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An Expedient Synthesis of LAF389, a Bengamide B Analogue

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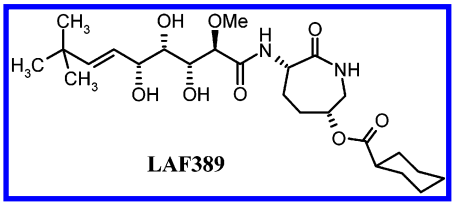
Abstract:

An optimized, convergent, safe synthesis of LAF389 (9), an anticancer agent analogous to bengamide B, is described. Starting from α-D-glucoheptonic (D-glycero-D-gulo-heptonic acid) γ-lactone (10), the lactone 15 was constructed in five steps. Major improvements were made in the preparation of the aldehyde precursor 14 and subsequent olefination to yield 15 via a modified Julia protocol. This olefination was significantly improved by using TMSCl as an additive. The second fragment of the drug substance, ϵ-caprolactam 7, was obtained in two *one-pot* operations from (5*R*)-5-hydroxy-L-lysine (1). Finally, opening 15 with 7 using sodium 2-ethyl hexanoate (Na-EH) gave 8, which on deprotection yielded LAF389.

Introduction

LAF389 is an analogue of bengamide B, a member of the bengamides isolated from *Jaspidae* sponges.[1] Like its natural congeners, the synthetic bengamide is a general inhibitor of cell proliferation[2] and, hence, was developed as an anti-cancer agent. Several syntheses of bengamides A, B, and E have been reported.[3] However, all are either too long or contain unacceptable reagents and operations and are thus unsuitable for large-scale preparation of LAF389. To support the ongoing campaign, a short and convergent synthesis of bengamides B and E has been devised by us earlier.[4] This synthesis of LAF389 involved the coupling of a polyhydroxylated lactone fragment **15** with a substituted 2-aminocaprolactam **7** (Scheme 1) to construct the key intermediate **8**. It is a much shorter synthesis of bengamide compared to other published ones. It utilizes commercially available natural products **1** and **10** which contain all of stereogenic centers of bengamide B. This synthesis was used for the preparation of initial batches of the drug substance to support the preclinical studies.



LAF389

Although short and convergent, this synthesis was not feasible for large-scale preparation of the drug substance. The pitfalls in the procedure to prepare **15** included conversion of the α-D-glucoheptonic-γ-lactone to aldehyde **14**. It involved protection and selective deprotection of the hydroxyl groups followed by periodate oxidation. The solution of product **14** was found to be acid- as well as base sensitive and handling during the conversion to **15** was difficult. The olefination step itself needed major improvements. The Takai conditions[5] using chromium dichloride and corresponding *gem*-diiodide[6] were not suitable for scale-up work. Also, the conversion of lysine **1** to lactam **7** was a tedious multistep operation and needed to be simplified, and coupling of **7** with **15** must be improved to avoid epimerization at C2 of lactone **15**.

Results and Discussion

After brief review of different options,[3] we concluded that further optimization of synthesis shown in Scheme 1 was a better option. For the sake of discussion this is divided into three parts: (a) preparation of the lactone **15**, (b) preparation of ϵ-caprolactam **7**, and (c) coupling of **15** with **7** and conversion to the drug substance.

Preparation of Lactone 15. In the preparation of **15**, the bis-acetonide protection of D-glycero-D-gulo-heptonic acid γ-lactone **10** was initially carried out in acetone with iodine as the catalyst.[7] This procedure suffered from a long reaction time, inconsistent regioselectivity, and poor quality of the isolated product. Therefore, the reaction conditions were modified, and a much milder and more selective procedure

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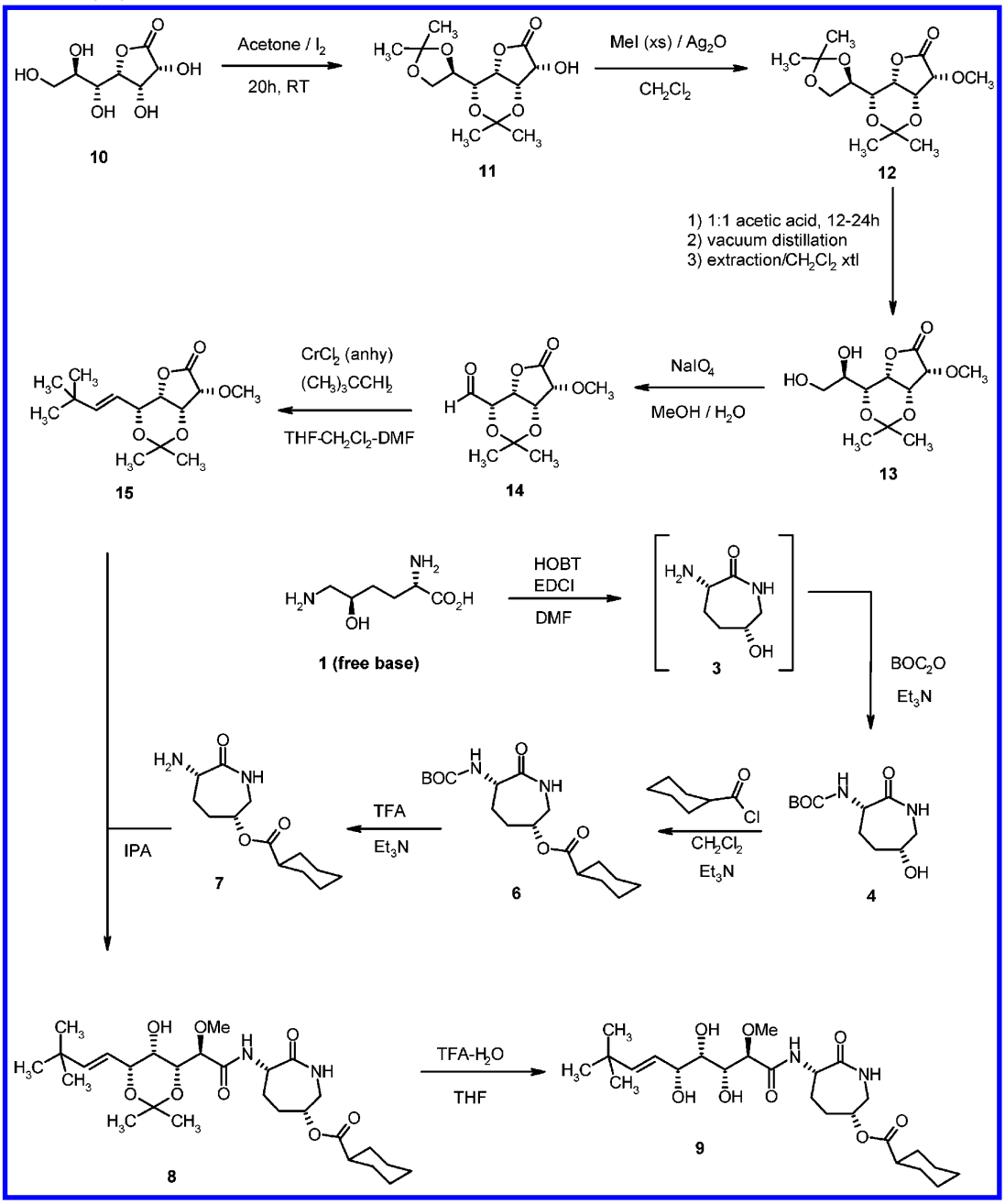
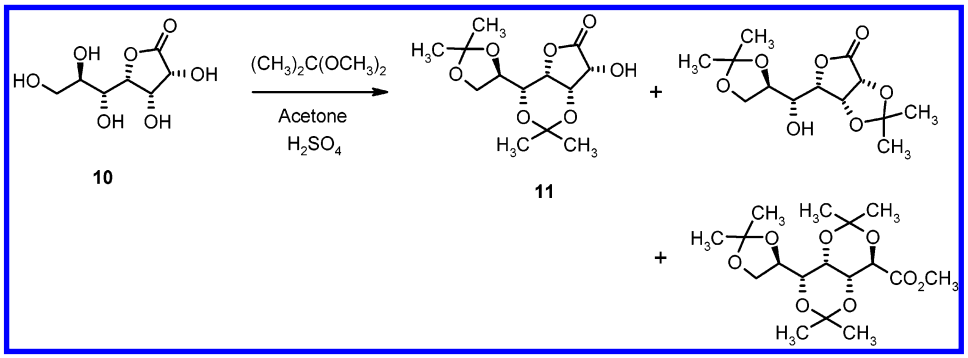
Scheme 1. **Discovery synthesis of LAF389**

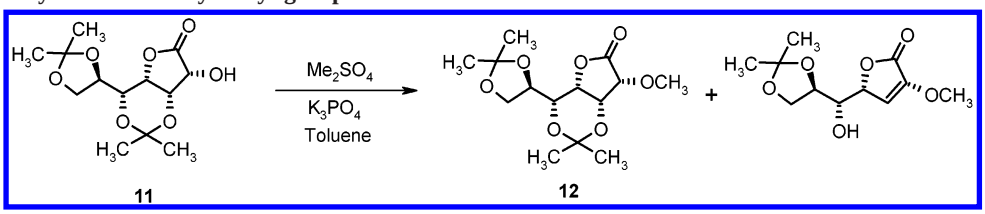


Scheme 2. **D-Glycero-D-gulo-heptonic acid γ-lactone 10 to bis-acetonide 11**

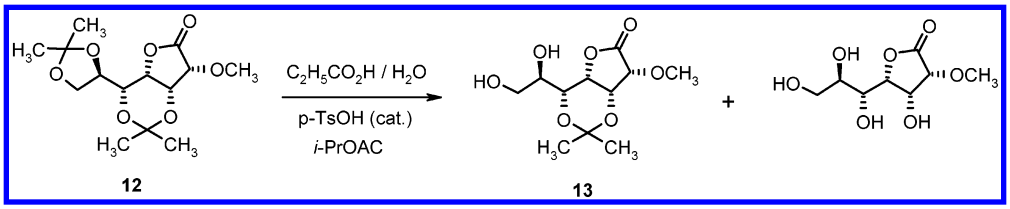


was developed, as shown in Scheme 2. We found that formation of the bis-acetonide of **10** proceeded much more rapidly in acetone in the presence of 2,2-dimethoxypropane (DMP) and concentrated sulfuric acid as the catalyst. The reaction could be run at 0 °C, ensuring consistent regioselectivity of about 5:1 (3,5 and 6,7 vs 2,3 and 6,7). The byproduct, the tris-acetonide, was not observed under these reaction conditions.

Scheme 3. **O-Methylation of the hydroxyl group of bis-acetonide 11**



Scheme 4. **Selective removal of the terminal acetonide group of bis-acetonide 12**



In the conversion of **11** to **12**, we found that these two compounds are very sensitive to both acid and base. As a result, we were forced to find nonhomogeneous conditions for methylation. Several methylating agents such as dimethyl carbonate, dimethyl methylphosphonate, (trimethylsilyl)-diazomethane, dimethyl sulfite, and methyl trifluoromethanesulfonate in combination with bases such as K_2CO_3, $KHCO_3$, Cs_2CO_3, and K_3PO_4 in different solvents were investigated (Scheme 3). The combination of potassium phosphate (3 equiv, screened through 14 mesh) and dimethyl sulfate (3 equiv) in toluene at room temperature gave the best results. Product 12 was isolated in 50% yield and in high purity by filtration of the heterogeneous reaction mixture, followed by precipitation with heptane. Since the reaction is heterogeneous, the particle size of the solid base was found to be critical for achieving consistent reactivity. Sieving of the commercial potassium phosphate through screen (mesh 14) was found to be necessary for large-scale preparation.

Our next objective was to achieve a selective removal of the terminal acetonide group of **12**. The earlier procedure used 1:1 acetic acid and water to affect the hydrolysis of the terminal acetonide.[8] The reaction was very selective for removing only the terminal acetonide group. However, the method necessitated a high-vacuum distillation to remove water and acetic acid at ambient temperature, and this resulted in overdeprotection. To avoid this problem, several solvents and catalysts were screened. It was found that the 6,7-acetonide can be selectively removed with a controlled amount of water (5 equiv) in propionic acid and a catalytic amount of *p*-toluenesulfonic acid in isopropyl acetate (Scheme 4). More importantly, under these reaction conditions, product **13** was precipitated out directly from the reaction mixture, thus avoiding vacuum distillation and extractive workup. The different acids and workup conditions tried are summarized in Table 1. Initially, the reaction was difficult to reproduce with reaction time varying significantly from run to run. It was later found that it was the acid impurity (from hydrolysis or partial hydrolysis of dimethyl sulfate) from the previous step that caused the problem. A catalytic amount of *p*-toluenesulfonic acid was added to ensure a consistent reaction time (Table 1, entry 6). With this modification, the hydrolysis step was found to be reproducible and complete within 2−3 h, offering the product in 83% yield.

Table 1. **Optimization of selective acetonide cleavage of Bis-acetonide 12**

entry	acid (with 5 equiv H_2O)	conditions	yield (%)
1	acetic acid	18 h RT, filtered, *i*-PrOAc wash	69
2	isobutyric acid	64 h RT, 5 h 50 °C, cold *i*-PrOAc wash	81
3	butyric acid	19 h RT, 5 h 45 °C, ∼75% conversion, cold *i*-PrOAc wash	72
4	propionic acid	19 h RT, 5 h 45 °C, cold *i*-PrOAc	76
5	propionic acid	5 h 50 °C, 60 h RT, cold *i*-PrOAc	67
6	propionic acid/*i*-PrOAc, 1:2, *p*-TsOH (cat.)	2 h 40 °C, 0.5 h 0 °C, cold *i*-PrOAc	83

Conversion of the diol **13** to aldehyde **14** using sodium periodate (aqueous) in acetonitrile was found to be problematic for scale-up. The aldehyde intermediate is thermally labile, highly sensitive to both acidic and basic conditions and readily prone to hydration. The reaction conditions were modified (Scheme 5) using a minimum amount of water to avoid extraction of the product from water. After completion of the reaction, the reaction mixture was diluted with isopropyl acetate and water was absorbed onto magnesium sulfate. The crude product (mostly in the hydrate form) was dried and dehydrated by azeotropic distillations of isopropyl acetate. The desired product **14** was precipitated from the concentrate in 70% yield.

The olefination of aldehyde **14** to obtain the lactone fragment **15** was one of the most difficult and low-yielding step in this synthesis. The Takai procedure[5] using a large excess of chromium dichloride and the expensive and thermally unstable 1,1-diiodo-2,2-dimethylpropane[6] was very demanding, and the reaction outcome very much depended upon the quality of the $CrCl_2$. Good results could only be obtained with a freshly opened bottle of anhydrous $CrCl_2$. The sensitivity of **14** and **15** to basic solution was found to

(8) Shing, T. K. M.; Zhou, Z. H.; Mak, C. W. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1907.

Scheme 5. **Oxidative cleavage of diol 13 to aldehyde 14**

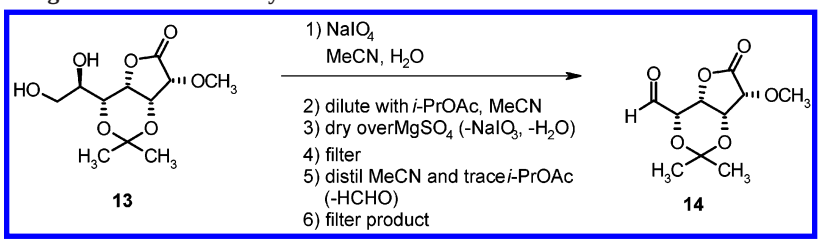
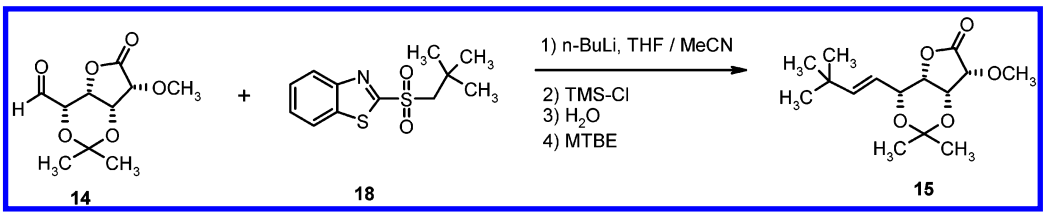


Table 2. **Effect of the additive (with 1.0 equiv of 15)**

entry	18 (equiv)	base (equiv)	solvent	additive (equiv)	addition mode temp (time)	yield selectivity (trans/cis)
1	2.0	*n*-BuLi (1.0)	THF/MeCN	TMSCl 2.0	**18** → **14** 0 °C; 50 °C (1 h)	50% (3:1)
2	1.2	*n*-BuLi (1.0) $HN(TMS)_2$ (1.2)	toluene	TMSCl 2.0	**14** → **18** −75 °C; 50 °C (1 h)	50% (1:1)
3	1.2	*n*-BuLi (1.0) $HN(TMS)_2$ (1.2)	THF/MeCN	$BF_3{\cdot}OEt_2$ 1.0	**14** → **18** −75 °C; 50 °C (1 h)	48% (6:1)
4	2.0	*n*-BuLi (1.8) $HN(TMS)_2$ (2.0)	THF/MeCN	$BF_3{\cdot}OEt_2$ 2.0	**14** → **18** −75 °C; 50 °C (1 h)	50% (6:1)
5	1.2	*n*-BuLi (1.2) $HN(TMS)_2$ (1.2)	THF/MeCN	$BF_3{\cdot}OEt_2$ 0.12	**14** → **18** −75 °C; 50 °C (1 h)	41% (10:1)

Scheme 6. **Formation of olefin 15 via Julia olefination**



be a major hurdle. Therefore, Julia olefination[9] was selected as an option as the reaction conditions are relatively mild. Olefination, initially, under these conditions gave poor yield (<10%) again due to the sensitivity of **14** to base. A breakthrough was realized in a serendipitous manner. It was found that the reaction actually required an elevated temperature to be completed. When we attempted to remove the solvent on a rotavap at about 40 °C from a "failed" reaction in which no desired product was detected (TLC), the desired product had formed! Since in all the previous "failed" attempts (in which product yields were <10%), the aldehyde **14** was always completely consumed, we believed that the rate-limiting step of Julia olefination was the elimination step. After the above finding, a systematic screening of additives and reaction conditions were carried out. Selected results are listed in Table 2. To summarize, we found that both TMSCl and BF_3 etherate were excellent additives showing significant improvement in yield. The sulfone anion was shown to be stable only at low temperatures (<−20 °C) and had to be generated at a low temperature (−55 to −78 °C). The sequence of addition also showed significant impact on the outcome of the reaction, with the best results being obtained when TMSCl was mixed with the sulfone anion in THF at low temperatures (e.g., −70 °C), and this mixture was added to a precooled solution of aldehyde in MeCN at 0 °C (Scheme 6). The choice of solvent was limited by the poor solubility of the aldehyde in less polar solvents. Acetonitrile was a good compromise with respect to solubility, selectivity, and product yield.

It is postulated that TMSCl plays a dual role by (1) attenuating the basicity of the reaction mixture and (2) stabilizing the intermediate (Scheme 7). In the presence of TMSCl, neither the starting aldehyde nor the reaction product is exposed to either the sulfone anion or the alkoxide adduct, and therefore, the decomposition of these compounds through the elimination pathway is minimized. The cyclized intermediate after the sulfone anion addition had been only speculated.[9] We were able to isolate an intermediate such as **19** (R = diphenylmethyl) as a relatively stable white solid.[10] The NMR data is in agreement with structure **19** (R = diphenylmethyl); however, no effort was made to establish exact stereochemistry. Julia and co-workers have studied the relationship between stereochemistry of formation of olefins (*E*/*Z*) from syn/anti heterocyclic β-hydroxysulfone.[9] We further found that the cyclic intermediate, **19** (R = diphenylmethyl), can be *selectively* converted to exclusively trans- or a mixture of cis/trans olefination products (Scheme 8). When compound **19** (R = diphenylmethyl) was subjected to acidic conditions (e.g., $MeSO_3H$), the trans product was obtained *exclusively*. On the other hand, when **19** (R = diphenylmethyl) was treated with base (TBAF, anhydrous

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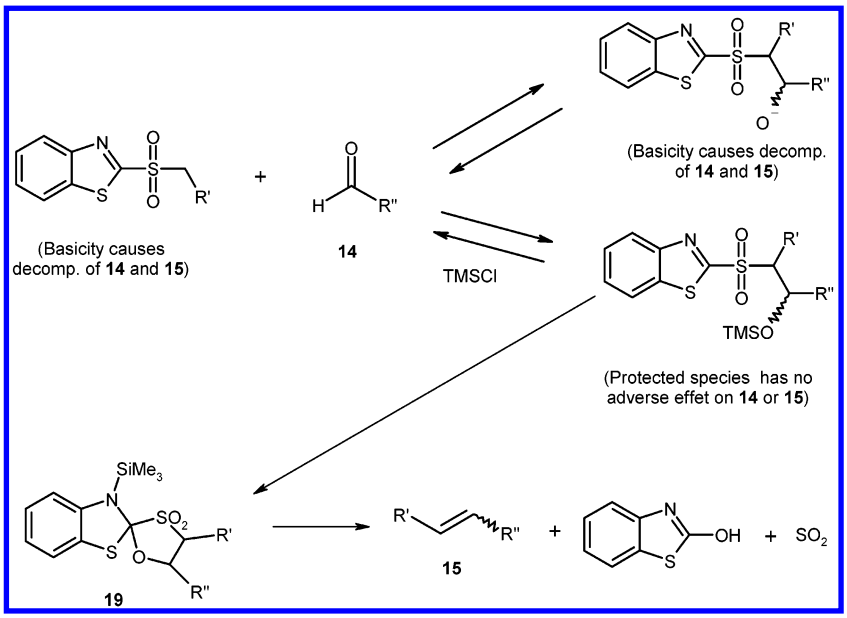
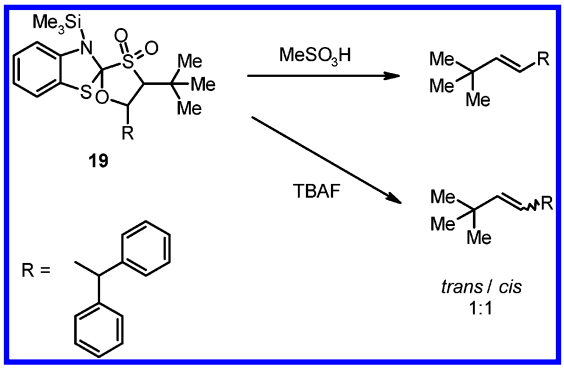
Scheme 7. **Postulated role of TMSCl in the formation of olefin 15**



Scheme 8. **Selective olefination of "trapped" intermediate as 19 (R = diphenylmethyl)**

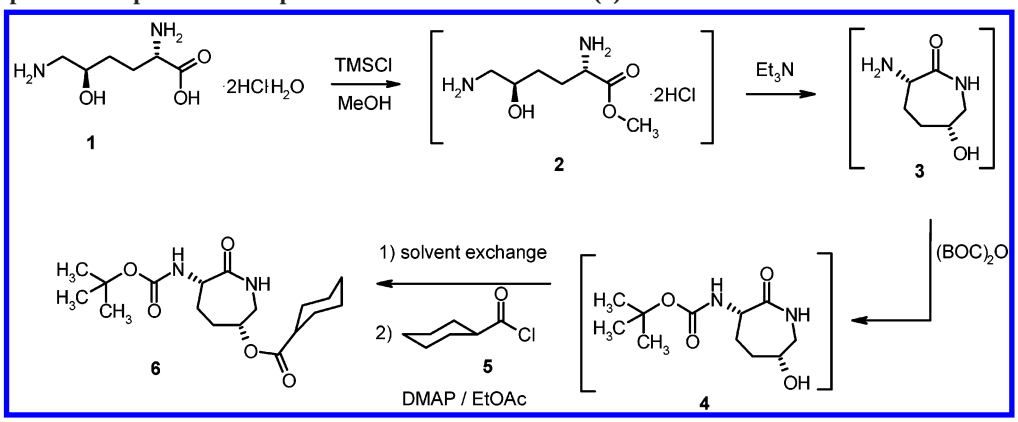


reagent grade), the trans/cis product ratio was 1:1. We could not obtain exclusive cis-olefination product for this substrate probably because of the bulkiness of the substituent. In the absence of exact diastereomeric composition of the bicyclic intermediate and the absolute stereochemistry of the central carbon having four heteroatoms attached, these results could not be unambiguously explained. Since formation of trans/cis olefin will depend not only on the stereochemistry of substituents but also on which bond cleavage occurs first. We are investigating this observation currently to make this method a choice for selective trans/cis olefination. If proved fruitful, the results will be published later. It was found that only the trans product crystallized from *tert*-butyl methyl ether, simplifying further the product isolation and purification. The desired trans isomer was simply crystallized from the extract aqueous workup. In the current case, a trans/cis ratio of 4/1 was routinely obtained by simply heating the reaction mixture.

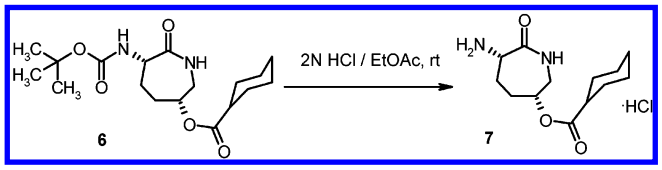
Preparation of ϵ-Caprolactam. Our next objective was to improve and simplify the preparation of **7**. The previous process suffered from high dilution (low throughput), expensive and hazardous reagents (HOBT, EDCI), and low efficiency (chromatographic separations, high-vacuum distillation). The removal of a large quantity of DMF and the extraction of fairly water soluble intermediate **4** into methylene chloride were unacceptable for scale-up. To overcome these problems, an alternative approach was (Scheme 9) designed. The idea was to attenuate the reactivity of the carboxylic acid so that the intermolecular-competing amide bond formation is suppressed, and the reaction can be run at higher concentration. The (5*R*)-5-hydroxy-L-lysine **(1)** was easily converted to methyl ester by treatment with TMSCl in methanol. The critical lactam formation was effected by a unique cooperative acid-conjugate base catalysis resulting from the base triethylamine and HCl (from TMSCl). Isolation of **4** proved to be problematic because of water solubility and contamination with Et_3N-HCl. Therefore, **4** was converted in situ to **6**, which could be easily isolated and purified. A solvent exchange was necessary for a complete esterification. The major portion of methanol was removed by distillation, and the residual methanol was azeotropically distilled with EtOAc. The esterification of **4** with **6** proceeded smoothly in the presence of a stoichiometric amount of DMAP. A substoichiometric amount of DMAP resulted in an incomplete reaction. Other amine bases such as triethylamine, catalytic DMAP, and Na-2-ethylhexanoate[11] gave unsatisfactory results.

(10) Compound **19** (R = diphenylmethyl): To the solution of 2-(2,2-dimethylpropylsulfonyl)benzothiazole **18** (32.4 g, 0.12 mol) in 400 mL of anhydrous THF at −78 °C was added a solution of $LiN(TMS)_2$ (130 mL, 0.13 mol). Reaction mixture was stirred for 1 h at −78 °C and treated dropwise with TMS−Cl (16.6 mL, 0.13 mol). To the resulting suspension at −78 °C was added a solution of diphenylacetaldehyde (17.8 mL, 0.1 mol) in 300 mL of THF over the period of 50 min. The mixture was stirred at −78 °C for 1 h, at 0 °C for 30 min, at RT for 30 min, and at 50 °C for 1 h. The mixture was quenched with water (300 mL) at 10 °C and concentrated under reduced pressure (35 °C, 50 mbar) to an aqueous oily phase. Heptane (150 mL) was added and stirred at 40 °C for 20 min. The crude solid **19** was filtered and washed with water (30 mL). Filtrate phases were separated, and the crude trans olefin was in the organic phase (heptane). The crude material **19** was purified by crystallization from MeOH to obtain (18.6 g, 0.034 mol) as a white crystalline solid. ^{1}H NMR (DMSO): δ 0.07 (s, 9H), 1.13 (s, 9H), 4.15 (s, 1H), 5.02 (d, J = 10.7 Hz, 1H), 5.43 (d, 10.7 Hz, 1H), 8.49−7.36 (m, 14H). ^{13}C NMR (CDCl3): δ 0.00, 27.66, 34.13, 57.36, 72.70, 73.48, 122.59, 123.73, 125.97, 126.20, 126.97, 127.13, 127.61, 127.73, 128.12, 128.51, 134.98, 140.67, 141.93, 150.48, 171.06. MS *m*/*z*: 538.0 [MH^+], 560.2 [M + Na^+].

Scheme 9. **Preparation of protected ϵ-caprolactam 6 from amino acid (1)**



Scheme 10. **Removal of the *tert*-butyloxycarbonyl protecting group from ϵ-caprolactam 6**



The discovery method used trifluoroacetic acid for the deprotection of the amino group. The resulting product was isolated as its free base via basification and chromatography. This method was very difficult to reproduce on a large scale because of (a) the difficulty in complete removal of TFA, (b) the difficulty of extraction of **7** from aqueous solution, and (c) chromatography. Attempts to achieve the deprotection using HCl (g) in MeOH/EtOAc (1:1) and HCl (g) in EtOH/EtOAc (1:6) gave lower yield because of solubility of the product in solvents. We found that **6** can be cleanly deprotected under anhydrous conditions in EtOAc using HCl (Scheme 10). The deprotected product was precipitated directly from the reaction as its HCl salt.

Coupling 15 with 7 Followed by Deprotection To Obtain 10. Because of low reactivity between **15** and **7**, the coupling was initially realized under forced high concentration conditions. These conditions led to the formation of up to 5% of the epimer[12] (at the C-2 position). The removal of the epimer was achieved by HPLC purification. Further, despite the high cost of the starting material and the difficulty in its preparation, **7** was used in excess (>2 equiv) in this coupling reaction, making the transformation very inefficient. Early attempts to couple the lactam hydrochloride **7** with lactone **15** in the presence of inexpensive base sodium 2-ethyl hexanoate (Na-EH, 1.5 equiv) gave the product **8** in 70−85% yield along with 5−30% of unknown byproducts. Use of 2-hydroxypyridine[13] (0.4 equiv) to facilitate opening of lactone and Na-EH (1.5 equiv) as a base gave the product **8** in 90% yield without byproducts. Similarly, use of the combination of triethylamine (0.5 equiv) and Na-EH (1.5 equiv) gave **8** in 70% yield. Our experience in the formation of **7** suggested the possibility of coordinated acid−base catalysis for the amide formation. Sodium 2-ethyl hexanoate was found to be an ideal base in promoting the amide formation and easy isolation of the product.[14] In the presence of 2 equiv of Na-EH, the coupling of **15** and **7** proceeded smoothly at room temperature without epimerization (Scheme 11). The product was obtained in 85−92% yield upon dilution of the reaction mixture with water and heptane. Two equivalents of the base were necessary for this coupling reaction. A smaller amount of the base led to isomeric acetonide-migrated byproduct formation.

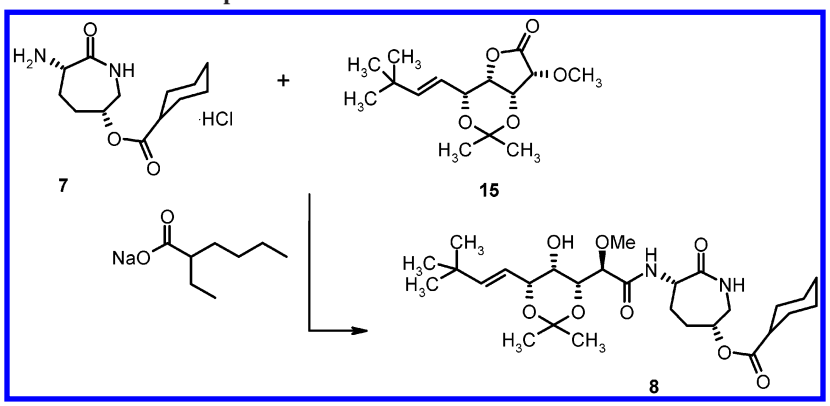
For the conversion of **8** to **9**, many of the known acid-catalyzed acetonide deprotection methods were evaluated. Use of *p*-TsOH/MeOH, PPTS/MeOH, and HCl/MeOH/EtOAc resulted in decomposition. Amberlyst-15/THF/water and TFA/THF/water gave **9** in 80−90% yield, accompanied by 5−10% of acetonide migration byproduct. Aqueous HCl (1 N) and THF (2:1) mixture gave good results. The reaction proceeded at room temperature and gave **9** with very little byproduct formation (<1% by HPLC, Scheme 12).

Initially, a two-stage crystallization was designed for achieving the desired purity and the crystal form. MTBE proved to be the best solvent for this purpose**.** Although the process removed most of the impurities, the product was a solvate with MTBE. A recrystallization from ethanol and water to furnish the preferred polymorph E and subsequent exposure to moisture produced the hemihydrate of **10** as the final drug substance. In a later process, it was found that removal of the acetonide of **8** could be achieved using 0.5 N HCl in ethanol at ambient temperature. After concentration of the reaction mixture to 66% of the original volume, the desired polymorph E of the drug substance **10** precipitated in high yield and good purity.

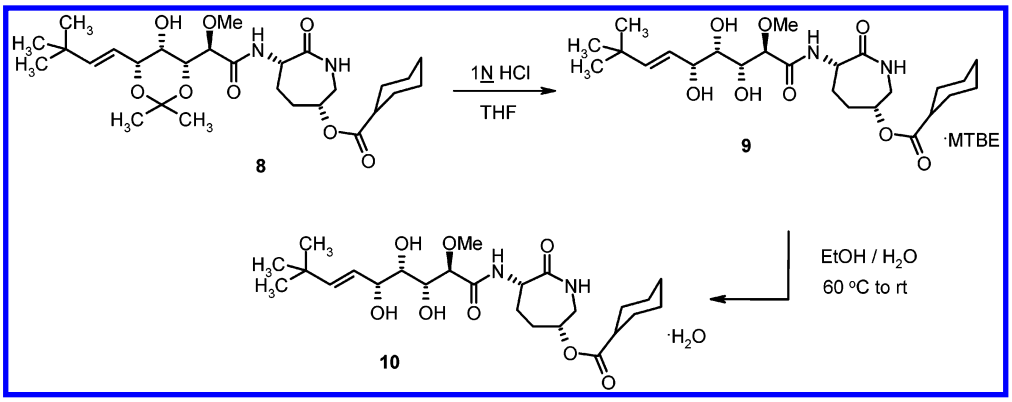
Thus, a general acid−base-catalyzed amide formation (opening of a lactone with an amine) was realized intermolecularly between lactone **15** and ϵ-caprolactam **7**. The mild conditions circumvented the problems of decomposition and epimerization encountered with the initial procedure. Also, a simple and much milder method (aq HCl-EtOH) for the deprotection of the acetonide group in **8** was developed.

(11) Fitt, J.; Prasad, K.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **1998**, *39*, 6991.
(12) NMR data (NOE experiments) indicated epimerization at CHOMe position next to the amide bond.
(13) (a) Swain, C. G.; Brown, J. F., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2538. (b) Kim, S. *Org. Prep. Proced. Int.* **1988**, *20*, 145.
(14) Liu, W.; Xu, D. D.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 2439.

Scheme 11. **Opening of lactone 15 with ϵ-caprolactam 7**



Scheme 12. **Conversion of 8 to 9**



These conditions lead to direct crystallization of the desired polymorph of drug substance.

Summary

In summary, the synthesis of LAF389 has been optimized and the process has been successfully scaled up in the pilot plant. Major improvements were made to O-methylation (K_3PO_4/Me_2SO_4) and regioselective hydrolysis of the bis-acetonide **12**. Modified Julia olefination using TMSCl (and BF_3-etherate) offered much-improved reproducibility. These conditions were thoroughly optimized to obtain the desired trans isomer via direct crystallization. A multistep, one-pot process using general acid-conjugate base-catalyzed cyclization of (5*R*)-5-hydroxy-L-lysine offered the seven-membered lactam very efficiently. Also, a mild general acid−base-catalyzed amide formation (opening of a lactone with an amine) was realized.

Experimental Section

General. ^1H and ^{13}C NMR spectra were measured on a 300 mHz spectrometer in either $CDCl_3$ or DMSO-d_6. The chemical purities were determined by HPLC qualitative and quantitative analysis using a C_{18} steel column, 5 μm particle size (4.6 mm × 250 mm). UV detection and mobile phase were varied depending upon substrate. Optical purities were determined by chiral HPLC (**6**) using a Chiracel-OD-R steel column (4.6 mm × 250 mm) (the mobile phase was varied depending upon substrate) or by Capillary Zone Electrophoresis analysis (ϵ-caprolactam **7** and bengamide B analogue **9**). In-process control TLC was run using silica gel precoated plates with a 250 μm layer thickness. Plates were visualized with either 5% ethanolic phosphomolybdic acid solution and heat or 254 UV light depending upon substrate. Specific analysis information and sample preparation is available upon request.

Materials. The starting material (5*R*)-5-hydroxy-L-lysine dihydrochloride monohydrate (**1**) was purchased from vendor. All other reagents and solvents were purchased from various commercial sources and used without further purification. All of the isolated intermediates were analyzed as indicated above and used directly in subsequent steps. All reactions were run in an inert nitrogen atmosphere unless otherwise indicated.

3,5:6,7-Bis-*O*-(1-methylethylidene)-D-glycero-D-gulo-heptonic Acid γ-Lactone (11). To a stirred slurry of D-glycero-D-gulo-heptonic acid γ-lactone **10** (260.0 g, 1.25 mol) in acetone (1870 mL) at 25 °C was added 2,2-dimethoxypropane (390 g, 461 mL, 3.75 mol). The slurry was cooled to 0 ± 5 °C, sulfuric acid (28.2 g, 15.5 mL, 0.287 mol) was added, and the mixture was stirred for 8 h. The solution was quenched with 8% sodium bicarbonate (1157 mL, gas evolution). The mixture was stirred for 30 min at 10−15 °C (pH = 8−8.5) and then stored in a refrigerator for 8 h. The acetone and methanol were distilled under reduced pressure (50 mmHg, 25 ± 5 °C). Ethyl acetate was added (2000 mL), and the mixture was stirred at 25 ± 5 °C for 15 min. The phases were separated, and the organic layer was washed with dilute aqueous sodium chloride solution (966 mL) and saturated sodium chloride solution (380 mL). The organic phase was concentrated at

ambient pressure to a residual volume of 500 mL. Heptane (1500 mL) was added at 65 ± 5 °C. The slurry was cooled to 25 °C, held for 30 min, cooled to 0 ± 5 °C, and held for 1 h. The solids were filtered and washed with heptane/ethyl acetate (3:1) containing 30 ppm of the antistatic agent Stadis 450 (2 × 100 mL). The product was dried at 45 °C to give **11** as a white crystalline solid (207.9 g, 0.72 mol, 57.7%), mp 156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.35 (s, 3H), 1.43−1.40 (d, 6H), 1.50 (s, 3H), 3.83−3.86 (m, 1H), 3.90−3.95 (m, 1H), 4.07−4.13 (m, 1H), 4.29−4.35 (m, 1H), 4.48−4.53 (m, 1H), 4.61−4.63 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ ppm 19.95, 25.24, 27.30, 29.24, 67.30, 68.46, 69.08, 69.84, 71.99, 73.42,99.20, 110.05, 175.16.

2-*O*-Methyl-3,5:6,7-bis-*O*-(1-methylethylidene)-D-glycero-D-gulo-heptonic Acid γ-Lactone (12). To a slurry of 3,5:6,7-bis-*O*-(1-methylethylidene)-D-glycero-D-gulo-heptonic acid γ-lactone **11** (200 g, 0.694 mol) in toluene (1400 mL) was added delumped tripotassium phosphate (441.6 g, 2.08 mol) at 20−25 °C. Dimethyl sulfate (262.3 g, 2.08 mol) was charged, and the slurry was stirred at 20−25 °C for 4 h. The solids were filtered, and the filter cake was rinsed with toluene (2 × 240 mL). Heptane (1900 mL) was added to the filtrate, and the product precipitated. The mixture was stirred at 20−25 °C for 15 min, cooled to 0 ± 5 °C, and held for 1 h. The solids were filtered and slurried in heptane/toluene (400 mL, 1:1) at −5 ± 5 °C for 15 min to reduce the dimethyl sulfate content. The solids were again filtered and slurried in heptane/toluene (400 mL, 1:1) containing 30 ppm Stadis 450. The solids were filtered and dried at 45 °C to give **12** as a white crystalline solid (108 g, 0.36 mol, 48.6%), mp 117 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.06 (s, 6H), 1.26 (s, 3H), 1.42 (s, 3H), 3.39 (s, 3H), 3.77−3.81 (m, 1H), 3.90−3.94 (m, 1H), 3.99−4.03 (m, 1H), 4.07−4.13 (m, 1H), 4.29−4.30 (d, 1H), 4.48−4.49 (d, 1H), 4.80, (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ ppm 19.78, 25.22, 27.34, 29.33, 59.6, 67.32, 67.95, 68.94, 69.92, 73.43, 76.98, 98.97, 110, 172.9. MS *m*/*z*: 287 [M − CH_3]. Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33; O, 37.04. Found: C, 53.44; H, 6.93; O, 39.17.

2-*O*-Methyl-3,5-*O*-(1-methylethylidene)-D-glycero-D-gulo-heptonic Acid γ-Lactone (13). To a stirred solution of 2-*O*-Methyl-3,5:6,7-bis-*O*-(1-methylethylidene)-D-glycero-D-guloheptonic acid γ-lactone **12** (98 g, 0.324 mol) in isopropyl acetate (490 mL), propionic acid (243 g, 245 mL, 3.284 mol), and water (29.2 g) was added a solution of *p*-toluenesulfonic acid (0.308 g, 0.0016 mol) dissolved in water (5.6 mL), and the resulting solution was heated at 40 °C for 2 h. The resulting slurry was cooled to 4 °C, held for 1 h, filtered, washed with cold isopropyl acetate (2 × 225 mL), and dried at 50 °C to afford **13** as a white, crystalline solid (71 g, 0.27 mol, 83%), mp 120 °C. ^{1}H NMR (DMSO-d_6): δ ppm 1.24 (s, 3H), 1.42 (s, 3H), 3.15−3.37 (m, 1H), 3.39 (s, 3H), 3.48−3.56 (m, 2H), 3.93 (dd, J = 1.6, 9.1 Hz, 1H), 4.36 (m, 1H), 4.41 (m, 1H), 4.48 (d, J = 3.8 Hz, 1H), 4.78 (dd, J = 2.1, 3.8 Hz, 1H), 4.96 (d, J = 5.8 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ ppm 19.69, 29.45, 57.90, 62.67, 67.61, 67.72, 69.11, 69.33, 78.80, 98.01, 173.86. MS *m*/*z*: 285.1 [M + Na^+]. Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.42; H, 6.95. $[\alpha]^{25}_D$ −97.63° (*c* 1.01, MeOH).

5-*O*-Methyl-2,4-*O*-(1-methylethylidene-L-glucoronic Acid γ-Lactone (14). In a 5-L, 4-necked round-bottomed flask equipped with a mechanical stirrer and a thermocouple were placed 2-*O*-methyl-3,5-*O*-(1-methylethylidene)-D-glycero-D-gulo-heptonic acid γ-lactone (**13**, 50 g, 190.65 mmol), water (175 mL), and acetonitrile (350 mL). The mixture was stirred at 25 °C until a clear solution was obtained (10 min) and then cooled to 5 °C. Sodium periodate (44.9 g, 209.7 mmol) was added in portions at such a rate as to maintain a temperature of 5−10 °C. The reaction mixture was vigorously stirred at 5−10 °C for 1 h, then acetonitrile (300 mL) and isopropyl acetate (900 mL) were added. The mixture was cooled to 8 °C, and anhydrous magnesium sulfate (56.25 g) was added portionwise at or below 15 °C. The suspension was cooled back to 8 °C, and sodium bicarbonate (16.25 g) was added, followed immediately by the portionwise addition of magnesium sulfate (168.8 g) at or below 20 °C. The reaction mixture was warmed to 25 °C and stirred for 1 h. Magnesium sulfate (87.5 g) was added, and the suspension was stirred for 1 h. The solids were filtered and washed with a mixture of acetonitrile (200 mL) and isopropyl acetate (600 mL). The filtrate was transferred to a 5-L, 4-necked round-bottomed flask, and the solvent was distilled at 30−35 °C (100−75 Torr) to a final volume of 450 mL. Isopropyl acetate (1200 mL) was added, and the solvent was distilled at ambient pressure (81−89 °C) to a volume of 800 mL. (Caution: The material is unstable. Exposure to temperatures above 70 °C must not exceed 1 h.) The mixture was cooled to 25 °C, and the product precipitated. The solids were filtered, washed with isopropyl acetate (105 mL), and dried (25 °C, 50 mbar) to afford 5-*O*-methyl-2,4-*O*-(1-methylethylidene)-L-glucoronic acid γ-lactone (**14**, 35.1 g, 80%) as a white solid, mp 152−154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.52 (s, 1H), 4.88−4.84 (m, 2H), 4.67 (dd, 1H, J = 2.3, 2.1 Hz), 4.51 (d, 1H, J = 4.0 Hz), 3.41 (s, 3H), 1.49 (s, 3H), 1.37 9s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.2, 137.2, 98.7, 78.3, 73.4, 68.7, 67.3, 58.1, 29.2, 19.6. MS *m*/*z*: 231 (M + 1), 213, 203, 181, 173, 163. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.01; H, 5.96.

8-Methyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-6,7,8,9-tetradeoxy-D-gulo-6-nonenonic Acid (6E)-γ-Lactone (15). A stirred solution of 2-(2,2-dimethylpropylsulfonyl) benzothiazole **18** (168.5 g, 0.63 mol) in anhydrous THF (2000 mL) was treated dropwise at −55 °C with 1 M lithium bis-(trimethylsilyl)amide solution in THF (677.6 mL, 0.68 mol). The solution was cooled to −78 °C and stirred for 1.5 h and then treated dropwise with chlorotrimethylsilane (86 mL, 0.68 mol). The resulting suspension (−78 °C) was transferred to a cold (0 to −15 °C) solution of 5-*O*-methyl-2,4-*O*-(1-methylethylidene)-L-glucoronic acid γ-lactone **14** (120.0 g, 0.52 mol) and dry $NaHCO_3$ (1.96 g, 0.029 mol) in anhydrous acetonitrile (1960 mL) over 20 min. The resulting mixture was warmed to 0 °C over 20 min, stirred for 1 h, warmed to 22 °C over 30 min, stirred for 1 h, warmed to 50 °C over 30 min, and stirred for 1 h. The mixture was cooled to 10 °C,

quenched with water (1.5 L), and concentrated under reduced pressure (35 °C, 50 mbar) to a paste. MTBE (4.0 L) was added, and the phases were separated. The organic phase was washed with water (0.8 L) and concentrated at atmospheric pressure to a volume of 640 mL. The concentrate was cooled to 22 °C over 1 h, stirred for 30 min, cooled to 0 °C, and stirred for 30 min. The solids were filtered and washed with cold (0 °C) MTBE (200 mL) to afford **15** as a white crystalline solid (65.9 g, 0.23 mol, 44.5%), mp 179−181 °C. ^{1}H NMR ($CDCl_3$): δ ppm 1.04 (s, 9H), 1.49, 1.54 (2s, 6H), 3.36 (s, 3H), 4.00 (dd, J = 4.1 Hz, 1H), 4.10 (d, J = 3.9 Hz, 1H), 4.46 (dd, J = 7.3, 2.4 Hz 1H), 4.72 (dd, J = 3.9, 2.1 Hz, 1H), 5.59 (dd, J = 15.8, 7.5 Hz, 1H), 5.84 (dd, J = 15.8, 0.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 19.28, 29.24 (*t*-bu), 33.24, 59.18, 67.57, 70.34, 71.90, 79.07, 98.72, 120.07, 147.07, 172.97. MS *m*/*z*: 301.8 [M + NH_4^+]. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.27; H, 8.42. $[\alpha]^{25}_D$ −148.12° (*c* 1.04, MeOH).

[(3*R*-*cis*)-6-(1,1-Dimethylethoxy)carbonylamino-hexahydro-7-oxo-1*H*-azepin-3-yl]cyclohexanecarboxylic Acid Ester (6). A stirred solution of (5*R*)-5-hydroxy-L-lysine dihydrochloride monohydrate **1** (126.6 g, 0.50 mol) in methanol (1500 mL) at 25 °C was treated dropwise with chlorotrimethylsilane (135.8 g, 159 mL, 1.25 mol). The solution was heated to 63 °C, stirred for 3 h, cooled to 50 °C, and treated dropwise with triethylamine (253 g, 349 mL, 2.5 mol). A precipitate immediately formed. The suspension was stirred at 50 °C for 3 h, cooled to 25 °C, and treated in one portion with di-*tert*-butyl dicarbonate (131 g, 0.6 mol). A solution resulted within a few minutes, and it was stirred for 1 h and concentrated under reduced pressure (50 °C, 100 mbar) to a thick paste. Ethyl acetate (2 L) was added, and the concentration was repeated. Fresh ethyl acetate (2 L) was charged, and the methanol content was monitored by GC analysis. The charge/concentrate/charge sequence was repeated until the methanol content was ≤0.05 mg/mL. To the suspension was added 4-(dimethylamino)-pyridine (79.4 g, 0.65 mol). The suspension was heated to 50 °C, treated dropwise with cyclohexanecarbonyl chloride (88 g, 0.6 mol), and stirred for 3 h. The mixture was quenched with water (1 L), and the phases were separated. The organic phase was washed with water, azeotropically dried (1 atm), and concentrated to a volume of 800 mL. Heptane (1.4 L) was added, the resulting suspension was stirred for 1 h at 4 °C, and the solids were filtered, washed with 500 mL of a 2:1 mixture of heptane/ethyl acetate, and dried at 50 °C to afford **6** as a white crystalline solid (146 g, 0.41 mol, 82.5%), mp 220 °C. ^{1}H NMR ($CDCl_3$): δ ppm 1.17−1.38 (m, 5H), 1.43 (s, 9H), 1.59−1.67 (m, 1H), 1.68−1.82 (m, 3H), 1.85−2.05 (m, 4H), 2.08−2.13 (m, 1H), 2.25−2.35 (m, 1H), 3.39−3.55 (m, 2H), 4.29 (dd, J = 9.8, 5.8 Hz, 1H), 4.88 (d, J = 2.6 Hz, 1H), 5.90 (d, J = 5.6 Hz, 1H), 6.29 (t, J = 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 25.72, 25.74, 26.02, 27.17, 28.75 (*t*-bu), 29.32, 29.36, 32.42, 43.54, 43.67, 53.27, 67.27, 80.00, 155.54, 175.46, 175.64. MS *m*/*z*: 377.1 [M + Na^+]. Anal. Calcd for $C_{18}H_{30}N_2O_5$: C, 61.00; H, 8.53; N, 7.90. Found: C, 61.21; H, 8.53; N, 7.84. $[\alpha]^{25}_D$ +79.84° (*c* 1.02, MeOH).

(3*S*,6*R*)-3-Aminohexahydro-6-cyclohexanecarboxy-2*H*-azepin-2-one Hydrochloride (7). 6 (300 g, 0.85 mol) was added in portions to a 2 N solution of HCl in ethyl acetate (3.0 L) at 15 °C. The mixture was stirred at 23 °C for 6 h. The resulting suspension was filtered and washed with ethyl acetate (1200 mL). The solids were collected and dried at 40 °C (50 mbar) to give **7** as a white, crystalline solid (240.0 g, 98%), mp 285 °C (dec). ^{1}H NMR (D_2O, 300 MHz): δ 4.91 (s, 1 H), 4.25 (m, 1 H), 3.44 (s, 2 H), 2.34 (m, 1 H), 2.13 (m, 1 H), 1.72−2.00 (m, 5 H), 1.42−1.68 (m, 3 H), 1.00−1.39 (m, 5 H). ^{13}C NMR (D_2O, 75 MHz): δ 177.9, 173.1, 67.1, 52.2, 42.9, 42.0, 30.4, 28.6, 28.3, 25.1, 24.8, 24.7, 22.6. MS *m*/*z*: 255.2, 238.2. Anal. Calcd for $C_{13}H_{23}ClN_2O_3$: C, 53.69; H, 7.99; N, 9.64. Found: C, 53.67; H, 7.91; N, 9.56; $[\alpha]^{24}_D$ +72.5° (*c* 1.0, H_2O).

(6*S*)-6-[2-[(4*R*,5*S*,6*R*)-6-[(1*E*)-3,3-Dimethyl-1-butenyl]-5-hydroxy-2,2-dimethyl-[1,3]-dioxan-4-yl]-(2*R*)-2-methoxyacetylamino]hexahydro-7-oxo-(3*R*)-1*H*-azepin-3-ylcyclohexanecarboxylic Acid Ester (8). A flask was charged with **7 (**112.49 g, 0.39 mol), sodium 2-ethylhexanoate (116.34 g, 0.70 mol), **15** (100.0 g, 0.35 mol), and tetrahydrofuran (1.75 L). The solution was stirred at 23 °C for 20 h. Water (350 mL) was added, followed by a slow addition of heptane (3.5 L) at 23 °C. The resulting suspension was stirred at room temperature for 3 h, cooled to 2 °C, and stirred for an additional 2 h. The mixture was filtered and washed with water (200 mL) and heptane (400 mL). The solids were collected and dried at 40 °C (50 mbar) to give **8** as a white solid (166.55 g, 88%), mp 209−211 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (d, 1 H, J = 6.4 Hz), 6.49 (t, 1 H, J = 6.2 Hz), 5.69 (d, 1 H, J = 15.8 Hz), 5.43 (dd, 1 H, J = 15.8, 6.7 Hz), 4.83 (d, 1 H, J = 3.6 Hz), 4.52 (m, 1 H), 4.20 (d, 1 H, J = 6.7 Hz), 3.99 (d, 1 H, J = 7.3 Hz), 3.83 (d, 1 H, J = 7.4 Hz), 3.40−3.50 (m, 3 H), 3.39 (s, 3 H), 2.79 (br s, 1 H), 2.21 (m, 1 H), 1.78−2.05 (m, 5 H), 1.50−1.70 (m, 4 H), 1.34 (s, 6 H), 1.10−1.30 (m, 5 H), 0.93 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, 174.5, 169.4, 145.1, 121.4, 99.4, 80.3, 74.3, 73.0, 66.7, 65.6, 59.0, 51.5, 43.0, 32.9, 31.8, 29.4, 29.2, 28.8, 28.7, 25.7, 25.5, 25.2, 25.1, 18.9. MS *m*/*z*: 538.9, 481.2. Anal. Calcd for $C_{28}H_{46}N_2O_8$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.51; H, 8.58; N, 5.13. $[\alpha]^{24}_D$ +57.7° (*c* 1.0, MeOH).

Hexahydro-7-oxo-(6*S*)-6-[(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-1-oxo-6-nonenylamino]-(3*R*)-1*H*-azepin-3-ylcyclohexanecarboxylic Acid Ester (10). To a solution of tetrahydrofuran (1.80 L) and 1 N hydrochloric acid (3.60 L) at 22 °C was added **8 (**180.0 g, 0.335 mol). The solution was stirred at 22 °C for 4 h, cooled to 5 °C, and neutralized to pH 7.0 with 5.0 N aqueous sodium hydroxide solution. Sodium chloride (1260 g) was added, and the mixture was warmed to 22 °C. Ethyl acetate (1.80 L) was added, the mixture was shaken, and the phases were separated. The organic phase was distilled under vacuum, and 3.14 L of distillate was collected. Toluene (0.27 L) was added, and the solution was again distilled under vacuum until 0.30 L of distillate was collected. *tert*-Butyl methyl ether (0.72 L) was charged at 50 °C, and the solution was stirred at 50 °C for 0.5 h, cooled further to 22 °C, and stirred for

10 h. The resulting suspension was then cooled to 2 °C and stirred for 2 h. The solids were filtered and washed with *tert*-butyl methyl ether (0.16 L) and dried at 40 °C (50 mbar) to give crude **9** as a white solid (160.8 g). The crude solids (160.3 g) and ethanol (0.20 L) were charged to a 1-L flask, and the suspension was heated to 60 °C. Water (0.60 L) was slowly added. The resulting mixture was stirred at 60 °C for 15 min, cooled slowly to 22 °C, and stirred for 6 h. The suspension was cooled to 0 °C and stirred for 2 h, filtered and washed with of water (0.20 L), and dried at 40 °C (50 mbar). The solids were exposed to air for 24 h to give **10** (133.6 g, 79%) as a white solid, mp 148−149 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, 1 H, J = 6.4 Hz), 6.32 (t, 1 H, J = 6.2 Hz), 5.83 (d, 1 H, J = 14.9 Hz), 5.42 (dd, 1 H, J = 15.7, 7.3 Hz), 4.95 (m, 1 H), 4.57 (m, 1 H), 4.36 (d, 1 H, J = 2.5 Hz), 4.24 (m, 1 H), 3.85 (s, 2 H), 3.60 (m, 2 H), 3.52 (s, 3 H), 3.45 (m, 2 H), 3.30 (s, 1 H), 2.35 (m, 1 H), 1.60−2.20 (m, 9 H), 1.15−1.50 (m, 5 H), 1.01 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.6, 174.7, 172.4, 146.0, 123.6, 81.6, 74.8, 73.0, 72.9, 67.1, 60.2, 52.0, 43.6, 33.4, 32.3, 29.8, 29.4, 29.3, 26.1, 26.0, 25.8, 25.7. MS *m*/*z*: 499.0, 481.1, 445.3, 355.2. Anal. Calcd for $C_{25}H_{42}N_2O_8$: C, 60.22; H, 8.49; N, 5.62. Found: C, 59.94; H, 8.37; N, 5.54. $[\alpha]^{24}_D$ +98.5° (*c* 1.0, MeOH).

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