

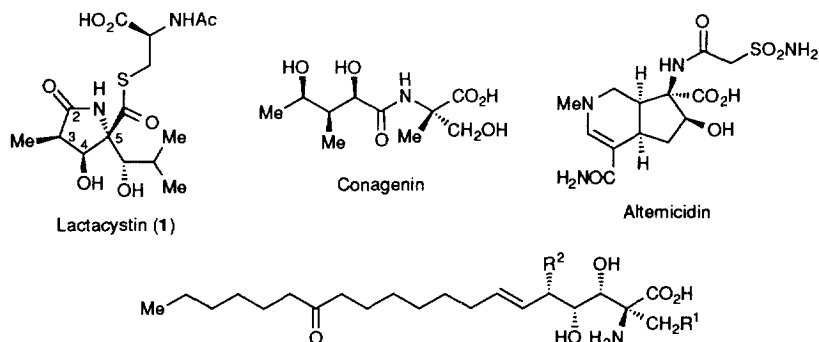
Stereoselective Total Synthesis of (+)-Lactacystin from D-Glucose

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Abstract: The chiral and stereoselective synthesis of (+)-lactacystin **1**, the first non-protein neurotrophic factor having an α,α -disubstituted α -amino acid structure, is described. The highly functionalized γ -lactam portion possessing a tetra-substituted carbon with nitrogen in **1** was effectively constructed from D-glucose using allylic trichloroacetimidate rearrangement (Overman rearrangement) as the key reaction. © 1997 Elsevier Science Ltd.

Lactacystin **1**, isolated from the culture broth of *Streptomyces* sp. OM-6519, is reported to inhibit cell proliferation and induce neurite outgrowth in the mouse neuroblastoma cell line Neuro 2A.¹ The structural elucidation study of lactacystin by Omura's group revealed that **1** has an α,α -disubstituted α -amino acid structure containing novel γ -lactam thioester.² Such interesting neurotrophic activity as well as its unique structure stimulated the synthetic interest and three elegant total syntheses (Corey,^{3a} Sunazuka, Omura and Smith,^{3b,c} and Uno and Baldwin^{3d}) of **1**, all employing amino acids as the starting material, have been reported to date. Reports on the synthesis⁴ and the structure-activity relationship study^{3c,5} of the analogs of **1**, and the



$R^1 = OH, R^2 = H$: Myriocin

$R^1 = R^2 = \text{OH}$: Sphingofungin E

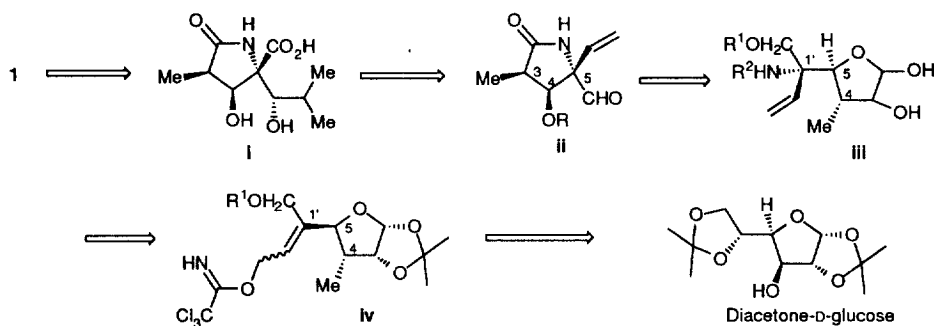
$R^1 = H, R^2 = OH$: Sphingofungin F

(The relative and absolute stereochemistry of sphingofungin E and F has not been determined)

biosynthetic pathway of lactacystin have also appeared.⁶ Recently, lactacystin has been reported to be a potent 20S proteasome peptidase inhibitor and attracted biological attention.⁷ The most interesting structural feature of **1** would be the presence of highly functionalized γ -lactam with four contiguous chiral centers including a tetra-substituted carbon possessing a nitrogen function. For stereoselective construction of the tetra-substituted carbon, Corey and Sunazuka's group adopted Seebach's protocol⁸ using aldol reaction of oxazolidine^{3a} and oxazoline^{3b,c} derivatives, whereas Uno and Baldwin applied the Mukaiyama-aldol reaction of the bicyclic siloxypyrrole.^{3d}

Recently, natural products with α,α -disubstituted α -amino acid structures, such as sphingofungin E and F,⁹ conagenin,¹⁰ altemicidin,¹¹ and ISP-I^{12a} (a.k.a. myriocin^{12b}) have been isolated. Due to their interesting and important biological activities (antibiotic,^{9,11a} immunomodular,^{10a} immunosuppressive,^{12a,b} and enzyme inhibitory⁹), α,α -disubstituted α -amino acid derivatives are expected to be potent lead compounds for novel drugs, and the development of efficient chiral synthetic pathway to these compounds should be a highly important work.¹³ In this paper, we report a stereoselective synthesis of **1** starting from D-glucose, which involved the stereoselective generation of the tetra-substituted carbon possessing amino functionality by the rearrangement of the allylic trichloroacetimidate (Overman rearrangement).¹⁴

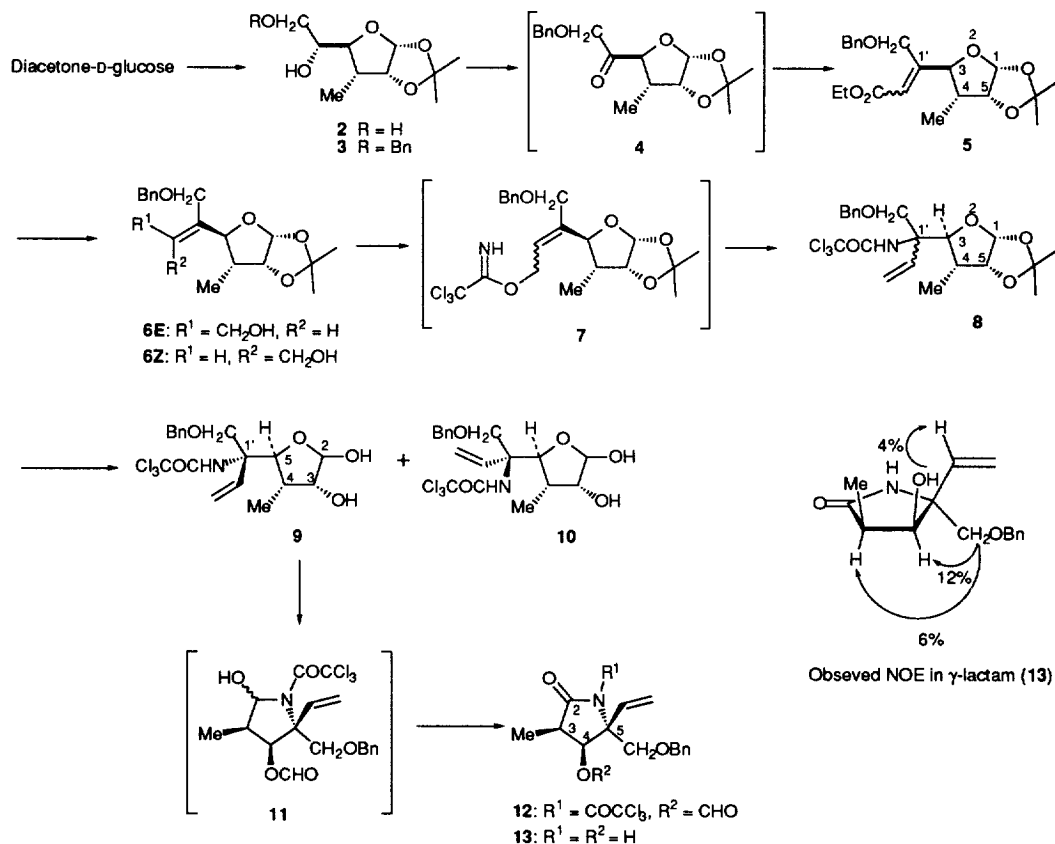
Retrosynthetically, we reasoned that the lactam-aldehyde (**ii**) would be a suitable precursor for the synthesis of **1** and its analogs containing various functional groups at C5. Construction of the tetra-substituted carbon possessing amino group (C5) in **ii** was envisioned to arise from trichloroacetimidate (**iv**) by Overman rearrangement.¹⁵⁻¹⁷ The imidate **iv**, which contains suitable asymmetric centers (C4 and C5) corresponding to C3 and C4 in lactacystin, was planned to be derived from diacetone-D-glucose.



The known 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl- α -D-allofuranose **2**,¹⁸ prepared from diacetone-D-glucose in four steps, was chosen as the starting material. Reaction of **2** with dibutyltin oxide¹⁹ followed by treatment with benzyl bromide afforded **3** in 66% yield. The physical and spectral properties of **3** were fully identical with those of the authentic compound, prepared in a different manner from D-glucose by Yonemitsu.²⁰ Jones oxidation of **3** gave **4**, which was subjected to Wittig reaction to give olefin **5** as an inseparable mixture of *E*- and *Z*-isomers (1:1) in 78% yield from **3**. Reduction of the ester function in **5** with diisobutylaluminum hydride (DIBAL) gave **6E** and **6Z**, the substrate for Overman rearrangement (*E*:*Z* = 1:1), in 90% yield. A 1:1 mixture of allylic alcohols **6E** and **6Z** was converted into trichloroacetimidate **7**, which, without isolation, was heated in toluene at 140 °C (in a sealed tube) for 89 h to provide the rearranged product **8** as an inseparable

diastereomeric mixture at C1' in a ratio of 4:1 (determined with 270 MHz ^1H NMR spectrum) in 60% yield from the mixture of **6E** and **6Z**. Acid hydrolysis of the mixture, followed by chromatographic separation afforded **9** in 72% isolated yield as an equilibrium mixture of C2 epimers (6:1) and **10** in 19% yield (8:1 epimeric mixture), respectively. The configuration at C2 in major isomers of **9** and **10** were tentatively assigned to be both *R* (2,3-*trans* relationship), judging from the observed coupling constants ($J_{2,3} \sim 0$ Hz for compounds **9** and **10**).²¹

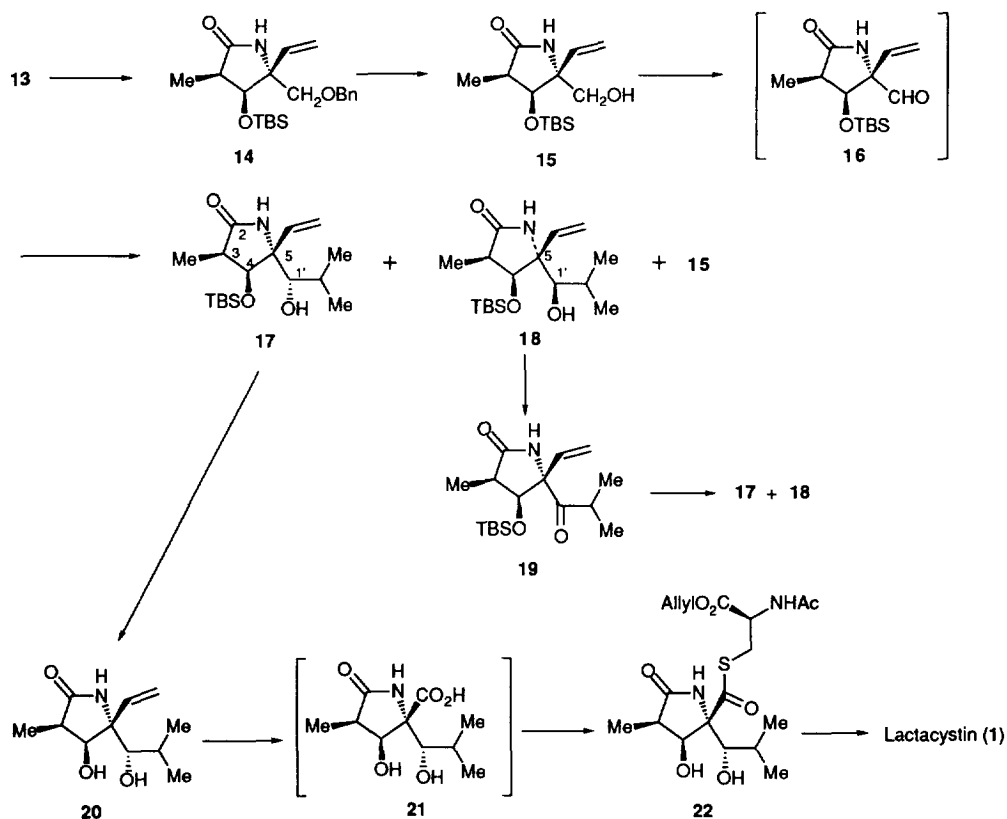
It has been reported that the rearrangement of allylic trichloroacetimidate is greatly accelerated by addition of $\text{Hg}^{15,22a}$, Pd^{22} , Pt^{22b} , Ir^{22b} and Rh^{22b} salts. However, for compound **7**, it was found that the addition of metal salts [Hg(II) , Pd(0) , and Pd(II)] gave disappointing results; recovery of the starting material or, under more vigorous condition, only decomposition of the imidate were observed. Addition of Lewis acids (AlCl_3 or $\text{BF}_3 \cdot \text{OEt}_2$) also resulted in a decomposition of the imidate. By the separate experiments, it was shown that rearrangement of the isomerically pure allylic alcohol **6E** (isolated in a small quantity by repeated chromatographic separation) afforded **9** and **10** in a ratio of 2.7 : 1, and that of **6Z** gave **9** and **10** in a ratio of 5.0 : 1, respectively.



Scheme 1. Bn = $-\text{CH}_2\text{Ph}$.

With the rearranged product, obtained in a moderate stereoselectivity and yields in hand, transformation of **9** into γ -lactam was next explored. Periodate oxidation of **9** provided an equilibrium mixture consisting of hemiaminal derivative **11** and acyclic aldehyde. Jones oxidation of the mixture gave the corresponding lactam **12**, whose protecting (*N*-trichloroacetyl and *O*-formyl) groups were cleanly removed by treatment with NaBH_4 to furnish the γ -lactam **13** in 75% yield from **9**. The observed NOE in **13** clearly supported the assigned structure, revealing that the newly formed stereocenter at C(5) should be *R* (Scheme 1).

Silylation of the hydroxyl group in **13** gave **14** (92% yield), whose *O*-benzyl group was removed to afford **15** in 77% yield (Scheme 2). Moffatt oxidation of **15** afforded **16**, which, without isolation, was treated with isopropylmagnesium bromide in tetrahydrofuran to give adducts **17**, **18** and reduced product **15** in 30, 35 and 21% isolated yields from **15**, respectively, after separation by silica gel chromatography. Since attempted conversion of the undesired isomer **18** to **17** via $\text{S}_{\text{N}}2$ -type reaction failed, **18** was subjected to oxidation-reduction procedure. Oxidation of **18** gave ketone **19** (78% yield), whose reduction with various reagents was carried out (Table 1). Although reduction of **19** with NaBH_4 afforded undesired **18** as the major isomer and with $\text{Zn}(\text{BH}_4)_2$ or DIBAL showed low stereoselectivity, use of triisobutylaluminum in dichloroethane proceeded stereoselectively and gave **17** as the major product in 70% yield (**18**; 7% yield). The possible



Scheme 2. TBS = $-\text{SiMe}_2(t\text{-Bu})$, Allyl = $-\text{CH}_2\text{CH}=\text{CH}_2$.

Table 1. Reduction of Ketone (**19**).

run	reagents	solvent	temp (°C)	ratio ^a (17 : 18)	yields ^b (%)
1	NaBH ₄	MeOH	0	1.0 : 4.1	84
2	L-Selectride®	THF	0 → room temp.	---	no reaction
3	Zn(BH ₄) ₂	Et ₂ O	-15 → 0	1.8 : 1.0	(98)
4	DIBAL	toluene	-78 → 0	1.4 : 1.0	(97)
5	Red-Al®	toluene	-78	1.0 : 1.2	(97)
6	(<i>i</i> -Bu) ₃ Al	(ClCH ₂) ₂ -hexane	0 → room temp.	10.0 : 1.0	78

a) Ratio was determined with 270 MHz ¹H NMR spectrum. b) Combined isolated yields of compound **17** and **18**, number in parentheses are crude yields of **17** and **18** before purification.

conformational change in **19** caused by coordination of bulky triisobutylaluminium to ketone carbonyl, and the different mode of reduction (intramolecular β -hydride transfer from coordinated triisobutylaluminium) from other reagents might be responsible for the observed stereoselectivity. Treatment of **17** with aqueous trifluoroacetic acid (TFA) provided **20** in 76% yield. Ozonolysis of **20** (dimethyl sulfide workup) followed by selective oxidation of the resulting aldehyde afforded carboxylic acid **21**, which, without isolation, was coupled with *N*-acetyl-L-cysteine allyl ester by the procedure reported by Corey^{3a} to provide lactacystin allyl ester **22** {m.p. 183-185 °C (dec); [α]_D²³ +38 (c 0.74, acetone). lit.^{3d} m.p. 181-182 °C (dec); [α]_D²² + 39.8 (c 0.55, acetone)} in 60% yield from **20**. The spectral data for **22** were fully identical to those reported previously^{3c,d} in all respects. Finally, removal of the allyl protecting group^{3a} gave (+)-lactacystin **1** in 70% yield. The physical property of synthetic **1** {m.p. 234-236 °C (dec); [α]_D¹⁵ + 75 (c 0.4, MeOH). lit.² m.p. 237-238 °C (dec); [α]_D²⁵ + 71.3 (c 0.5, MeOH)}, as well as spectroscopic data for **1** (¹H and ¹³C NMR) showed a good accord with those reported for the natural product.²

In summary, stereoselective total synthesis of lactacystin starting from D-glucose has been achieved. This work provided the novel pathway to lactacystin which would be applicable to its analog synthesis and proved that Overman rearrangement of allylic trichloroacetimidates derived from carbohydrates should be an effective method for the chiral synthesis of α,α -disubstituted amino acid derivatives. Study on synthesis of other natural products possessing α,α -disubstituted α -amino acid structures starting from carbohydrates is now under investigation in our laboratory.

EXPERIMENTAL

M.p.s were determined on a Mitamura-riken micro hot stage and are uncorrected. ¹H NMR spectra were measured with a JEOL JNM EX-90 (90 MHz), a JEOL JNM-GSX 270 (270 MHz) or a JEOL JNM-GX 400 (400 MHz) spectrometers, with tetramethylsilane as the internal standard for solutions in deuteriochloroform, unless otherwise noted, and J values are given in Hz. ¹³C NMR spectra were taken on a JEOL JNM-GSX 270 (67 MHz) or a JEOL JNM-GX 400 (100 MHz) spectrometer. Low and high resolution mass spectra were measured by a JEOL JMS-DX 303 spectrometer with EI mode (70 eV). Optical rotations were measured with a JASCO DIP-370 instrument with 1-dm tube and values of [α]_D are recorded in units of 10⁻¹ deg cm² g⁻¹. IR spectra were taken with a JASCO IR-810 spectrometer. Organic extracts were dried over anhydrous Na₂SO₄ and concentrated below 40 °C under reduced pressure.

6-O-Benzyl-3-deoxy-1,2-O-diisopropylidene-3-C-methyl- α -D-allofuranose (3). To a solution of 3-deoxy-1,2-O-isopropylidene-3-C-methyl- α -D-allofuranose (2, 714 mg, 3.27 mmol) in toluene (20 mL) was added di-*n*-butyltin oxide (815 mg, 3.27 mmol), and the resulting mixture was heated under reflux for 3 h. After cooling, the mixture was concentrated to give a residue, which was dissolved in DMF (25 mL). To this solution were added cesium fluoride (746 mg, 4.91 mmol) and benzyl bromide (0.778 mL, 6.54 mmol), and the mixture was stirred at room temperature for 18 h. To the reaction mixture was added 10% aqueous KF solution, and the mixture was stirred at room temperature for 1 h. The products were extracted with EtOAc (x3), and the combined organic layer was washed successively with 10% aqueous KF solution, water and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (80 g), with EtOAc-toluene (1:8) as eluent, to afford compound **3** (661 mg, 66%) as a colorless syrup. $[\alpha]_D^{20} + 18$ (c 1.0, CHCl₃) [lit.²⁰; $[\alpha]_D^{17} + 19$ (c 1.4, CHCl₃)]; ¹H NMR (90 MHz) δ 1.16 (d, J = 6.1 Hz, 3H), 1.31, 1.50 (2 s, 3H x 2), 1.88-2.27 (m, 2H), 3.42-4.01 (m, 4H), 4.48-4.58 (m, 3H), 5.74 (d, J = 4.0 Hz, 1H), 7.21-7.37 (m, 5H). Anal. Found: C, 65.81; H, 8.01. Calcd. for C₁₇H₂₄O₅: C, 66.21; H, 7.84%.

An Inseparable Mixture of (1*R*,3*S*,4*R*,5*R*)-3-[(*E*)-1-Benzylloxymethyl-2-ethoxycarbonylphenyl]-4-methyl-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane and its *Z*-isomer (5). To a stirred solution of **3** (353 mg, 1.14 mmol) in acetone (8 mL) at 0 °C was added Jones reagent (2.67 mol/L solution of CrO₃ in aqueous sulfuric acid; 0.514 mL, 1.37 mmol), and the resulting mixture was stirred at 0 °C for 1 h. After addition of 2-propanol, the mixture was diluted with EtOAc and then washed successively with saturated aqueous NaHCO₃ solution and brine, and dried. Removal of the solvent gave crude ketone **4**, which was dissolved in toluene (12 mL). To this solution was added (carbethoxymethylene)-triphenylphosphorane (688 mg, 2.29 mmol), and the mixture was stirred at room temperature for 1 h and then at 60 °C for 15 h. The reaction mixture was evaporated to afford a residue, which was chromatographed on a column of silica gel (30 g), with acetone-hexanes (1:15) as eluent, to afford compound **5** as an inseparable mixture (1:1) of *E*- and *Z*-isomers as a colorless syrup. ¹H NMR (270 MHz) δ 1.07 (d, J = 6.6 Hz, 1/2 x 3H), 1.09 (d, J = 6.6 Hz, 1/2 x 3H), 1.27 (t, J = 7.3 Hz, 1/2 x 3H), 1.29 (t, J = 7.3 Hz, 1/2 x 3H), 1.34, 1.57 (2 s, 3H x 2), 1.91-2.18 (m, 1H), 4.13-4.20 (m, 3H), 4.39 (d, J = 12.5 Hz, 1/2 x 1H), 4.44 (d, J = 11.4 Hz, 1/2 x 1H), 4.47-4.59 (m, 3H), 4.87 (d, J = 12.5 Hz, 1/2 x 1H), 5.77 (d, J = 11.4 Hz, 1/2 x 1H), 5.78 (d, J = 3.7 Hz, 1/2 x 1H), 5.82 (d, J = 3.7 Hz, 1/2 x 1H), 6.07 (s, 1/2 x 1H), 6.22 (s, 1/2 x 1H), 7.22-7.41 (m, 5H). Anal. Found: C, 67.21; H, 7.49. Calcd. for C₂₁H₂₈O₆: C, 67.00; H, 7.50%.

(1*R*,3*S*,4*R*,5*R*)-3-[(*E*)-1-Benzylloxymethyl-3-hydroxy-1-propenyl]-4-methyl-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane (6*E*) and its *Z*-isomer (6*Z*). To a solution of compound **5** (760 mg, 2.02 mmol, a 1:1 mixture of *E*- and *Z*-isomers) in CH₂Cl₂ (30 mL) at -15 °C was added dropwise 1.02 mol/L solution of diisobutylaluminumhydride in CH₂Cl₂ (4.95 mL, 5.05 mmol). After stirring at -15 °C for 30 min, the reaction was quenched by addition of methanol. The mixture was diluted with EtOAc and washed successively with 1 M aqueous HCl solution, saturated aqueous NaHCO₃ solution and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (20 g), with acetone-hexanes (1:4) as eluent, to afford a mixture (1:1) of compounds **6E** and **6Z** (611 mg, 90%) as a colorless syrup. Repeated chromatography afforded small quantity of isomeric pure **6E** and **6Z**, respectively, which were used as analytical samples. **6E**: $[\alpha]_D^{13} + 26$ (c 0.88, CHCl₃); IR γ_{\max} (neat) 3430 cm⁻¹; ¹H NMR (270 MHz) δ 1.02 (d, J = 6.6 Hz, 3H), 1.33, 1.52 (2 s, each 3H), 1.91 (m, 1H), 2.04 (bs, 1H), 4.02, 4.06 (2 d, J = 11.4 Hz, each 1H), 4.13 (d, J = 10.3 Hz, 1H), 4.15-4.28 (m, 2H), 4.47 (d, J = 11.7 Hz, 1H), 4.52 (m, 1H), 4.55 (d, J = 11.7 Hz, 1H), 5.76 (d, J = 3.3 Hz, 1H), 5.98 (dd, J = 6.2, 7.0 Hz, 1H), 7.33 (m, 5H). **6Z**: $[\alpha]_D^{13} + 11$ (c 0.94, CHCl₃); IR γ_{\max} (neat) 3420 cm⁻¹; ¹H NMR (270 MHz) δ 1.00 (d, J = 7.0 Hz, 3H), 1.33, 1.53 (2 s, each 3H), 1.69 (bs, 1H), 2.15 (m, 1H), 3.95, 4.17 (2 d, J = 12.8 Hz, each 1H), 4.18 (m, 1H), 4.36 (dd, J = 7.3, 13.5 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.53 (m, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 5.78 (d, J = 3.7 Hz, 1H), 6.01 (dd, J = 6.2, 7.3 Hz, 1H), 7.33 (m, 5H). Anal. (as an *E*- and *Z*-mixture) Found: C, 67.64; H, 8.15. Calcd. for C₁₉H₂₆O₅•1/8H₂O: C, 67.78; H, 8.15%.

An Inseparable Mixture of (1*R*,3*S*,4*R*,5*R*)-3-[(1*R*)-1-Benzoyloxymethyl-1-trichloroacetyl-amino-2-propenyl]-4-methyl-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane and its 1*S*-isomer (8). To a mixture of NaH (60% in oil, washed twice with *n*-hexane, 45 mg, 1.11 mmol) in diethyl ether (1.5 mL) at -15°C under Ar was added dropwise a solution of compounds **6E** and **6Z** (1:1 mixture, 186 mg, 0.56 mmol) in diethyl ether (1.5 mL). After stirring at room temperature for 15 min, the reaction mixture was cooled to -15°C . To this solution was added trichloroacetonitrile (0.084 mL, 0.83 mmol), and the mixture was stirred at -15°C for 20 min, then at room temperature for 2 h. The reaction mixture was carefully neutralized by addition of acetic acid at 0°C , and diluted with EtOAc. The insoluble material were removed by filtration through a pad of celite and the filtrate was concentrated to give crude acetimidate **7**, which was dissolved in toluene (4 mL) and heated in a sealed tube at 140°C for 89 h. The mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (14 g), with EtOAc-toluene (1:40) as eluent, to afford syrupy compound **8** (160 mg, 60%) as an inseparable mixture (4:1). IR γ_{max} (neat) 3400, 1720 cm^{-1} ; ^1H NMR (270 MHz) δ 1.12 (d, $J = 7.0$ Hz, $1/5 \times 3\text{H}$), 1.15 (d, $J = 7.0$ Hz, $4/5 \times 3\text{H}$), 1.32, 1.52 (2 s, each 3H), 2.12-2.28 (m, 1H), 3.81 (d, $J = 9.2$ Hz, $1/5 \times 1\text{H}$), 3.87 (d, $J = 9.2$ Hz, $4/5 \times 1\text{H}$), 3.99 (d, $J = 9.2$ Hz, $1/5 \times 1\text{H}$), 4.10 (d, $J = 9.2$ Hz, $4/5 \times 1\text{H}$), 4.11 (d, $J = 9.9$ Hz, $1/5 \times 1\text{H}$), 4.33 (d, $J = 9.9$ Hz, $4/5 \times 1\text{H}$), 4.53 (dd, $J = 3.7, 4.8$ Hz, $4/5 \times 1\text{H}$), 4.49-4.62 (m, $2\text{H} + 1/5 \times 1\text{H}$), 5.24-5.40 (m, 2H), 5.71 (d, $J = 3.7$ Hz, 1H), 5.86-5.97 (m, $1/5 \times 1\text{H}$), 6.06 (dd, $J = 11.0$ and 17.6 Hz, $4/5 \times 1\text{H}$), 7.04 (bs, 1H), 7.23-7.38 (m, 5H). Anal. Found: C, 52.28; H, 5.78; N, 2.92. Calcd. for $\text{C}_{21}\text{H}_{26}\text{NO}_5\text{Cl}_3$: C, 52.68; H, 5.47; N, 2.93%.

(2*R*,3*R*,4*R*,5*S*)-5-[(1*R*)-1-Benzoyloxymethyl-1-trichloroacetyl-amino-2-propenyl]-2,3-dihydroxy-4-methyltetrahydrofuran and its 2*S* isomer (9), and (2*R*,3*R*,4*R*,5*S*)-5-[(1*S*)-1-Benzoyloxymethyl-1-trichloroacetyl-amino-2-propenyl]-2,3-dihydroxy-4-methyltetrahydrofuran and its 2*S* isomer (10). A solution of compounds **8** (203 mg, 0.424 mol, 4:1 mixture) in trifluoroacetic acid- H_2O [3:2 (v/v), 4 mL] was stirred at 0°C for 5 h. The reaction mixture was neutralized with 10% aqueous NaOH solution and the products were extracted with EtOAc. The extract was successively washed with water and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (14 g), with EtOAc-toluene (1:40) as eluent, to afford first, compound **10** (36 mg, 19%) as a colorless syrup. This compound was an equilibrium mixture (ca. 8:1) of 2*R*- and 2*S*- isomers. IR γ_{max} (neat) 3250-3430, 1710 cm^{-1} ; ^1H NMR (270 MHz, for the major isomer) δ 1.13 (d, $J = 7.0$ Hz, 3H), 1.75 (d, $J = 4.5$ Hz, OH, disappeared by addition of D_2O), 2.32-2.48 (m, 1H), 3.47 (d, $J = 4.4$ Hz, 1H, disappeared by addition of D_2O), 3.79 (d, $J = 8.8$ Hz, 1H), 4.02 (dd, $J = 4.5, 5.1$ Hz, 1H), 4.14 (d, $J = 8.8$ Hz, 1H), 4.42 (d, $J = 9.5$ Hz, 1H), 4.57 (s, 2H), 5.32 (d, $J = 4.4$ Hz, 1H), 5.30-5.40 (m, 2H), 5.96 (dd, $J = 11.0, 18.0$ Hz, 1H), 7.24-7.37 (m, 5H), 8.00 (bs, 1H, disappeared by addition of D_2O). Anal. Found: C, 49.57; H, 5.31; N, 3.14. Calcd. for $\text{C}_{18}\text{H}_{22}\text{NO}_5\text{Cl}_3$: C, 49.28; H, 5.05; N, 3.19%.

Further elution gave compound **9** (134 mg, 72%) as a colorless syrup. This compound was an equilibrium mixture (ca. 6:1) of 2*R*- and 2*S*- isomers. IR γ_{max} (neat) 3280-3420, 1710 cm^{-1} ; ^1H NMR (270 MHz, for the major isomer) δ 1.17 (d, $J = 6.6$ Hz, 3H), 1.86 (d, $J = 5.1$ Hz, 1H, disappeared by addition of D_2O), 2.53-2.66 (m, 1H), 3.71 (d, $J = 4.8$ Hz, 1H, disappeared by addition of D_2O), 3.94 (d, $J = 9.5$ Hz, 1H), 4.00-4.05 (m, 1H), 4.17 (d, $J = 9.5$ Hz, 1H), 4.25 (d, $J = 9.2$ Hz, 1H), 4.51 (s, 2H), 5.27 (d, $J = 4.8$ Hz, 1H), 5.25-5.35 (m, 2H), 6.03 (dd, $J = 11.0, 17.2$ Hz, 1H), 7.24-7.38 (m, 5H), 7.95 (bs, 1H, disappeared by addition of D_2O). Anal. Found: C, 49.23; H, 5.17; N, 3.09. Calcd. for $\text{C}_{18}\text{H}_{22}\text{NO}_5\text{Cl}_3$: C, 49.28; H, 5.05; N, 3.19%.

(3*R*,4*S*,5*R*)-5-Benzoyloxymethyl-4-hydroxy-3-methyl-5-vinyl-2-pyrrolidinone (13). To a stirred solution of compound **9** (3.01 g, 6.86 mmol) in methanol (30 mL) at 0°C was added a solution of sodium periodate (2.93 g, 13.7 mmol) in water (30 mL). After sitting at 0°C for 1 h then at room temperature for 5 h, sodium periodate (1.47 g, 6.86 mmol) was added at 0°C , and the whole mixture was further stirred at

room temperature for 22 h. The mixture was diluted with CH_2Cl_2 and then washed with brine, and dried. Removal of the solvent left crude hemi-aminal **11** as a colorless syrup, which was dissolved in acetone (55 mL). To this solution at 0 °C was added Jones reagent (3.83 mL, 10.2 mmol), and the mixture was stirred at 0 °C for 5 h, and then at 5 °C for 17 h. After addition of 2-propanol, the reaction mixture was diluted with CH_2Cl_2 and washed with water, and dried. The organic solvent was evaporated to give a crude lactam **12**, which was dissolved in methanol (55 mL). To this solution, NaBH_4 (239 mg, 6.33 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized by addition of acidic resin (Amberlite IR-120B, H^+ form). The insoluble material were removed filtration and the filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (70 g), with acetone-toluene (1:3) as eluent, to afford compound **13** (1.34 g, 75%) as a colorless syrup. $[\alpha]_{\text{D}}^{23} + 75$ (*c* 1.6, CHCl_3); IR γ_{max} (neat) 3250-3400, 1690 cm^{-1} ; ^1H NMR (270 MHz) δ 1.18 (d, *J* = 7.3 Hz, 3H), 1.57 (d, *J* = 6.2 Hz, 1H), 2.75 (m, 1H), 3.46 (s, 2H), 4.22 (dd, *J* = 6.2, 6.2 Hz, 1H), 4.53 (s, 2H), 5.43 (dd, *J* = 0.7, 17.6 Hz, 1H), 5.46 (dd, *J* = 0.7, 11.0 Hz, 1H), 5.59 (bs, 1H), 5.97 (dd, 1H, *J* = 11.0, 17.6 Hz, 1H), 7.25-7.40 (m, 5H). Anal. Found: C, 68.71; H, 7.44; N, 5.36. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_3$: C, 68.94; H, 7.33; N, 5.36%.

(3R,4S,5R)-5-Benzoyloxymethyl-4-(tert-butyldimethylsilyl)oxy-3-methyl-5-vinyl-2-pyrrolidinone (14). To a solution of compound **13** (277 mg, 1.05 mmol) in CH_2Cl_2 (8 mL) at 0 °C were added 2,6-lutidine (0.447 mL, 3.16 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.441 mL, 1.58 mmol). After stirring at room temperature for 7 h, 2,6-lutidine (0.149 mL, 1.05 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.147 mL, 0.53 mmol) were added at 0 °C, and the mixture was stirred at room temperature for 36 h. The reaction mixture was diluted with CH_2Cl_2 and then washed with brine, and dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (25 g), with EtOAc-toluene (1:3) as eluent, to afford compound **14** (367 mg, 92%) as crystals. M.p. 107-108.5 °C; $[\alpha]_{\text{D}}^{23} + 38$ (*c* 1.3, CHCl_3); IR γ_{max} (KBr) 3180, 1700 cm^{-1} ; ^1H NMR (270 MHz) δ 0.03, 0.04 (2s, each 3H), 0.89 (s, 9H), 1.11 (d, *J* = 7.7 Hz, 3H), 2.57 (m, 1H), 3.40 (s, 2H), 4.37 (d, *J* = 7.7 Hz, 1H), 4.52 (s, 2H), 5.25 (dd, *J* = 0.9, 10.6 Hz, 1H), 5.26 (dd, *J* = 0.9, 17.6 Hz, 1H), 5.81 (bs, 1H), 5.96 (dd, 1H, *J* = 10.6, 17.6 Hz, 1H), 7.30 (m, 5H). Anal. Found: C, 66.81; H, 9.18; N, 3.71. Calcd. for $\text{C}_{21}\text{H}_{33}\text{NO}_3\text{Si}$: C, 67.16; H, 8.86; N, 3.73%.

(3R,4S,5R)-4-(tert-Butyldimethylsilyl)oxy-5-hydroxymethyl-3-methyl-5-vinyl-2-pyrrolidinone (15). To 4 mL of dry ammonia at -78 °C under Ar was added small pieces of sodium (424 mg, 16.3 mmol). To the resulting blue solution at -78 °C was added dropwise a solution of compound **14** (61 mg, 0.16 mmol) in THF (2 mL). After stirring at -78 °C for 30 min, the reaction mixture was quenched with solid ammonium chloride (1.48 g, 24.4 mmol), and the solvent was removed by evaporation. The residue was dissolved in CH_2Cl_2 and water, and the organic layer was dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (2 g), with acetone-toluene (1:2) as eluent, to afford compound **15** (35 mg, 75%) as crystals. M.p. 121-122 °C; $[\alpha]_{\text{D}}^{23} + 36$ (*c* 1.3, CHCl_3); IR γ_{max} (KBr) 3240-3350, 1660 cm^{-1} ; ^1H NMR (270 MHz) δ 0.07, 0.09 (2s, each 3H), 0.91 (s, 9H), 1.10 (d, *J* = 7.7 Hz, 3H), 2.57 (m, 1H), 3.45 (bs, 1H), 3.51, 3.57 (2d, *J* = 11.7 Hz, each 1H), 4.46 (d, *J* = 7.7 Hz, 1H), 5.26 (d, *J* = 10.6 Hz, 1H), 5.27 (d, *J* = 17.6 Hz, 1H), 5.95 (dd, 1H, *J* = 10.6, 17.6 Hz, 1H), 7.33 (bs, 1H). Anal. Found: C, 58.71; H, 9.85; N, 5.04. Calcd. for $\text{C}_{14}\text{H}_{27}\text{NO}_3\text{Si}$: C, 58.91; H, 9.53; N, 4.91%.

(3R,4S,5R)-4-(tert-Butyldimethylsilyl)oxy-5-[(1S)-1-hydroxy-2-methylpropyl]-3-methyl-5-vinyl-2-pyrrolidinone (17) and its 1R-isomer (18). To a solution of compound **15** (100 mg, 0.35 mmol) in dimethylsulfoxide-benzene (1:1, 3 mL) at room temperature were added pyridine (28 μL , 0.35 mmol), trifluoroacetic acid (14 μL , 0.18 mmol), and *N,N'*-dicyclohexylcarbodiimide (218 mg, 1.06 mmol). After stirring at room temperature for 5 h, the reaction mixture was diluted with cold EtOAc, and the insoluble material were removed by filtration. The filtrate was washed successively with 1M aqueous HCl

solution, saturated aqueous NaHCO_3 solution and brine, and dried. Removal of the solvent gave crude aldehyde **16**, which was used in the next reaction without further purification. A solution of the crude aldehyde **16** in THF (5 mL) was slowly added to the 0.68 M solution of isopropylmagnesium bromide in THF (10 mL) at $-15\text{ }^\circ\text{C}$ under Ar over 45 min, and the mixture was gradually warmed up to room temperature over 1 h, and further stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the products were extracted with CH_2Cl_2 (x3). The combined organic layer was dried and concentrated to give a residue, which was chromatographed on a column of silica gel (5 g), with acetone-toluene (1:11) as eluent, to afford first, compound **18** (41 mg, 35%) as crystals. M.p. $156\text{--}156.5\text{ }^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} \sim 0$ (c 0.8, CHCl_3); IR γ_{max} (KBr) $3430, 1670\text{ cm}^{-1}$; ^1H NMR (270 MHz) δ 0.07, 0.09 (2s, each 3H), 0.90 (s, 9H), 0.93, 0.99 (2d, $J = 7.0\text{ Hz}$, each 3H), 1.12 (d, $J = 7.3\text{ Hz}$, 3H), 1.60 (bs, 1H), 1.88 (m, 1H), 2.61 (m, 1H), 3.39 (d, $J = 3.3\text{ Hz}$, 1H), 4.54 (d, $J = 7.3\text{ Hz}$, 1H), 5.28 (dd, $J = 1.1, 17.6\text{ Hz}$, 1H), 5.33 (dd, $J = 1.1, 11.0\text{ Hz}$, 1H), 5.67 (bs, 1H), 6.10 (dd, $J = 11.0, 17.6\text{ Hz}$, 1H). Anal. Found: C, 61.40; H, 10.51; N, 4.38. Calcd. for $\text{C}_{17}\text{H}_{33}\text{NO}_3\text{Si} \cdot 1/4\text{H}_2\text{O}$: C, 61.49; H, 10.16; N, 4.22%. Second elution gave compound **17** (34 mg, 30%) as a colorless syrup. $[\alpha]_{\text{D}}^{24} - 8$ (c 0.7, CHCl_3); IR γ_{max} (neat) $3330\text{--}3430, 1700\text{ cm}^{-1}$; ^1H NMR (270 MHz) δ 0.08, 0.12 (2s, each 3H), 0.79 (d, $J = 6.6\text{ Hz}$, 3H), 0.93 (s, 9H), 1.01 (d, $J = 7.0\text{ Hz}$, 3H), 1.10 (d, $J = 7.7\text{ Hz}$, 3H), 1.92 (m, 1H), 1.98 (bs, 1H), 2.52 (m, 1H), 3.48 (d, $J = 2.2\text{ Hz}$, 1H), 4.61 (d, $J = 8.4\text{ Hz}$, 1H), 5.26 (d, $J = 10.6\text{ Hz}$, 1H), 5.27 (d, $J = 17.6\text{ Hz}$, 1H), 5.97 (dd, $J = 10.6, 17.6\text{ Hz}$, 1H), 6.02 (bs, 1H). Anal. Found: C, 62.20; H, 10.55; N, 4.11. Calcd. for $\text{C}_{17}\text{H}_{33}\text{NO}_3\text{Si}$: C, 62.34; H, 10.15; N, 4.28%. Further elution afforded compound **15** (22 mg, 21%), whose spectral data were fully identical with those of the starting material.

(3R,4S,5R)-4-(tert-Butyldimethylsilyloxy)-3-methyl-5-(1-oxo-2-methylpropyl)-5-vinyl-2-pyrrolidinone (19). To a solution of compound **18** (56 mg, 0.17 mmol) in dimethylsulfoxide-benzene (1:1, 1.5 mL) at room temperature were added pyridine (14 μL , 0.17 mmol), trifluoroacetic acid (7 μL , 0.086 mmol), and N,N' -dicyclohexylcarbodiimide (106 mg, 0.52 mmol). After stirring at room temperature for 7 h, the reaction mixture was diluted with cold EtOAc, and the insoluble material were removed by filtration. The filtrate was washed successively with 1M aqueous HCl solution, saturated aqueous NaHCO_3 solution and brine, and dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (5 g), with acetone-toluene (1:11) as eluent to afford compound **19** (44 mg, 78%) as a colorless syrup. $[\alpha]_{\text{D}}^{24} + 68$ (c 1.2, CHCl_3); IR γ_{max} (neat) $3200, 1705\text{ cm}^{-1}$; ^1H NMR (270 MHz) δ 0.08, 0.10 (2s, each 3H), 0.90 (s, 9H), 1.05 (d, $J = 7.0\text{ Hz}$, 6H), 1.12 (d, $J = 7.3\text{ Hz}$, 3H), 2.39 (m, 1H), 3.03 (m, 1H), 4.64 (d, $J = 5.9\text{ Hz}$, 1H), 5.32 (d, $J = 18.0\text{ Hz}$, 1H), 5.33 (d, $J = 11.0\text{ Hz}$, 1H), 5.93 (dd, $J = 11.0, 18.0\text{ Hz}$, 1H), 7.25 (bs, 1H). Anal. Found: C, 62.51; H, 10.00; N, 4.34. Calcd. for $\text{C}_{17}\text{H}_{31}\text{NO}_3\text{Si}$: C, 62.73; H, 9.60; N, 4.30%.

Reduction of Ketone 19. To a 0.92 M solution of triisobutylaluminum in *n*-hexane (1.29 mL, 1.19 mmol) was added a solution of compound **19** (19 mg, 0.059 mmol) in dichloroethane (1 mL) at $0\text{ }^\circ\text{C}$ dropwise over 20 min. After stirring at $0\text{ }^\circ\text{C}$ for 1.5 h and then at room temperature at 3 h, the reaction was quenched with methanol at $0\text{ }^\circ\text{C}$. The mixture was diluted with EtOAc and washed successively with 1M aqueous HCl solution, saturated aqueous NaHCO_3 solution and brine, and dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (1.5 g), with acetone-toluene (1:11) as eluent to afford compound **18** (1.3 mg, 7%) and compound **17** (14 mg, 70%). The physical and spectral data of **17** and **18** were fully identical with those of compounds prepared by Grignard reaction (*vide supra*).

(3R,4S,5R)-4-hydroxy-5-[(1S)-1-hydroxy-2-methylpropyl]-3-methyl-5-vinyl-2-pyrrolidinone (20). A solution of compound **17** (127 mg, 0.39 mmol) in trifluoroacetic acid-water [4:1 (v/v), 5 mL] was stirred at room temperature for 15 h and then at $50\text{ }^\circ\text{C}$ for 2 h. The reaction mixture was concentrated and co-distilled with ethanol to give a residue, consisting of compound **20** and its *O*-trifluoroacetate derivative, which was dissolved in methanol (4 mL) and treated with 1M solution of sodium methoxide in methanol (0.4 mL) at $0\text{ }^\circ\text{C}$ for 3 h. The reaction mixture was neutralized with acidic resin

(Amberlite IR-120B, H⁺ form) and the insoluble material were removed by filtration. The filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (8 g), with acetone-toluene (2:3) as eluent to afford compound **20** (63 mg, 76%) as a colorless syrup. $[\alpha]_D^{20} + 17$ (c 1.2, CHCl₃); IR γ_{\max} (neat) 3350-3420, 1680 cm⁻¹; ¹H NMR (270 MHz) δ 0.87, 1.03 (2d, J = 6.8 Hz, each 3H), 1.16 (d, J = 7.8 Hz, 3H), 1.66 (bs, 2H), 1.95 (m, 1H), 2.82 (m, 1H), 3.57 (d, J = 2.9 Hz, 1H), 4.46 (d, J = 7.3 Hz, 1H), 5.42 (d, J = 17.0 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H), 5.94 (bs, 1H), 5.98 (dd, J = 10.8, 17.0 Hz, 1H). Anal. Found: C, 62.11; H, 9.33; N, 6.69. Calcd. for C₁₁H₁₉NO₃: C, 61.95; H, 8.98; N, 6.57%.

(3R,4S,5R)-4-Hydroxy-5-[(1S)-1-hydroxy-2-methylpropyl]-3-methyl-2-pyrrolidinone-5-carboxylic acid (21). Ozone was introduced into a solution of compound **20** (31 mg, 0.15 mmol) in methanol (2 mL) at -78 °C for 5 min. Confirming the complete consumption of starting material (TLC analysis), excess ozone was removed with a stream of Ar. To this mixture at -78 °C was added dimethyl sulfide (1.1 mL, 14.5 mmol) and the resulting mixture was stirred at room temperature for 5 h. The mixture was concentrated to give crude aldehyde, which was dissolved in *tert*-butanol-water [1:1 (v/v), 2.5 mL]. To this solution were added HOSO₂NH₂ (42 mg, 0.43 mmol), NaH₂PO₄·2H₂O (45 mg, 0.29 mmol) and NaClO₂ (39 mg, 0.43 mmol), and the whole mixture was stirred for 15 min. The reaction mixture was concentrated and co-distilled with ethanol to give a residue, which was suspended in methanol and the insoluble material were removed by filtration with sintered glass. The filtrate was concentrated to afford a residue, which was chromatographed on a column of silica gel (2 g), with methanol-CHCl₃ (1:3) containing 1% acetic acid as eluent to afford compound **21** (27 mg, 81%) as a colorless syrup. This compound was used in the next reaction without further purification. ¹H NMR (270 MHz, CD₃OD) δ 0.93, 0.97 (2d, J = 6.8 Hz, each 3H), 1.07 (d, J = 7.8 Hz, 3H), 1.73 (m, 1H), 2.98 (m, 1H), 3.95 (d, J = 6.8 Hz, 1H), 4.42 (d, J = 6.3 Hz, 1H).

N-Acetyl-L-cysteine Allyl Ester. A mixture of *N*-acetyl-L-cystein (200 mg, 1.23 mmol), 2-propene-1-ol (1.67 mL, 24.5 mmol), and p-TsOH·H₂O (47 mg, 0.245 mmol) in benzene (5 mL) under Ar was heated at reflux temperature for 1 h. After cooling, the mixture was diluted with EtOAc and washed with saturated aqueous NaHCO₃ solution (x3) and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (12 g), with acetone-hexanes (1:3) as eluent to afford the title compound (112 mg, 45%) as a colorless syrup. $[\alpha]_D^{21} + 16$ (c 0.9, CHCl₃); IR γ_{\max} (neat) 3280, 1740, 1650 cm⁻¹; ¹H NMR (90 MHz) δ 1.38 (t, J = 9.0 Hz, 1H), 2.08 (s, 3H), 3.04 (dd, J = 3.8, 9.0 Hz, 1H), 4.69 (d, J = 5.4 Hz, 2H), 4.92 (dt, J = 3.8 and 6.3 Hz, 1H), 5.20-5.49 (m, 2H), 5.95 (ddt, J = 5.4, 9.9, 17.1 Hz, 1H), 6.51 (bd, J = 6.3 Hz, 1H). MS *m/z* 204 (M+1, 5.1%), 203 (M, 1.8), 170 (2.9), 162 (19.6), 144 (72.7). HRMS Found: 203.0606. Calcd. for C₈H₁₃NO₃S (M⁺): 203.0613.

Lactacystin Allyl Ester (22). To a suspension of crude **21** (27 mg, 0.12 mmol) in CH₂Cl₂ (2 mL) at 0 °C were added Et₃N (61 μ L, 0.43 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (44 mg, 0.17 mmol), and *N*-acetyl-L-cysteine allyl ester (44 mg, 0.22 mmol). After stirring at room temperature for 19 h, the reaction mixture was concentrated to give a residue. This was chromatographed on a column of silica gel (9 g), with methanol-CHCl₃ (1:10) containing 1% acetic acid as eluent and further purified with preparative thin layer chromatography [acetone-toluene (1:1)] to afford compound **22** (36 mg, 60% from compound **20**) as a white solid. M.p. 183-185 °C (dec) [lit.^{3c,3d} 182-184 °C (dec)]; $[\alpha]_D^{24} + 38$ (c 0.7, acetone) [lit. $[\alpha]_D^{22} + 39.8$ (c 0.55, acetone)]; IR γ_{\max} (KBr) 3370, 1650-1690 cm⁻¹; ¹H NMR (400 MHz, pyridine-*d*₅) δ 1.20 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 7.3 Hz, 3H), 2.02 (s, 3H), 2.26 (m, 1H), 3.48 (dq, J = 7.3, 7.3 Hz, 1H), 3.67 (dd, J = 7.3, 13.4 Hz, 1H), 3.91 (dd, J = 4.9, 13.4 Hz, 1H), 4.59 (m, 1H), 4.63 (d, J = 5.5 Hz, 2H), 5.10 (d, J = 10.4 Hz, 1H), 5.28 (m, 1H), 5.30 (d, J = 17.1 Hz, 1H), 5.35 (m, 1H), 5.85 (m, 1H), 6.95 (bs, 1H), 7.74 (bs, 1H), 9.06 (d, J = 7.9 Hz, 1H), 9.96 (s, 1H); ¹³C NMR (100 MHz, pyridine-*d*₅) δ 10.1, 19.9, 21.4, 22.7, 30.7, 32.0, 41.8, 52.8, 65.8, 75.9, 79.9, 81.2, 118.0, 132.4, 170.3, 170.9, 181.3, 202.9. Anal. Found: C, 51.70; H, 7.14; N, 6.66. Calcd. for C₁₈H₂₈N₂O₇S: C, 51.91; H, 6.78; N, 6.73%.

Lactacystin (1). A mixture of compound **22** (15 mg, 0.036 mmol), $(\text{PPh}_3)_4\text{Pd}$ (3.7 mg, 3.2 μmol), Et_3N (45 μL , 0.32 mmol), and formic acid (12 μL , 0.32 mmol) in THF (1 mL) under Ar was stirred at room temperature for 5 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (2.3 g), with methanol- CHCl_3 (1:3) containing 1% acetic acid as eluent to afford compound **1** (9.4 mg, 70%) as a white solid. M.p. 234–236 °C (dec) [lit.² 237–238 °C (dec)]; $[\alpha]_{\text{D}}^{15} + 75$ (c 0.4, MeOH) {lit.² $[\alpha]_{\text{D}}^{25} + 71.3$ (c 0.5, MeOH)}; IR γ_{max} (KBr) 3240–3280, 1680–1700 cm^{-1} ; ^1H NMR (270 MHz, pyridine- d_5) δ 1.19 (d, $J = 6.8$ Hz, 3H), 1.27 (d, $J = 6.8$ Hz, 3H), 1.56 (d, $J = 7.3$ Hz, 3H), 2.03 (s, 3H), 2.24 (m, 1H), 3.48 (m, 1H), 3.82 (m, 1H), 4.08 (m, 1H), 4.59 (d, $J = 7.3$ Hz, 1H), 5.31 (m, 1H), 5.33 (d, $J = 6.8$ Hz, 1H), 8.63 (m, 1H), 9.81 (s, 1H); ^{13}C NMR (67 MHz, pyridine- d_5) δ 10.1, 19.8, 21.3, 23.0, 31.4, 31.9, 41.8, 53.4, 75.9, 79.9, 81.2, 170.4, 173.4, 181.3, 203.0. Anal. Found: C, 44.59; H, 6.35; N, 7.21. Calcd. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_7\text{S} \cdot 1.5\text{H}_2\text{O}$: C, 44.65; H, 6.74; N, 6.94%.

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