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A Concise Route to (+)-Lactacystin

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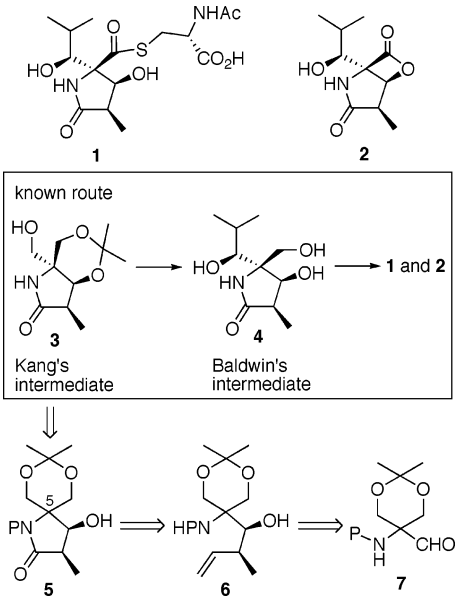
Abstract: A facile chromatography-free route to Kang's intermediate for the synthesis of (+)-lactacystin, a potent proteasome inhibitor, has been developed starting with Brown's asymmetric crotylation of *tert*-butyl 5-formyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate, easily available from 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris).

Lactacystin (**1**), a metabolite isolated from *Streptomyces* sp. OM-6519,[1] has attracted considerable interest due to its highly potent and selective inhibition of the 20S proteasome.[2] Since the 20S proteasome participates in an extraordinarily wide range of cellular processes (e.g., cell cycle progression, antigen presentation to the immune system, and inflammatory responses through protein processing), lactacystin and clasto-lactacystin (**2**) (omuralide), an active species inhibiting the proteasome in cells, are very important tools for the study of protein biochemistry and cell biology.[3] In addition, these biological features make lactacystin a potential drug candidate for the treatment of arthritis, asthma, and stroke.[4] Their high demand in biological research and the intriguing chemical structure have spurred much research on the synthesis of lactacystin and a number of total and formal syntheses have been achieved[5,6] since Corey et al. reported the first synthesis of (+)-lactacystin in 1992.[7] We describe herein a new concise route to (+)-lactacystin from 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris).

Kang et al.[8] developed a highly stereoselective route to Baldwin's intermediate **4**[9] from lactam **3** through reaction of the corresponding ester with isopropylmagnesium bromide involving a concomitant addition−reduction process (vide infra). We envisaged that lactam **3** could be expeditiously accessed from prochiral aldehyde **7** via **6** and **5** by transformations involving asymmetric crotylation, formation of the lactam ring, and transposition of the acetonide group creating the C5 quaternary chiral center (Scheme 1).

SCHEME 1. Retrosynthetic Analysis



2-Amino-2-(hydroxymethyl)propane-1,3-diol (Tris) (**8**) was successively subjected to *tert*-butoxycarbonylation and acetalization in one pot to give alcohol **9** in 87% yield. Swern oxidation of **9** afforded aldehyde **10** in 98% yield, asymmetric crotylation of which was then examined using crotylboronate **12**[10] and crotylborane **13**.[11] When **10** was reacted with **12** at 0 °C in toluene, alcohol **11** was obtained almost quantitatively with excellent diastereoselectivity (>98% de) but the enantioselectivity was very low (16% ee). To attain better enantioselectivity, we carried out this reaction at −78 °C but **10** did not react with **12** at all under such conditions. On the other hand,

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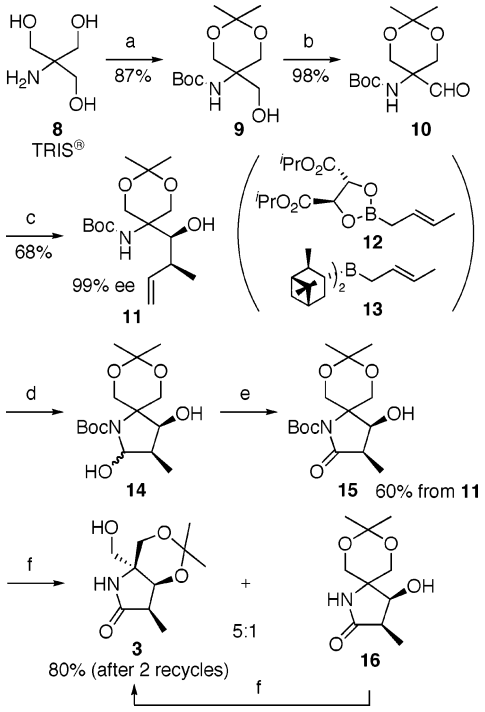
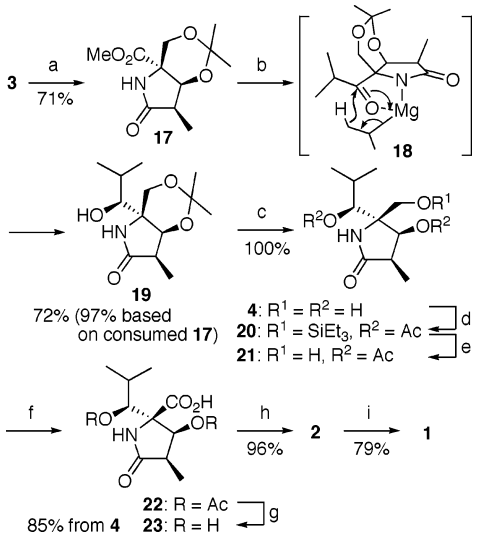
SCHEME 2[a]



[a] Reagents and conditions: (a) Boc_2O, DMF then $(MeO)_2CMe_2$, *p*-TsOH·H_2O; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (c) **13**, THF-Et_2O, −78 °C, then 3 M NaOH, 30% H_2O_2, reflux; (d) O_3, $NaHCO_3$, CH_2Cl_2-MeOH, −78 °C, then Me_2S; (e) PDC, CH_2Cl_2; (f) *p*-TsOH·H_2O, acetone.

crotylborane **13** reacted smoothly with **10** at −78 °C in THF−Et_2O, and after oxidative workup of the reaction mixture with alkaline hydrogen peroxide, removal of isopinocampheol by vacuum distillation followed by recrystallization of the residue from Et_2O−hexane gave **11** with 99% ee in 68% yield. This crotylation reaction was found to proceed with the enantioselectivity of 90% ee by HPLC analysis using a chiral column of the corresponding benzoate prepared from a sample purified by column chromatography of the crude product. Ozonolysis of **11** gave **14** which was then selectively oxidized with PDC[12] to give lactam **15** in 60% yield. TPAP,[13] Dess−Martin,[14] and Swern oxidations were not effective for this chemoselective transformation. Treatment of **15** with *p*-TsOH·H_2O in acetone at room temperature led to cleavage of the *tert*-butoxycarbonyl group and concomitant migration of the acetonide group to produce a 5:1 equilibrium mixture of **3** and **16**, quantitatively (Scheme 2). Pure lactam **3** was obtained by fractional crystallization of the mixture and the residue was again treated with *p*-TsOH·H_2O in acetone to convert it to the above-mentioned equilibrium mixture. As a result of this sequence, lactam **3** was obtained in 80% yield from **15**. The spectral data of **3** were identical with those reported by Kang et al.[8] It should be stressed that the above-mentioned synthesis of **3** from Tris did not require any chromatographic purification.

SCHEME 3[a]



[a] Reagents and conditions: (a) PDC, DMF, then CH_2N_2-Et_2O, THF; (b) *i*-PrMgBr, Et_2O, CH_2Cl_2; (c) *p*-TsOH·H_2O, MeOH, 60 °C; (d) Et_3SiCl, pyridine, then Ac_2O, DMAP; (e) 47% HF, 0 °C; (f) H_2CrO_4, acetone, 0 °C; (g) 0.2 M NaOH; (h) bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), Et_3N, CH_2Cl_2; (i) *N*-acetyl-L-cysteine, Et_3N, CH_2Cl_2.

According to the procedure developed by Kang et al.,[8] lactam **3** was successfully converted to Baldwin's intermediate **4**[9] in 69% overall yield although the initial Jones oxidation was performed via PDC oxidation to attain good reproducibility. Thus, PDC oxidation of **3** followed by esterification of the resulting carboxylic acid with diazomethane gave ester **17** in 71% yield. Upon treatment of **17** with isopropylmagnesium bromide at room temperature in Et_2O, alcohol **19** was obtained stereoselectively through a concomitant addition−reduction process as depicted in **18**. Acidic methanolysis of **19** gave triol **4** quantitatively, the specific rotation and spectral data of which were identical with those reported by Baldwin et al.[9] Following Baldwin's method,[9] triol **4** thus prepared was transformed into carboxylic acid **23** in good overall yield. Finally, according to the established procedure,[15] (−)-omuralide (**2**) and (+)-lactacystin (**1**) were successfully synthesized from **23** (Scheme 3).

In conclusion, we have developed a practical method for the synthesis of Kang's intermediate **3** starting from 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris), which does not require any column chromatography for purification. Using this method, a total synthesis of (+)-lactacystin has been achieved in 16 steps and 13% overall yield from Tris.

Experimental Section

Where appropriate, reactions were performed in flame-dried glassware under argon. All extracts were dried over $MgSO_4$ andconcentrated by rotary evaporation below 30 °C at ca. 25 Torr.

(12) When PCC was used in place of PDC, the α,β-unsaturated lactam, a dehydration product of **15**, was also obtained in 19% yield along with **15** (46%).

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***tert*-Butyl 5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (9).** To a suspension of Tris **8** (5.0 g, 41.3 mmol) in DMF (37.5 mL) was added Boc_2O (10.0 g, 45.3 mmol), and the mixture was stirred at room temperature for 1 h. 2,2-Dimethoxypropane (6.0 mL, 49.5 mmol) and *p*-toluenesulfonic acid monohydrate (400 mg, 2.07 mmol) were added to the mixture, and stirring was continued overnight. The reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Recrystallization of the residue from Et_2O−hexane afforded **9** (9.42 g, 87%) as colorless crystals: mp 100−102 °C; FTIR (film) 3309, 1689, 1509, 1371, 1253, 1166, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.46 (s, 12H), 3.73 (d, J = 6.5 Hz, 2H), 3.81 (d, J = 12.5 Hz, 2H), 3.85 (d, J = 12.5 Hz, 2H), 4.25 (br s, 1H), 5.33 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 26.9, 28.3, 53.3, 64.4, 64.7, 80.4, 98.7, 156.4; HRMS (EI) calcd for $C_{12}H_{23}NO_5$ (M^+) 261.1576, found 261.1595. Anal. Calcd for $C_{12}H_{23}NO_5$: C, 55.16; H, 8.87; N, 5.36. Found: C, 54.96; H, 8.53; N, 5.62.

***tert*-Butyl 5-Formyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (10).** To a solution of oxalyl chloride (6.7 mL, 76.7 mmol) in CH_2Cl_2 (200 mL) was added DMSO (8.2 mL, 0.12 mol) at −78 °C. After the mixture was stirred for 30 min at −78 °C, a solution of **9** (10.0 g, 38.4 mmol) in CH_2Cl_2 (25 mL) was added, and stirring was continued at −78 °C for 30 min. The reaction mixture was treated with triethylamine (32.1 mL, 0.23 mol), allowed to warm to room temperature, and stirred for 30 min. The reaction mixture was diluted with 1 M HCl (20 mL), washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Recrystallization of the residue from Et_2O−hexane gave **10** (9.78 g, 98%) as colorless crystals: mp 116−119 °C; FTIR (film) 3328, 1697, 1513, 1375, 1253, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 15H), 3.96 (br d, J = 12.0 Hz, 2H), 4.07 (d, J = 12.0 Hz, 2H), 5.55 (br s, 1H), 9.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 27.3, 28.2, 59.9, 62.7, 81.0, 98.8, 151.9, 155.4, 199.3; HRMS (EI) calcd for $C_{11}H_{18}NO_5$ [(M − Me) $^+$] 244.1185, found 244.1203. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.48; H, 7.92; N, 5.47.

***tert*-Butyl (1′*S*,2′*S*)-5-(1′-Hydroxy-2′-methylbut-3′-enyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (11).** To a solution of potassium *tert*-butoxide (33.4 g, 0.297 mol) in THF (150 mL) was added *trans*-2-butene (46.9 mL, 0.595 mol) at −78 °C, and then *n*-butyllithium (1.56 M in hexane, 191 mL, 0.297 mol) was added over 2 h. The reaction mixture was allowed to warm to −50 °C, and stirring was continued for 10 min. The mixture was then recooled to −78 °C, and a solution of (−)-*B*-methoxydiisopinocamphenylborane (78.3 g, 0.247 mol) in Et_2O (247 mL) was added over 1 h. After the mixture was stirred for 30 min at −78 °C, $BF_3{\cdot}Et_2O$ (62.8 mL, 0.496 mol) was added over 30 min, and then a solution of **10** (25.7 g, 99.1 mmol) in THF (300 mL) was added over 40 min. After being stirred at −78 °C for 14 h, the mixture was allowed to warm to 0 °C and treated with 3 M NaOH (465 mL) and 30% H_2O_2 (190 mL). The mixture was refluxed for 16 h, extracted with Et_2O, dried, and concentrated. After removal of the resulting isopinocampheol by vacuum distillation (1 mmHg, 60−70 °C), the residue was recrystallized from Et_2O−hexane to give **11** (21.2 g, 68%, 99% ee) as colorless crystals: mp 127−128 °C; $[\alpha]^{24}_D$ −17.0 (*c* 1.27, $CHCl_3$); FTIR (film) 3305, 3077, 1673, 1558, 1448, 1369, 1309, 1259, 1180, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, J = 7.0 Hz, 3H), 1.42 (s, 6H), 1.44 (s, 9H), 2.28 (br t, J = 7.0 Hz, 1H), 3.52 (br d, J = 6.5 Hz, 1H), 3.72 (dd, J = 12.0, 2.5 Hz, 1H), 3.84 (d, J = 12.0 Hz, 1H), 3.94 (d, J = 12.0 Hz, 1H), 4.10 (dd, 1H, J = 12.0, 2.5 Hz, 1H), 4.98−5.04 (m, 2H), 5.10 (br d, J = 8.5 Hz, 1H), 5.20 (br s, 1H), 5.97 (dddd, J = 17.3, 10.5, 9.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 20.3, 28.1, 28.4, 40.3, 55.8, 63.4, 65.2, 77.1, 80.4, 98.3, 114.5, 139.5, 157.2; HRMS (EI) calcd for $C_{16}H_{29}NO_5$ (M^+) 315.2046, found 315.2049. Anal. Calcd for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 61.18; H, 9.04; N, 4.57. The benzoate, obtained from bonzoylation of a sample purified by SiO_2 column chromatography (hexane/AcOEt = 20/1) without recrystallization, showed an enantiomeric purity of 90% ee [HPLC: DAICEL CHIRALCEL OD-H, hexane/2-propanol = 40/1, flow: 0.5 mL/min, detect: UV 254 nm, retention time: 12.4 min (enantiomer: 13.8 min)].

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-hydroxy-3,8,8-trimethyl-2-oxo-1-aza-7,9-dioxaspiro[4.5]decane (15). O_3 was introduced into a mixture of **11** (10.2 g, 32.3 mmol) and $NaHCO_3$ (10.0 g) in CH_2Cl_2−MeOH (1:1) (400 mL) at −78 °C for 1 h. Dimethyl sulfide (4.75 mL, 64.8 mmol) was added, and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with brine, dried,, and concentrated to give **14** (11.4 g) as a crystalline solid. To a solution of crude **14** in CH_2Cl_2 (70 mL) were added PDC (24.4 g, 64.8 mmol) and Celite (10.0 g), and stirring was continued at room temperature for 60 h. The reaction mixture was diluted with Et_2O, filtered through a Celite pad, and concentrated. Purification of the residue by recrystalization from Et_2O−hexane afforded **15** (6.1 g, 60%) as colorless needles: mp 145−147 °C; $[\alpha]^{25}_D$ +3.9 (*c* 0.96, $CHCl_3$); FTIR (film) 3465, 1776, 1714, 1295, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, J = 7.5 Hz, 3H), 1.41 (s, 3H), 1.54 (s, 9H), 1.60 (s, 3H), 2.40 (br s, 1H), 2.71 (dt, J = 7.0, 13.5 Hz, 1H), 3.41 (dd, J = 11.5, 2.5 Hz, 1H), 4.04 (dd, J = 11.5, 2.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.64 (d, 1H, J = 5.5 Hz, 1H), 4.79 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2, 19.2, 28.1, 28.6, 40.0, 59.9, 61.3, 62.2, 83.7, 98.8, 150.5, 175.1; HRMS (EI) calcd for $C_{14}H_{22}NO_6$ [(M − Me)$^+$] 300.1446, found 300.1447. Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.96; H, 7.83; N, 4.42.

(4a*S*,7*R*,7a*S*)-Tetrahydro-4a-(hydroxymethyl)-2,2,7-trimethyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (3). To a solution of **15** (500 mg, 1.59 mmol) in acetone (20 mL) was added *p*-toluenesulfonic acid monohydrate (15.0 mg, 0.79 mmol), and the mixture was stirred at room temperature for 25 h. The reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$, dried, and concentrated to give a 5:1 mixture of **3** and **16 (**354 mg**)**. Compound **3** (197 mg) was obtained by fractional crystallization from CH_2Cl_2−Et_2O, and the mother liquor was treated again with *p*-toluenesulfonic acid monohydrate in acetone as described above. This equilibration−separation sequence was repeated three times to afford additional **3** (77 mg). Compound **3** (274 mg, 80% total yield) was obtained as colorless needles: mp 148−150 °C; $[\alpha]^{25}_D$ +29.4 (*c* 1.04, $CHCl_3$) [lit.[8] $[\alpha]^{20}_D$ +31.4 (*c* 1.10, $CHCl_3$)]; FTIR (neat) 3222, 2937, 1673, 1375, 1224, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, J = 7.5 Hz, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 2.79 (dt, J = 13.5, 7.5 Hz, 1H), 3.58 (d, J = 12.0 Hz, 1H), 3.62 (d, J = 11.5 Hz, 2H), 3.69 (dd, J = 12.0, 1.5 Hz, 2H), 4.15 (d, J = 6.0 Hz, 1H), 7.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.9, 22.0, 25.4, 40.4, 62.0, 62.7, 65.0, 70.9, 99.6, 180.5; HRMS (EI) calcd for $C_{10}H_{17}NO_4$ (M^+) 215.1158, found 215.1155. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.66; H, 7.73; N, 6.55.

Methyl (4a*S*,7*R*,7a*S*)-Hexahydro-2,2,7-trimethyl-6-oxo-[1,3]dioxino[5,4-*b*]pyrrole-4a-carboxylate (17). To a solution of **3** (1.38 g, 6.41 mmol) in DMF (25 mL) were added Celite (3.50 g) and PDC (7.20 g, 19.2 mmol), and the mixture was stirred at room temperature for 52 h. The reaction mixture was diluted with CH_2Cl_2, filtered through a Celite pad, and concentrated. The residue was dissolved in THF (50 mL), and an ethereal solution of diazomethane was added to this mixture at 0 °C until the carboxylic acid disappeared on TLC. The reaction mixture was concentrated and chromatographed (SiO_2, 40 g, $CHCl_3$/MeOH = 20/1) to afford **17** (1.11 g, 71%) as a yellow crystalline solid which was recrystallized from AcOEt−hexane to give colorless crystals: mp 155−158 °C; $[\alpha]^{25}_D$ +9.1 (*c* 1.08, $CHCl_3$); FTIR (film) 3251, 1720, 1440, 1382, 1249, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J = 7.5 Hz, 3H), 1.38 (d, J = 0.5 Hz, 3H), 1.49 (d, J = 0.5 Hz, 3H), 2.63 (m, 1H), 3.76 (d, J = 12.5 Hz, 1H), 3.78 (s, 3H), 4.27 (d, J = 12.5 Hz, 1H), 4.62 (dd, J = 5.0, 1.5 Hz, 1H), 6.26 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.4, 20.5, 26.8, 40.3, 53.1, 61.8, 63.2, 71.4, 98.9, 171.5, 178.5; HRMS (EI) calcd for $C_{10}H_{14}NO_5$ [(M − Me)$^+$] 228.0871, found 228.0891. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.62; H, 6.97; N, 5.82.

(4a*R*,7*R*,7a*S*,1′*S*)-Tetrahydro-4a-(1′-hydroxy-2′-methylpropyl)-2,2,7-trimethyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (19). To a solution of **17** (300 mg, 1.23 mmol) in Et_2O (50 mL) was added isopropylmagnesium bromide (0.44 M in Et_2O, 14 mL, 6.17 mmol) at −20 °C, and the mixture was stirred at

the same temperature for 30 min. After being stirred at room temperature for 20 h, the reaction was quenched with saturated NH_4Cl. The reaction mixture was extracted with AcOEt, washed with brine, dried, and concentrated. Purification of the residue by chromatography (SiO_2 10 g, hexane/AcOEt = 2/1 to 1/3) gave **17** (80 mg, 27%) and **19** (225 mg, 71%, 97% based on consumed **17**) each as colorless crystals: mp 191−193 °C; $[\alpha]^{23}_D$ −15.2 (*c* 0.83, $CHCl_3$); FTIR (film) 3249, 2935, 1706, 1376, 1143, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.5 Hz, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 1.96−2.02 (m, 1H), 2.28 (d, J = 7.5 Hz, 1H), 2.83−2.89 (m, 1H), 3.52 (d, J = 12.0 Hz, 1H), 3.65 (dd, J = 7.5, 3.5 Hz, 1H), 3.83 (d, J = 12.0 Hz, 1H), 4.30 (dd, J = 6.5, 1.5 Hz, 1H), 6.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2, 16.7, 22.2, 22.6, 24.9, 29.3, 39.4, 63.2, 65.0, 72.7, 77.5, 100.0, 180.1; HRMS (EI) calcd for $C_{12}H_{20}NO_4$ [(M − Me)$^+$] 242.1392, found 242.1405.

(3*R*,4*S*,5*R*,1′*S*)-4-Hydroxy-5-(hydroxymethyl)-5-(1′-hydroxy-2′-methylpropyl)-3-methylpyrrolidin-2-one (4). To a solution of **19** (200 mg, 0.78 mmol) in MeOH (5 mL) was added *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol), and the mixture was stirred at 60 °C for 24 h. The reaction was quenched with aqueous $NaHCO_3$ (4 mg/0.2 mL) and concentrated. Purification of the residue by chromatography (SiO_2 2 g, $CHCl_3$/MeOH = 4/1) gave **4** (182 mg, 100%) as colorless needles (recrystallized from AcOEt): mp 158−161 °C; $[\alpha]^{23}_D$ −10.9 (*c* 0.86, MeOH) [lit.[9] mp 162−163 °C; $[\alpha]^{22}_D$ −9.7 (*c* 1.0, MeOH)]; HRMS (EI) calcd for $C_9H_{16}NO_3$ [(M − CH_2OH)$^+$] 186.1130, found 186.1127. ^1H and ^{13}C NMR data were identical with those reported.[9]

(3*R*,4*S*,5*R*,1′*S*)-4-Acetoxy-5-(1′-acetoxy-2′-methylpropyl)-3-methyl-5-(triethylsiloxy)methylpyrrolodin-2-one (20). To a solution of **4** (100 mg, 0.46 mmol) in pyridine (2 mL) was added chlorotriethylsilane (118 μL, 0.70 mmol), and the mixture was stirred at room temperature for 3 h. 4-(Dimethylamino)pyridine (1 piece) and acetic anhydride (434 μL, 4.60 mmol) were added to the mixture, and stirring was continued at room temperature for 27 h. The reaction was quenched with MeOH (0.5 mL) with cooling in an ice bath. The reaction mixture was diluted with Et_2O, washed with 0.5% aqueous NaOH, water, and brine, dried, and concentrated. Purification of the residue by chromatography (SiO_2 5 g, hexane/AcOEt = 2/1) gave **20** (165 mg, 86%) as a colorless solid: mp 61−62 °C; $[\alpha]^{23}_D$ −26.7 (*c* 0.92, $CHCl_3$) [lit.[9] mp 61−62 °C; $[\alpha]^{23}_D$ −26.9 (*c* 1.0, $CHCl_3$)]; FTIR (film) 3201, 1745, 1706, 1373, 1232, 1108, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (q, J = 8.0 Hz, 6H), 0.91 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.99 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.5 Hz, 3H), 2.06 (m, 1H), 2.08 (s, 3H), 2.09 (s, 3H), 2.84 (quint, J = 7.5 Hz, 1H), 3.63 (d, J = 10.0, 1H), 3.67 (d, J = 10.0, 1H), 5.09 (d, J = 4.5 Hz, 1H), 5.54 (d, J = 7.5 Hz, 1H), 5.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.2, 6.7, 9.9, 18.0, 20.4, 20.7, 21.9, 28.9, 39.6, 63.1, 65.8, 72.6, 77.1, 169.4, 170.1, 176.9; HRMS (EI) calcd for $C_{18}H_{32}NO_6Si$ [(M − Et)$^+$] 386.1998, found 386.1995. Anal. Calcd. for $C_{20}H_{37}NO_6Si$: C, 57.80; H, 8.97; N, 3.37. Found: C, 58.02; H, 9.15; N, 3.42. ^1H and ^{13}C NMR data were identical with those reported.[9]

(3*R*,4*S*,5*R*,1′*S*)-4-Acetoxy-5-(1′-acetoxy-2′-methylpropyl)-5-hydroxymethyl-3-methylpyrrolodin-2-one (21). To a solution of **20** (180 mg, 0.43 mmol) in MeCN (5.0 mL) was added 47% HF (200 μL) at 0 °C, and the mixture was stirred at room temperature for 7 h. The reaction mixture was basified with saturated $NaHCO_3$ at 0 °C, extracted with $CHCl_3$, dried, and concentrated. Purification of the residue by chromatography (SiO_2 2 g, $CHCl_3$ to $CHCl_3$/MeOH = 10/1) afforded **21** (129 mg, 99%) as colorless crystals (recrystallized from Et_2O): mp 125−127 °C; $[\alpha]^{24}_D$ −50.3 (*c* 1.0, $CHCl_3$) [lit.[9] mp 122−123 °C; $[\alpha]^{24}_D$ −52.3 (*c* 0.77, $CHCl_3$)]; HRMS (EI) calcd for $C_{13}H_{20}NO_5$ [(M − CH_2OH)$^+$] 270.1341, found 270.1317. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65, Found: C, 55.46; H, 7.61; N, 4.62. ^1H and ^{13}C NMR data were identical with those reported.[9]

(3*R*,4*S*,5*R*,1′*S*)-4-Acetoxy-5-(1′-acetoxy-2′-methylpropyl)-3-methylpyrrolidin-2-one-5-carboxylic Acid (22). To a solution of **21** (100 mg, 0.33 mmol) in acetone (10 mL) was added Jones reagent (2.67 M, 3.7 mL, 9.9 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 h and at room temperature for 3 h. The reaction was quenched with *i*-PrOH (5 mL) at 0 °C, and the reaction mixture was diluted with brine, extracted with AcOEt−THF (2:3), dried, and concentrated. The residue was diluted with *i*-PrOH and filtered through a Celite pad, and the filtrate was concentrated. The residue was diluted with water and lyophilized to give **22** (105 mg, 100%) as a pale yellow powder, which was used for the next reaction without purification: mp 125−127 °C dec (lit.[9] mp 127 °C dec); ^1H and ^{13}C NMR data were identical with those reported.[9]

(3*R*,4*S*,5*R*,1′*S*)-4-Hydroxy-5-(1′-hydroxy-2′-methylpropyl)-3-methylpyrrolidin-2-one-5-carboxylic Acid (23). A mixture of **22** (125 mg, 0.396 mmol) in 0.2 M NaOH (6.0 mL) was stirred at room temperature for 10 h. The reaction mixture was acidified to pH 1−2 with 1 M HCl at 0 °C and lyophilized. The residue was dissolved in THF, and the resulting precipitate was removed by filtration. The filtrate was concentrated and diluted with CH_2Cl_2−hexane (1:1) to dissolve impurities. After filtration, **23** (92 mg, 100%) was obtained as a pale yellow powder, which was used for the next reaction without purification: mp 242−244 °C dec; $[\alpha]^{28}_D$ +16.1 (*c* 1.0, CH_3OH) [lit.[9] mp 241−243 °C; $[\alpha]^{21}_D$ +18.5 (*c* 1.0, MeOH)]; ^1H and ^{13}C NMR data were identical with those reported.[9]

***clasto*-Lactacystin *β*-Lactone (2).** To a solution of **23** (40 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (88.6 mL, 0.636 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (80.9 mg, 0.318 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was diluted with AcOEt, washed with H_2O, dried, and concentrated. Purification of the residue by chromatography (SiO_2, 2 g, AcOEt) afforded **2** (35.5 mg, 96%) as a colorless powder: mp 183−186 °C dec; $[\alpha]^{22}_D$ −87.0 (*c* 0.23, MeCN), [lit.[15b] mp 185 °C dec; $[\alpha]^{23}_D$ −93.9 (*c* 0.53, MeCN)]; FTIR (film) 3365, 1828, 1702, 1542 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 1.01 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.47 (d, J = 7.5 Hz, 3H), 2.12 (m, 1H), 3.04 (dq, J = 6.2, 7.5 Hz, 1H), 4.35 (d, J = 3.5 Hz, 1H), 5.00 (br s, 1H), 5.67 (d, J = 6.0 Hz, 1H), 7.78 (br s, 1H), 10.4 (s, 1H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 8.80, 16.5, 20.4, 29.9, 38.9, 70.6, 77.0, 80.5, 172.4, 177.3; MS (FAB, NBA) m/z 214 (M + H). These data were identical with those reported.[15]

Lactacystin (1). To a solution of **2** (30 mg, 0.14 mmol) in CH_2Cl_2 (4 mL) were added triethylamine (59 μL, 0.42 mmol) and *N*-acetyl-L-cysteine (19.6 mg, 0.12 mmol), and the mixture was stirred at room temperature for 14 h. The reaction mixture was concentrated and purified by chromatography (SiO_2 2 g, $CHCl_3$/MeOH/AcOH = 10/2/1) to afford **1** (41.5 mg, 79%) as a colorless powder: mp 233−235 °C dec; $[\alpha]^{22}_D$ +72.8 (*c* 0.40, MeOH) [lit.[15a] mp 236−238 °C dec, $[\alpha]^{23}_D$ +73 (*c* 0.5, MeOH)]; FTIR (neat) 3334, 2971, 1685, 1619, 1417 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 1.20 (d, J = 7.0 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.58 (d, J = 7.5 Hz, 3H), 2.05 (s, 3H), 2.26 (m, 1H), 3.49 (quint, J = 7.5 Hz, 1H), 3.85 (dd, J = 13.5, 7.0 Hz, 1H), 4.07 (dd, J = 13.5, 5.0 Hz, 1H), 4.61 (d, J = 7.0 Hz, 1H), 5.35 (d, J = 7.0 Hz, 1H), 5.42 (br dt, J = 5.0, 7.0 Hz, H), 8.74 (br d, J = 8.5 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 10.2, 19.9, 21.5, 23.0, 31.5, 32.1, 41.9, 53.0, 76.1, 80.0, 81.4, 170.2, 173.7, 181.3, 203.0; MS (FAB, NBA) m/z 377 (M + H). These data were identical with those reported.[15]

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of compounds **1**−**4**, **9**−**11**, **15**, **17**, and **19**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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