtOAc); ^{1}H NMR (400 MHz, acetone-d_6) δ 0.99 (dd, 6 H, $J = 6.7$; 8.1 Hz, $(CH_3)_2CH$), 1.85 (m, 1 H, CH), 2.98 (dd, 1 H, $J = 5.6$; 13.9 Hz, CH_2Ph), 3.04−3.14 (m, 2 H), 3.23 (dd, 1 H, $J = 8.6$; 13.9 Hz, CH_2Ph), 3.78 (dd, 1 H, $J = 5.6$; 11.7 Hz, CH_2OH), 4.01 (dd, 1 H, $J = 6.4$; 11.7 Hz, CH_2OH), 4.24 (t, 1 H, $J = 6.0$ Hz, *H*OCH_2), 4.56 (d, 1 H, $J = 4.6$ Hz, NCH_2O), 4.58 (t, 1 H, $J = 8.1$ Hz, C*H*OH), 4.71 (d, 1 H, $J = 7.8$ Hz, *H*OCH), 5.02 (d, 1 H, $J = 4.6$ Hz, NCH_2O), 7.10−7.35 (m, 5 H, ArH) ppm; ^{13}C NMR (100 MHz, acetone-d_6) δ 18.9, 21.2, 28.7, 32.5, 52.2, 59.6, 50.7, 71.4, 73.4, 76.4, 88.9, 126.6, 128.9, 129.8, 141.7, 179.4 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{17}H_{24}NO_4]^+$ 306.1705, found for $[M + H]^+$ 306.1715.

Acid 16, Ethyl Analogue: 75%; $[\alpha]^{23}_D$ −10° (*c* 0.01, MeOH); ^{1}H NMR (300 MHz, pyridine-d_5) δ 1.13 (t, 3 H, $J = 7.3$ Hz, CH_3CH$_2$), 1.29 (d, 3 H, $J = 6.8$ Hz, CH_3), 1.34 (d, 3 H, $J = 6.8$ Hz, CH_3), 2.26 (m, 2 H, CH_2CH$_3$), 2.37 (m, 1 H, C*H*$(CH_3)_2$), 3.54 (br q, 1 H, $J = 6.0$ Hz, CH), 4.76 (d, 1 H, $J = 5.9$ Hz, CHOH), 5.28 (d, 1 H, $J = 5.7$ Hz, CHOH), 9.36 (s, 1 H, NH) ppm; ^{13}C NMR (125 MHz, pyridine-d_5) δ 13.1, 18.3, 19.0, 21.2, 32.3, 49.2, 75.9, 76.8, 79.7, 174.9, 179.6 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{11}H_{20}NO_5]^+$ 246.1341, found for $[M + H]^+$ 246.1344.

Acid 16, *n*-Butyl Analogue: 78%; $[\alpha]^{23}_D$ −21° (*c* 0.01, MeOH); ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.78 (t, 3 H, $J = 7.3$ Hz, CH_3), 1.30 (d, 3 H, $J = 6.6$ Hz, CH_3), 1.35 (d, 3 H, $J = 6.6$ Hz, CH_3), 1.21−1.37 (br m, 2 H, CH_2), 1.48 (br m, 1 H), 1.63 (br m, 1 H), 2.23 (br m, 2 H, CH_2), 2.38 (sept, 1 H, $J = 6.1$ Hz, CHO*H*), 5.28 (d, 1 H, $J = 5.7$ Hz, HOC*H*), 9.30 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, pyridine-d_5) δ 14.3, 19.2, 21.1, 23.3, 24.7, 30.8, 32.3, 47.48, 76.0, 76.8, 79.8, 174.9, 179.7 ppm; HRMS (FAB, glycerol) *m*/*z* calcd for $[C_{13}H_{24}NO_5]^+$ 274.1654, found for $[M + H]^+$ 274.1662.

Acid 16, Isopropyl Analogue: 77%; $[\alpha]^{23}_D$ +15° (*c* 0.02, MeOH); ^{1}H NMR (400 MHz, pyridine-d_5) δ 1.28 (d, 3 H, $J = 6.8$ Hz, CH_3), 1.30 (d, 3 H, $J = 6.8$ Hz, CH_3), 1.33 (d, 3 H, $J = 6.6$ Hz, CH_3), 1.58 (d, 3 H, $J = 6.6$ Hz, CH_3), 2.36 (sept, 1 H, $J = 6.6$ Hz, CH), 2.66 (m, 1 H, CH), 2.40 (dd, 1 H, $J = 5.2$; 9.6 Hz, CH), 4.73 (d, 1 H, $J = 5.7$ Hz, C*H*OH), 5.28 (d, 1 H, $J = 5.3$ Hz, *H*OCH), 9.11 (s, 1 H, NH) ppm; ^{13}C NMR (125 MHz, pyridine-d_5) δ 18.9, 21.2, 21.7, 22.5, 26.1, 32.3, 53.0, 76.0, 76.9, 79.5, 174.8, 179.3 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{12}H_{21}NO_5Na]^+$ 282.1317; found for $[M + Na]^+$ 282.1323.

Acid 16, Benzyl Analogue: 76%; $[\alpha]^{23}_D$ −30° (*c* 0.02, MeOH); ^{1}H NMR (500 MHz, pyridine-d_5) δ 1.27 (d, 3 H, $J = 6.6$ Hz, CH_3), 1.34 (d, 3 H, $J = 6.6$ Hz, CH_3), 2.36 (m, 1 H, CH), 3.64 (br d, 2 H, CH_2-Ph), 4.08 (br m, 1 H, CH), 4.65 (d, 1 H, $J = 5.5$ Hz, C*H*OH), 5.13 (d, 1 H, $J = 5.6$ Hz, C*H*OH), 7.15−7.60 (m, 5 H, ArH), 9.50 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, pyridine-d_5) δ 19.1, 21.1, 30.8, 32.2, 49.7, 75.5, 76.9, 79.3, 125.9, 128.7, 129.5, 142.8, 174.7, 178.6 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{16}H_{22}NO_5]^+$ 308.1498; found for $[M + H]^+$ 308.1487.

***β*-Lactone 18a:** $[\alpha]^{23}_D$ −215° (*c* 0.01, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 3 H, $J = 6.8$ Hz, CH_3), 1.07 (d, 3 H, $J = 6.8$ Hz, CH_3), 1.12 (t, 3 H, $J = 7.5$ Hz, CH_3CH$_2$), 1.73 (m, 1 H, CH_2CH$_3$), 1.89 (m, 1 H, C*H*CH$_3$), 1.96 (m, 1 H, CH_2CH$_3$), 2.10 (d, 1 H, $J = 6.5$ Hz, CHO*H*), 2. 59 (m, 1 H, CH), 3.96 (dd, 1 H, $J = 4.60$; 6.5 Hz, C*H*OH), 5.28 (d, 1 H, $J = 6.0$ Hz, CH), 6.26 (br s, 1 H, NH) ppm; ^{13}C NMR(125 MHz, $CDCl_3$) δ 12.4, 16.5, 18.0, 19.7, 29.8, 45.2, 72.1, 75.5, 78.5, 162.1, 179.2 ppm; HRMS (CI, NH_3) *m*/*z* calcd for $[C_{11}H_{21}N_2O_4]^+$ 245.1501, found for $[M + NH_3]^+$ 245.1499.

***β*-Lactone 18b:** $[\alpha]^{23}_D$ −253° (*c* 0.015, EtOAc); ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.80 (t, 3 H, $J = 7.3$ Hz, CH_3CH$_2$), 1.03 (d, 3 H, $J = 6.7$ Hz, CH_3), 1.12 (d, 3 H, $J = 6.7$ Hz, CH_3), 1.27 (br m, 2 H, CH_2), 1.49 (br m, 2 H), 1.89 (br m, 1 H, CH), 2.13 (br m, 2 H), 3.01 (m, 1 H), 4.36 (br s, OH), 5.81 (d, 1 H, $J = 6.0$ Hz, CH−O), 7.84 (br s, 1 H, OH), 10.46 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, pyridine-d_5) δ 14.0, 16.6, 20.4, 23.0, 25.0, 29.9, 30.3, 44.4, 70.7, 76.5, 80.5, 172.3, 177.0 ppm; HRMS (CI, NH_3) *m*/*z* calcd for $[C_{13}H_{25}N_2O_4]^+$ 273.1814, found for $[M + NH_4]^+$ 273.1809.

***β*-Lactone 18c:** $[\alpha]^{23}_D$ −280° (*c* 0.015, EtOAc); ^{1}H NMR (400 MHz, pyridine-d_5) δ 1.02 (d, 3 H, $J = 6.7$ Hz, CH_3), 1.11 (d, 3 H, $J = 6.9$ Hz, CH_3), 1.18 (d, 3 H, $J = 6.7$ Hz, CH_3), 1.42 (d, 3 H, $J = 6.9$ Hz, CH_3), 2.10 (br m, 1 H, CH), 2.39 (m, 1 H, CH), 2.80 (dd, 1 H, $J = 6.1$; 8.6 Hz, CH), 4.32 (br s, 1 H, C*H*OH), 5.82 (d, 1 H, $J = 6.0$ Hz, CH−OCO), 7.84 (br d, 1 H, OH), 10.40 (s, 1 H, NH) ppm; ^{13}C NMR (125 MHz, pyridine-d_5) δ 16.8, 20.4, 20.7, 22.0, 27.0, 29.9, 49.6, 70.8, 77.3, 79.9, 172.1, 176.3 ppm; HRMS (CI, NH_3) *m*/*z* calcd for $[C_{12}H_{23}N_2O_4]^+$ 259.1658, found for $[M + NH_4]^+$ 259.1657.

***β*-Lactone 18d:** $[\alpha]^{23}_D$ −320° (*c* 0.01, EtOAc); ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.90 (d, 3 H, $J = 6.4$ Hz, CH_3), 1.07 (d, 3 H, $J = 6.4$ Hz, CH_3), 2.07 (br m, 1 H, CH), 3.20 (t, 1 H, $J = 12.8$ Hz, CH_2Ar), 3.45 (m, 1 H, O−CH), 3.58 (dd, 1 H, $J = 3.6$; 12.8 Hz, CH_2Ar), 4.33 (br m, 1 H, C*H*OH), 5.62 (d, 1 H, $J = 5.8$ Hz, HCOCO), 7.20−7.45 (m, 5 H, ArH), 7.83 (d, 1 H, $J = 6.7$ Hz, OH), 10.69 (s, 1 H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 19.6, 29.8, 30.1, 46.4, 72.0, 75.1, 78.4, 126.9, 128.9, 128.9, 169.2 ppm; HRMS (FAB, NBA + NaI) *m*/*z* calcd for $[C_{16}H_{19}NO_4Na]^+$ 312.1212, found for $[M + Na]^+$ 312.1217.

Acknowledgment. We are grateful for a supporting grant from the National Institutes of Health.

JA973444C