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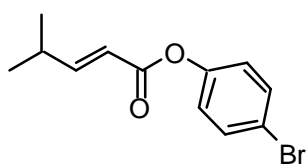
Angew. Chem. **1999**.

Total Synthesis of (+)-Lactacystin

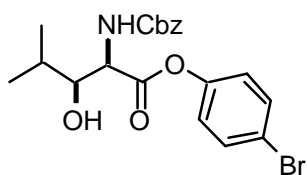
James S. Panek* and Craig E. Masse

Experimental Section

¹H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature. ¹³C NMR were recorded on a 75.5 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (¹H, δ 7.24; ¹³C, δ 77.0), deuterium oxide (¹H, δ 4.76), methanol (¹H, δ 3.31; ¹³C, δ 49.15), or pyridine (¹H, δ 8.74, 7.58, 7.22; ¹³C, δ 150.35, 135.91, 123.87). All ¹³C NMR were recorded with complete proton decoupling. Infrared spectra were recorded on a FT-spectrophotometer. Optical rotations were recorded on a digital polarimeter at 589 nm. High resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described.^[1] When specified as "anhydrous", solvents were distilled and / or stored over 4 Å sieves prior to use. All reactions were carried out in oven dried glassware under a dry argon atmosphere. Yields refer to chromatographically pure materials, unless otherwise stated. Tetrahydrofuran was freshly distilled under argon from sodium / benzophenone ketyl. Benzene was freshly distilled from sodium. Dichloromethane (CH₂Cl₂), triethylamine (Et₃N), and pyridine were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO) was vacuum distilled from calcium hydride. Titanium (IV) chloride was distilled from copper powder under vacuum immediately prior to use. Benzyl carbamate was recrystallized from water, the *p*-toluenesulfonic acid (*p*-TsOH) was recrystallized from EtOH/H₂O (1:1). All other reagents were purchased from Aldrich and used as received.

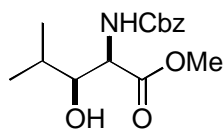


(para-Bromophenyl)-(E)-4-methyl-2-pentenoate (7). To a solution of *p*-bromophenol (41.4 g, 0.24 mole) and (*E*)-4-methyl-2-pentenoic acid^[2] (30.0 g, 0.26 mole, 1.1 equiv) in 520 mL of dry CH₂Cl₂ (0.5 M) at 0 °C was added 1,3-dicyclohexylcarbodiimide (DCC, 54.5 g, 0.26 mole, 1.1 equiv.) followed by a catalytic amount of 4-dimethylaminopyridine (DMAP, 0.30 g, 2.40 mmol, 0.01 equiv). The reaction mixture was warmed to room temperature with stirring over 12 hours and then recooled to 0 °C. The reaction was filtered through Celite and washed with cold 10% EtOAc/PE and concentrated *in vacuo*. Purification on SiO₂ (20% EtOAc/PE) afforded **7** as a white solid (54.1 g, 80%): ¹H NMR (400 MHz, CDCl₃) 7.47 (d, 2H, J = 9.2 Hz), 7.14 (dd, 1H, J = 22.4 Hz, 6.8 Hz), 6.99 (d, 2H, J = 9.2 Hz), 5.93 (dd, 1H, J = 17.2 Hz, 1.2 Hz), 2.53-2.51 (m, 1H), 1.10 (d, 6H, J = 6.4 Hz); ¹³C (75.5 MHz, CDCl₃) 165.0, 158.3, 149.8, 132.4, 123.4, 118.7, 117.6, 31.2, 21.1; IR (neat) ν_{max} 3449, 2967, 2119, 1740, 1653; CIMS (NH₃ gas) 286.2, 269.1, 207.3, 114.1, 97.1; CIHRMS M+H⁺ (calculated for C₁₂H₁₄BrO₂): 269.0178, found: 269.0162, mp 38-40 °C.



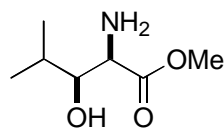
(2R,3S)-(para-Bromophenyl)-2-benzylcarbamate-3-hydroxy-4-methylpentanoate (9). A solution of 0.4 N sodium hydroxide (280 mL, 3.05 equiv) was stirred in an ambient temperature water bath in a dimly lit hood. A small amount of this solution (20 mL) was used to dissolve potassium osmate dihydrate (0.69 g, 1.86 mmol, 0.05 equiv) in a separate vial. To the remaining sodium hydroxide solution was added *n*-propanol (150 mL) followed by benzyl carbamate (17.4 g, 0.115 mole, 3.1 equiv). Freshly prepared *t*-butyl hypochlorite^[3] (13.0 mL, 0.113 mole, 3.05 equiv) was added to the reaction mixture and the mixture stirred for five minutes. To this homogeneous solution was added a solution of (DHQ)₂-AQN ligand (1.6 g, 1.86 mmol, 0.05 equiv) in *n*-propanol (160 mL, 0.011 M) followed by (*p*-bromophenyl)-(*E*)-4-methyl-2-pentenoate (**1**) (10.0 g, 37.2 mmol, 1.0 equiv) in *n*-propanol (50 mL, 0.75 M) and the potassium osmate dihydrate solution. The reaction mixture was stirred at ambient temperature for 4 hours at which time sodium bisulfite (18.6 g) was added and the reaction subsequently diluted with EtOAc (100 mL). The reaction mixture was extracted with EtOAc (3 x 50 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification on SiO₂ (30% EtOAc/PE) afforded **9** as a white solid (9.7 g, 60%, 87% ee). Subsequent recrystallization from EtOH/H₂O (1:1) afforded **9** (8.3 g, 51 %) as a single enantiomer (ee > 99%) as

determined by HPLC analysis. ^1H NMR (400 MHz, CDCl_3) 7.47 (d, 2H, $J = 8.8$ Hz), 7.35-7.30 (m, 5H), 6.97 (d, 2H, $J = 8.0$ Hz), 5.60 (d, 1H, $J = 9.2$ Hz), 5.14 (d, 2H, $J = 2.4$ Hz), 4.76 (d, 1H, $J = 9.6$ Hz), 4.10 (s, 1H), 3.88 (d, 1H, $J = 9.2$ Hz), 1.85-1.79 (m, 1H), 1.04 (d, 3H, $J = 6.4$ Hz), 1.0 (d, 3H, 2.4 Hz); ^{13}C NMR (75.5 MHz, CDCl_3) 170.3, 156.6, 149.5, 136.1, 132.5, 128.6, 128.3, 128.0, 123.2, 119.3, 77.6, 77.2, 67.3, 56.3, 30.9, 18.9; IR (neat) ν_{max} 3417, 2089, 1653; CIMS (NH_3 gas) 438.0, 436.0, 394.0, 392.0, 264.1, 192.1; CIHRMS $\text{M}+\text{H}^+$ (calculated for $\text{C}_{20}\text{H}_{23}\text{BrNO}_5$): 436.0761, found 436.0739; $[\alpha]_{23}^{\text{D}} = +5.00$ ($c = 0.75$, CHCl_3); mp 70-71 °C, HPLC: Chiralcel OD-H 0.46 cm x 25 cm, hexane / $^i\text{PrOH}$ 85/15, 0.6 mL/min, wavelength = 230 nm, 12.89 min (2*S*, 3*R*), 16.50 min (2*R*, 3*S*).



(2*R*,3*S*)-Methyl-2-benzylcarbamate-3-hydroxy-4-methylpentanoate. To a solution of **9** (8.0 g, 18.4 mmol) in anhydrous methanol (180 mL, 0.1 M) was added titanium

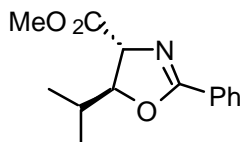
tetraisopropoxide (5.4 mL, 18.4 mmol, 1.0 equiv). The resulting yellow suspension was stirred at ambient temperature for 2 hours and subsequently diluted with H_2O (100 mL). The reaction mixture was extracted with EtOAc (3 x 50 mL), washed with 10% NaOH solution (2 x 25 mL), dried (MgSO_4), and concentrated *in vacuo* to afford the pure methyl ester as a yellow oil (5.4 g, 100%). ^1H NMR (400 MHz, CDCl_3) 7.35-7.32 (m, 5H), 5.54 (br d, 1H, $J = 9.2$ Hz), 5.11 (s, 2H), 4.53 (d, 1H, $J = 9.6$ Hz), 3.74 (s, 3H), 3.70 (d, 1H, $J = 8.0$ Hz), 1.73 (m, 1H), 0.99 (d, 3H, $J = 6.8$ Hz), 0.94 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (75.5 MHz, CDCl_3) 172.5, 156.9, 155.1, 132.3, 128.5, 128.0, 117.2, 112.3, 67.3, 56.1, 52.7, 30.7, 18.8; IR (neat) ν_{max} 3414, 1740, 1675, 1056; CIMS (NH_3 gas) 296.1, 252.1, 223.0, 162.0; CIHRMS $\text{M}+\text{H}^+$ (calculated for $\text{C}_{15}\text{H}_{22}\text{NO}_5$): 296.1498 found 296.1466; $[\alpha]_{23}^{\text{D}} = +7.00$ ($c = 0.50$, CHCl_3), mp 72-74 °C.



Methyl (2*R*, 3*S*)-3-hydroxyleucine (6). A dilute solution of the above methyl ester (5.0 g, 16.9 mmol) in anhydrous MeOH (170 mL, 0.1 M) was treated with 10% Pd-C (0.5 g, 10

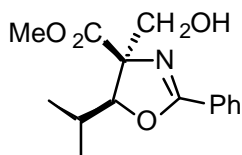
wt%). The suspension was stirred under 1 atmosphere of hydrogen for 12 hours. The resulting suspension was filtered through Celite, washed with MeOH, and concentrated *in vacuo* to afford **6** as a yellow solid (2.7 g, 99%). ^1H NMR (400 MHz, CDCl_3) 4.09 (s, br, 1H), 3.82 (s, 3H), 3.79 (s, br, 1H), 1.92 (s, br, 1H), 1.00 (d, 6H, $J = 12.8$

Hz); IR (neat) max 3433, 1646, 1457; CIMS (NH₃ gas) 162.1, 135.1, 102.1, 89.1; CIHRMS M+H⁺ (calculated for C₇H₁₆NO₃): 162.1130 found 162.1114; [α]₂₃^D = +9.4 (c = 0.34, CHCl₃), mp 98-99 °C.



(4R, 5S)-2-Phenyl-4-methoxycarbonyl-5-isopropylloxazoline (5). To a solution of **6** (1.00 g, 6.2 mmol) in dimethoxyethane (120 mL, 0.5 M) was added *p*-toluenesulfonic acid (0.56 g, 6.2 mmol, 1.0 equiv) followed by trimethylorthobenzoate (3.20 mL, 18.6 mmol, 3.0

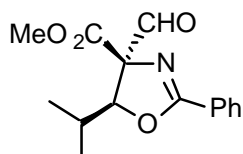
equiv). The reaction mixture was refluxed 4 hours and subsequently diluted with H₂O (20 mL). The reaction mixture was extracted with CHCl₃ (3 x 25 mL), dried (MgSO₄), and concentrated *in vacuo* to afford the crude oxazoline. Purification on SiO₂ (10% EtOAc/PE) afforded **5** as a light yellow oil (1.35 g, 85%): ¹H NMR (400 MHz, CDCl₃) δ 7.99-7.96 (m, 2H), 7.48-7.46 (m, 1H), 7.41-7.38 (m, 2H), 4.65 (t, 1H, J = 7.2 Hz), 4.55 (d, 1H, J = 7.2 Hz), 3.79 (s, 3H), 1.95-1.93 (m, 1H), 1.01 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 172.0, 165.7, 131.7, 128.5, 128.3, 127.1, 87.2, 71.2, 52.6, 32.4, 17.4, 17.2; IR (neat) ν_{max} 2963, 2877, 1740, 1646, 1581, 1451; CIMS (NH₃ gas) 247.1, 188.1, 105.0, 49.0, 30.0; CIHRMS M⁺ (calculated for C₁₄H₁₇NO₃): 247.1208, found: 247.1220; [α]₂₃^D = -105.7 (c = 1.32, CHCl₃), [α]₂₃^D (lit^[6e]) = -124 (c = 1.0, CHCl₃)



Primary Alcohol (10). To a solution of **5** (0.60 g, 2.44 mmol) in THF (24 mL, 0.1 M) at -78 °C was added dropwise a solution of lithium *bis*(trimethylsilyl)amide (0.5 M in THF, 5.4 mL, 2.69 mmol, 1.1 equiv). The bright yellow solution was stirred at -78 °C for 1 hour.

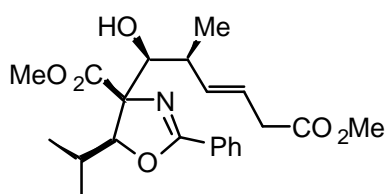
After 1 hour at -78 °C, a freshly prepared solution of monomeric formaldehyde^[4] in Et₂O (50 mL, *ca.* 50 mmol of HCHO, maintained at -78 °C) was cannulated into the enolate solution. The reaction mixture was stirred at -78 °C for 30 minutes and subsequently diluted with water (50 mL) and warmed to room temperature over a period of 15 minutes. The reaction mixture was extracted with Et₂O (3 x 25 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification on SiO₂, gradient elution (10% → 50% EtOAc/PE) afforded **10** as a white solid (0.57 g, 85%): ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, 2H, J = 8.0 Hz), 7.50-7.39 (m, 3H), 4.43 (d, 1H, J = 7.2 Hz), 3.97 (dd, 1H, J = 6.8, 11.6 Hz), 3.84 (dd, 1H, J = 7.2, 11.6 Hz), 3.76 (s, 3H), 2.21 (t, 1H, J = 7.2 Hz), 2.05-2.00 (m, 1H), 1.02 (d, 3H, J = 6.4 Hz), 1.00 (d, 3H, J = 6.4 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 171.4, 166.4, 131.8, 128.5, 128.2,

126.8, 89.1, 80.1, 66.7, 52.3, 29.5, 19.4, 18.6; IR (neat) ν_{\max} 3500, 1730, 1640; CIMS (NH₃ gas) 278.2, 246.2, 204.1, 176.0, 142.1, 105.0; CIHRMS M+H⁺ (calculated for C₁₅H₂₀NO₄): 278.1392, found: 278.1370; $[\alpha]_{23}^D = -2.0$ (c = 0.70, CHCl₃), mp 74-76 °C.



Aldehyde (4). A solution of **10** (0.5 g, 1.81 mmol) in benzene (10 mL, 0.18 M) and DMSO (2.7 mL, 0.67 M) was treated with DCC (0.75 g, 3.62 mmol, 3.0 equiv), pyridine (0.14 mL, 1.81 mmol, 1.0 equiv), and trifluoroacetic acid (70 μ L, 0.91 mmol, 0.5 equiv).

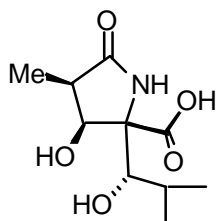
The cloudy mixture was stirred at ambient temperature for 12 hours and subsequently concentrated *in vacuo*. The residue was dissolved in cold pentane (25 mL) and filtered through Celite under an argon atmosphere. The filtrate was concentrated and exposed to high vacuum at ambient temperature for 16 hours to remove excess DMSO affording **4** as a light yellow oil which was used without further purification (crude yield ~ 98%). ¹H NMR (400 MHz, CDCl₃) δ 9.78 (s, 1H), 7.95 (d, 2H, J = 9.9 Hz), 7.55-7.35 (m, 3H), 4.85 (d, 1H, J = 8.2 Hz), 3.80 (s, 3H), 2.03 (m, 1H), 1.08 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 192.1, 168.3, 167.2, 132.4, 128.8, 128.5, 126.6, 86.8, 85.2, 55.8, 53.0, 25.5, 24.7; IR (neat) ν_{\max} 2932, 2118, 1640, 1451; CIMS (NH₃ gas) 276.1, 246.1, 204.1, 188.1, 105.0; CIHRMS M+H⁺ (calculated for C₁₅H₁₈NO₄): 276.1236, found: 276.1216; $[\alpha]_{23}^D = +9.8$ (c = 0.30, CHCl₃).



Homoallylic Alcohol (11). A solution of **4** (1.80 mmol) in CH₂Cl₂ (7.2 mL, 0.25 M) was cooled to -78 °C and treated with TiCl₄ (0.50 mL, 4.53 mmol, 2.5 equiv). The resulting red solution was stirred for 5 minutes at -78 °C and then treated with a solution of (*S*)-**8**^[5] (0.57 g, 2.17 mmol, 1.2 equiv) in

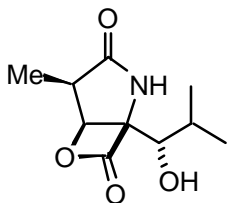
CH₂Cl₂ (2 mL, 1.0 M). The temperature of the reaction mixture was increased from -78 °C to -35 °C over a 3 hour period. The reaction was then stirred for an additional 12 hours at -35 °C and subsequently diluted with water (10 mL) and warmed to room temperature with stirring. The reaction mixture was extracted with CH₂Cl₂ (3 x 25 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification on SiO₂ (10% EtOAc/PE) afforded **11** as a light yellow oil (0.44 g, 60%). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, 2H, J = 8.0 Hz), 7.50-7.39 (m, 3H), 5.85 (m, 1H), 5.50 (dd, 1H, J = 7.6, 11.7 Hz), 4.85 (d, 1H, J = 8.2 Hz), 3.95 (s, 6H), 3.90-3.80 (m, 1H), 2.98 (d, 2H, J =

6.7 Hz), 2.65 (m, 1H), 2.05 (m, 1H), 1.07 (d, 3H, J = 6.4 Hz), 0.99 (d, 3H, J = 6.4 Hz), 0.70 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.4, 170.6, 166.7, 145.3, 131.8, 128.7, 128.5, 128.3, 113.6, 90.2, 82.2, 80.6, 70.6, 52.2, 39.8, 29.7, 21.6, 19.6, 18.8, 15.7; IR (neat) ν_{max} 3500, 1740, 1630, 1500; CIMS (NH_3 gas) 404.2, 387.5, 372.3, 250.4; CIHRMS $\text{M}+\text{H}^+$ (calculated for $\text{C}_{22}\text{H}_{30}\text{NO}_6$): 404.2073, found: 404.2065; $[\alpha]_{23}^{\text{D}} = -6.0$ ($c = 0.50$, CHCl_3).



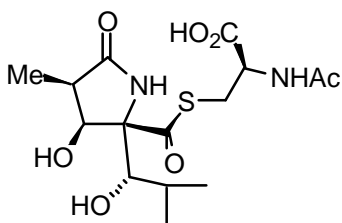
Dihydroxy Acid. A dilute solution of **11** (0.12 g, 0.30 mmol) in a 1 : 1 mixture of methanol / methylene chloride (0.1 M, 3.0 mL) was cooled to -78 C. Ozone was bubbled through the homogenous solution until a blue color persisted (*ca.* 10 minutes). The solution was then purged with argon to remove any excess ozone. The ozonide was reduced with methyl sulfide (0.2 mL, 3.0 mmol, 10.0 equiv) and gradually warmed to room temperature over a 12 hour period. The reaction mixture was concentrated *in vacuo* to afford the crude aldehyde. The crude aldehyde (0.30 mmol) was dissolved in a mixed solvent of $^t\text{BuOH}$ (3.0 mL, 0.1 M) and 2-methyl-2-butene (0.7 mL, 0.45 M). This solution was treated with a freshly prepared 1.18 M sodium chlorite solution in a 20% (wt/wt) aqueous sodium dihydrogen phosphate solution (2.5 mL, 3.0 mmol, 10.0 equiv) and the biphasic mixture stirred vigorously at ambient temperature for 45 minutes. The mixture was diluted with an aqueous sodium sulfite solution and stirred for 10 minutes. The crude mixture was concentrated *in vacuo* to remove excess solvent, extracted with CHCl_3 (3 x 20 mL), dried (MgSO_4), and concentrated *in vacuo* to give the labile acid which was used directly for the next step without further purification. The crude acid (~ 0.1 g, 0.30 mmol) was dissolved in acetic acid (AcOH , 9 mL, 0.032 M) and treated with ammonium formate (0.095 g, 1.5 mmol, 5.0 equiv) and palladium black (0.25 g). The mixture was refluxed for 4 hours, cooled to room temperature, and the catalyst filtered off through Celite and washed with CHCl_3 (25 mL). The filtrate was partially concentrated to remove the CHCl_3 and the solution neutralized with 2N NaOH to pH ~ 6 . The resultant solution was extracted with CHCl_3 (3 x 20 mL), dried (MgSO_4), and concentrated *in vacuo*. The crude dihydroxy ester was dissolved in EtOH (1 mL), treated with 0.1N NaOH (1.0 mL), and stirred for 10 hours at ambient temperature. The mixture was subsequently neutralized with 2N HCl to pH ~ 6 . The solution was concentrated *in vacuo* and subjected to a silica plug with MeOH as the eluent, affording the crude dihydroxy acid (0.060 g) which was used without further purification. ^1H NMR (400 MHz,

DMSO-*d*₆) δ 8.90 (s, br, 1H), 5.61 (d, 1H), 5.22 (d, 1H), 4.23 (d, 1H, *J* = 5.8 Hz), 3.78 (d, 1H, *J* = 6.0 Hz), 2.72 (m, 1H), 1.65 (m, 1H), 1.00 (d, 3H, *J* = 7.8 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 0.75 (d, 3H, *J* = 6.8 Hz).



β -Lactone (2). A suspension of the crude dihydroxy acid (0.060g, 0.26 mmol) in CH₂Cl₂ (3.7 mL, 0.07 M) was treated with Et₃N (0.11 mL, 0.78 mmol, 3.0 equiv), and *bis*(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 0.10 g, 0.39 mmol, 1.5 equiv) at ambient temperature. The reaction mixture was stirred for 0.5 hour at ambient temperature at

which point the mixture was diluted with water (10 mL), extracted with EtOAc (3 x 25 mL), dried (MgSO₄), and concentrated *in vacuo*. The crude residue obtained was plugged through a pad of silica gel and eluted with EtOAc (100 mL). The eluent was concentrated *in vacuo* to give **2** as a white powder (0.050 g, 80%, 3 steps). ¹H NMR (400 MHz, pyridine-*d*₅) δ 10.5 (s, br, 1H), 7.87 (d, 1H, *J* = 6.8 Hz), 5.69 (d, 1H, *J* = 6.0 Hz), 4.36 (dd, 1H, *J* = 3.2, 6.0 Hz), 3.07 (apparent q, 1H, *J* = 6.8, 7.2 Hz), 2.14-2.10 (m, 1H), 1.48 (d, 3H, *J* = 7.6 Hz), 1.13 (d, 3H, *J* = 6.8 Hz), 1.01 (d, 3H, *J* = 6.8 Hz); ¹³C NMR (75.5 MHz, pyridine-*d*₅) δ 177.8, 172.9, 81.0, 77.5, 71.0, 39.3, 30.3, 20.8, 16.9, 9.3; IR (neat) ν_{\max} 3425, 2088, 1653, 1646; CIMS (NH₃ gas) 214.1, 169.1, 136.1, 127.0; CIHRMS *M*+H⁺ (calculated for C₁₀H₁₆NO₄): 214.1079, found: 214.1069; [α]_D²³ = -96.0 (c = 0.25, CH₃CN), mp 183-184 (dec).



(+)-Lactacystin (1). A suspension of **2** (0.050 g, 0.23 mmol) in CH₂Cl₂ (2.3 mL, 0.1 M) was treated with *N*-acetyl-L-cysteine (0.038 g, 0.23 mmol, 1.0 equiv) and Et₃N (96 μ L, 0.69 mmol, 3.0 equiv) at ambient temperature. The reaction mixture was stirred for 4 hours at ambient temperature and then concentrated *in vacuo*. The residue was dissolved in dry pyridine (1 mL) and evaporated under reduced pressure. This process was repeated again to remove excess Et₃N. Generation of the free acid was accomplished by azeotropic distillation with THF/AcOH (5 : 1, v/v, 2 x 1 mL) followed by trituration of the mixture with EtOAc/AcOH (20 : 1, v/v, 2 x 1 mL) to afford (+)-lactacystin (**1**) as a white powder (60.0 mg, 70%). *R*_f 0.30 (THF/EtOAc/AcOH, 4 : 2 : 1); ¹H NMR (400 MHz, pyridine-*d*₅) δ 9.95 (s, br, 1H), 8.86 (d, 1H, *J* = 7.6 Hz), 5.41 (br q, 1H, *J* = 7.4 Hz), 5.36 (d, 1H, *J* = 6.8 Hz), 4.61 (d, 1H, *J* = 6.8 Hz), 4.07 (dd, 1H, *J* = 4.4, 13.2, Hz), 3.86 (dd, 1H, *J* = 6.8, 13.6 Hz), 3.41 (dq,

1H, J = 7.2, 7.6 Hz), 2.29-2.24 (m, 1H), 2.06 (s, 3H), 1.58 (d, 3H, J = 7.6 Hz), 1.27 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz); ¹³C NMR (75.5 MHz, pyridine-*d*₅) δ 203.3, 181.6, 173.9, 170.5, 81.5, 80.0, 76.1, 53.4, 42.0, 32.1, 31.5, 23.2, 21.5, 20.0, 10.2; IR (neat) ν_{max} 3580, 3482, 1698, 1670, 1640, 1620, 1617, 1550; CIHRMS M+H⁺ (calculated for C₁₅H₂₅N₂O₇S): 377.1382, found: 377.1340; [α]₂₃^D = +80 (c = 0.25, MeOH), [α]₂₃^D(lit^[6b]) = +78.6 (c = 0.49, MeOH), mp 234 (dec).

Additional Notes and References

[1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, 43, 2923-2925.

[²] (*E*)-4-Methyl-2-pentenoic acid was prepared in quantity by condensation of isobutyraldehyde with triethyl phosphonoacetate (see ref 7c), followed by saponification of the ethyl ester with LiOH/THF/H₂O. The crude acid was used without further purification.

[³] M. J. Mintz, C. Walling, *Org. Synth.* **1973**, Col. Vol 5, 184-187.

[⁴] For the preparation of the monomeric formaldehyde solution see: A. B. Smith III, S. J. Branca, M. A. Guaciaro, P. M. Wovkulich, A. Korn, *Org. Synth.* **1990**, Col. Vol. 7, 271-275.

[⁵] For the preparation of the silane reagents see: R. T. Beresis, J. S. Solomon, M. G. Yang, N. F. Jain, J. S. Panek, *Org. Synth.* **1997**, 75, 78-88.