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Enantioselective Synthesis of the (5*S*, 6*R*, 9*R*) and (5*S*, 6*R*, 9*S*) Analogs of Lactacystin β-Lactone

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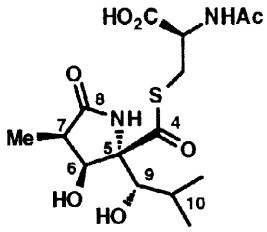
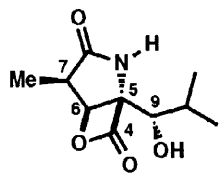
Abstract: *The synthesis of two diastereomers of lactacystin β-lactone (**2**), the β-lactones **3** and **4**, is described.*

Lactacystin (**1**), a microbial product first isolated by Ōmura *et al.*,[1,2] is a remarkably selective and potent inactivator of the 20 S proteasome.[3,4] The related β-lactone **2**, which can be formed spontaneously from **1** in solution, similarly deactivates the 20 S proteasome, but at a much faster rate.[4-7] Both **1** and **2** are now important tools in biochemical and cell biological research. Because of this fact and the scarcity of naturally derived **1**, there has been intense interest in the synthesis of **1**, **2** and their analogs.[8-13] We report herein on the synthesis and bioactivity of the (5*S*, 6*R*, 9*R*) and (5*S*, 6*R*, 9*S*) diastereomers of β-lactone **2**, **3** and **4**, respectively.

The synthesis of **3**, which is outlined in Scheme 1, commenced with (±)-dimethyl isopropenylmethylmalonate (**5**).[14] Enantioselective hydrolysis of **5** using pig liver esterase (Sigma-Aldrich) afforded the chiral mono acid **6** (configuration as shown, see below) in 97% yield and 83% enantiomeric excess. This transformation was quite satisfactory since the contamination by the minor enantiomer (*ca.* 8.5%) could be removed simply by recrystallization at a later point in the synthesis (intermediate **9**). Conversion of **6** to the corresponding acid chloride, coupling with *N*-(4-methoxybenzyl)glycine methyl ester and Dieckmann cyclization provided the keto lactam **7** in excellent overall yield. Base catalyzed hydroxymethylation with formalin in THF followed by ketone reduction with $NaBH(OAc)_3$ gave the diol **8**, which upon selective pivaloylation at the primary hydroxyl and recrystallization provided the enantiomerically pure, crystalline mono alcohol **9**. The structure of **9** was fully established by X-ray diffraction analysis.[15] The exceptionally strong control of stereochemistry in **9** is the result of (a) the diastereoselective hydroxymethylation of **7** due to greater steric screening by the 7-isopropenyl substituent relative to 7-methyl and (b) the diastereoselective, 5-hydroxymethyl controlled reduction of the 6-keto function through internal delivery of hydride.[16] Conversion of **9** to the *tert*-butyldimethylsilyl (TBS) ether and cleavage of the pivaloyl group (NaOMe) produced the crystalline hydroxy lactam **10**. Oxidation of **10** with sodium periodate and *cat.* OsO_4 led to the keto alcohol **11** which by further oxidation using the Dess-Martin periodinane gave the keto aldehyde **12**. Treatment of **12** with



Lactacystin (**1**)



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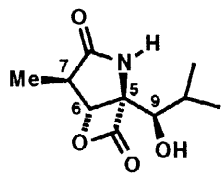

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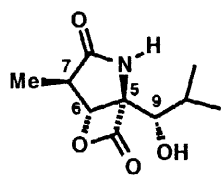

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trimethylchlorosilane in THF at -50 °C followed by isopropenylmagnesium bromide (cf. ref. 13a) afforded after aqueous extractive workup the unsaturated keto alcohol **13** which was hydrogenated and desilylated to the saturated keto alcohol **14**. A minor contaminant of **14**, the more polar (9*S*)-diastereomer (*ca.* 10% of total), was separated by column chromatography on silica gel.

Exposure of **14** to LiOH in 1 : 1 THF–H_2O at 23 °C effected unusually facile hydrolysis of the methoxycarbonyl function (probably via a β-lactone) to the lithium carboxylate. This salt upon removal of THF and heating in aqueous LiOH at 80 °C for 1 h underwent diastereoselective retro-Claisen deacetylation to form after acidification and extractive isolation a dihydroxy acid which was directly converted to the corresponding β-lactone **15** by treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). Deprotection of **15** provided the β-lactone **3** as a crystalline solid (mp. 160 °C) whose structure was verified by X-ray crystallographic analysis.[17, 15b] In a similar way the (9*S*)-diastereomer of **14** was converted to β-lactone **4**.

The (*R*) absolute configuration of acid **6** was determined by conversion to the dextrorotatory β-lactones **16** and **17** and comparison with the enantiomeric lactones **18** and **19** synthesized from the (*S*)-acid **20**[13a] (see Scheme 2). The stereocontrolled synthesis of **3** from ester acid **6** exemplifies a catalytic enantioselective synthesis in which the initial stereocenter which controls stereochemistry is itself modified in the target. The same is true for the previously described syntheses of lactacystin itself from serine[8,9] or from **20**. [13a]

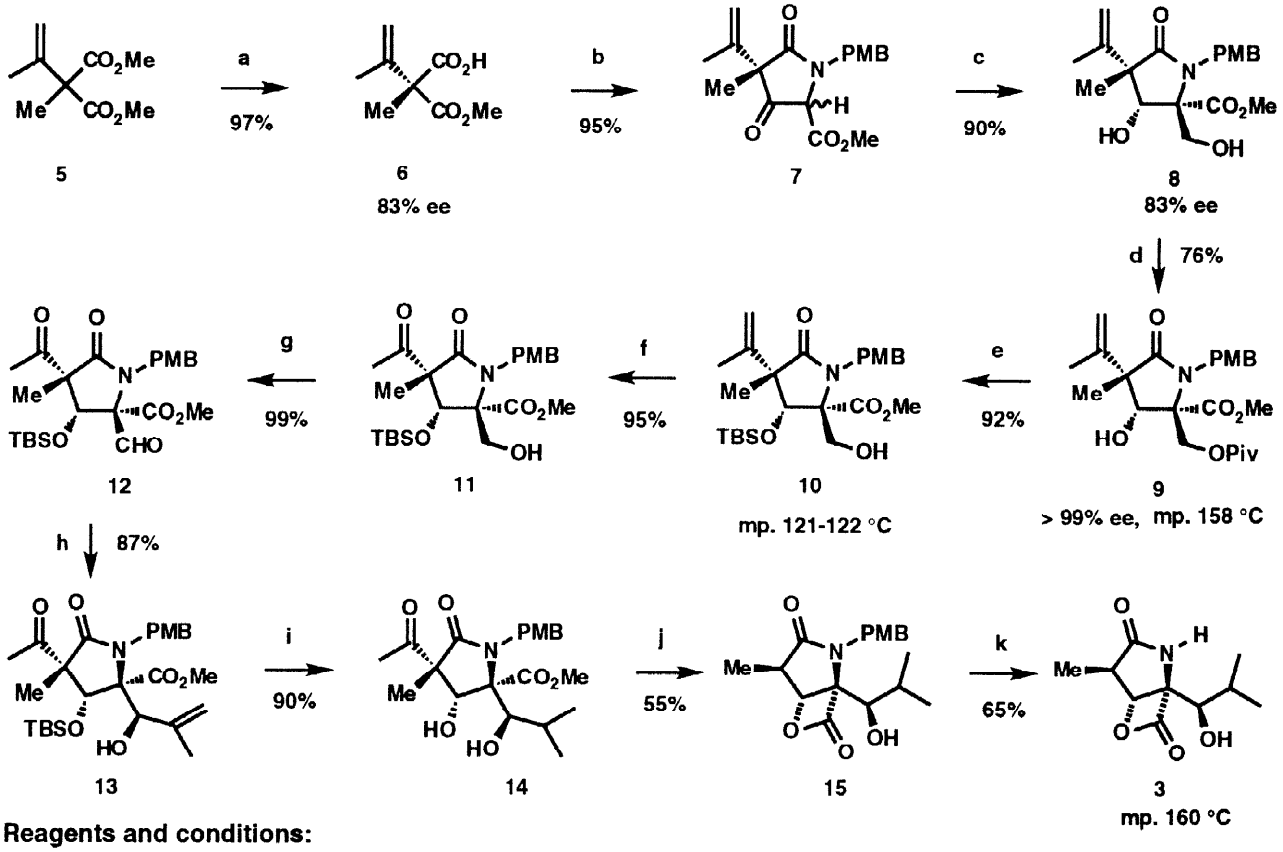
Although β-lactones **3** and **4** are similar to lactacystin β-lactone in terms of topology and functionality, they are very much less active as proteasome inactivators. The relative rates of inactivation were found to be 3000 for **2**, 121 for **3** and 0 (no inhibition) for **4**. This evidence underscores the importance of three dimensional geometry for effective proteasome inactivation as shown in a previous structure-activity study.[13b] In summary, the only modifications to the structure of lactacystin β-lactone which preserve high activity are the replacement of the 7-methyl substituent by ethyl, *n*-propyl or *i*-propyl or the replacement of the 7-hydrogen by methyl.

Detailed experimental procedures for the conversions **5** → **6** and **14** → **15** follow.

Preparation of (*R*)-Isopropenylmethylmalonic Acid Monomethyl Ester (6). To a stirred mixture of dimethyl isopropenylmethylmalonate (**5**)[14] [10.20 g, 54.84 mmol, prepared from dimethyl isopropylidenemalonate by methylation (NaH, DMF; then MeI)] in 20 mL of pH 7.30 phosphate buffer (0.1*M*) and 300 mL of distilled water was added Pig Liver Esterase (PLE, 1.0 g, crude acetonic powder from *Sigma* L8251). The pH of the resulting mixture was stirred and maintained at 7.30 by regular addition of a 2*N* aqueous NaOH solution with a syringe pump interfaced with a pH controller. After 24 - 30 h at 23 °C, one equiv of NaOH (27 mL) had been consumed. The reaction mixture was treated with Celite 545 (15 g) and filtered. The filtrate was acidified to pH 2 - 3 with 6*N* HCl and extracted with Et_2O (3 x 200 mL), and the combined extracts were washed with brine and dried. Evaporation of the solvent *in vacuo* gave the corresponding monomethyl ester [9.15 g, 97%, 83% ee as determined by ^{1}H-NMR spectroscopic analysis of the corresponding (*S*)-α-methylbenzylamine (>99% ee from *Aldrich* Co.) salt in $CDCl_3$] as a colorless oil. $[\alpha]_D^{23}$ +13.2 (*c* = 1.50, $CHCl_3$); FTIR (film) ν_{max}: 1120, 1273, 1728, 2958, 3206 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3C=), 3.75 (s, 3 H, CH_3O), 4.96 (s, 1 H, CH_2=), 5.07 (br s, 1 H, CH_2=) *ppm*; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.6; 52.8; 59.7; 114.7; 141.7; 171.8; 176.6 *ppm*; HRMS (CI, NH_3) *m/z* calcd for $C_8H_{16}NO_4$ 190.1079; found for $[M+NH_4]^+$ 190.1082.

Conversion of 14 to 15. A stirred mixture of the dihydroxy γ-lactam **15** (66 mg, 0.162 mmol) in THF / H_2O (*v/v*, 1 : 1, 0.5 mL) at 23 °C was treated with LiOH (10.0 mg, 0.417 mmol). The resulting mixture was stirred for 2 h at 23 °C and concentrated *in vacuo* at 23 °C. The residue was taken up in distilled water (1.0 mL) and treated with LiOH (10.0 mg, 0.417 mmol). The reaction mixture was heated to 80 °C, stirred for 1 h, then cooled to 0 °C, quenched with 2*N* HCl and extracted with EtOAc (4 x 8 mL). The combined extracts were washed with brine and dried. After evaporation of the solvent *in vacuo*, the resulting crude dihydroxy acid was taken up in CH_2Cl_2 (1.5 mL) and treated with Et_3N (66 μL, 0.48 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 60.0 mg, 0.24 mmol). The reaction mixture was stirred for 1 h at 23 °C, diluted with water and extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine and dried. After evaporation of the solvent *in vacuo*, the crude product was purified by flash chromatography on silica gel to afford the desired *N*-

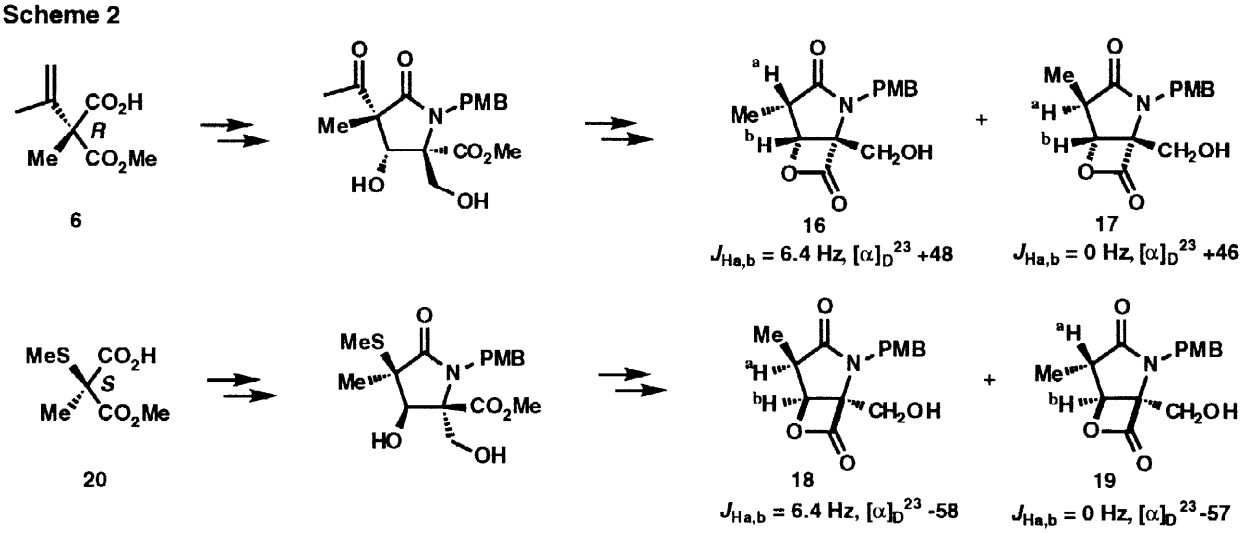
Scheme 1



Reagents and conditions:

(a) PLE, NaOH, pH 7.3, 23 °C, 30 h. **(b)** 1. $(ClCO)_2$, *cat.* DMF, PhH, 23 °C, 0.5 h; 2. $PMBNHCH_2CO_2Me$, Et_3N, CH_2Cl_2, 0 °C, 1 h; 3. LDA, THF, -78 °C - 0 °C, 2.5 h. **(c)** 1. HCHO, *cat.* DBU, THF, -78 °C, 1 h; 2. $NaBH(OAc)_3$, HOAc, 23 °C, 1 h. **(d)** PivCl, Py, 23 °C, 12 h; recrystallization from EtOAc / Hexane (1 : 1). **(e)** 1. TBSOTf, 2,6-Lutidine, CH_2Cl_2, 23 °C, 5 h; 2. NaOMe, MeOH, 23 °C, 4 h. **(f)** OsO_4 (5 mol %), $NaIO_4$, Dioxane-H_2O (1 : 1), 23 °C, 48 h. **(g)** Dess-Martin periodinane, CH_2Cl_2, 23 °C, 1 h. **(h)** CH_2=C(Me)MgBr, TMSCl, THF, -50 °C, 0.5 h. **(i)** 1. H_2, Pd-C (10%), EtOH, 23 °C, 2 h; 2. TFA-H_2O (4 : 1), 60 °C, 2 h. **(j)** 1. LiOH, THF-H_2O (1 : 1), 23 °C, 2 h; 2. LiOH, H_2O, 80 °C, 1 h; 3. BOPCl, Et_3N, CH_2Cl_2, 23 °C, 1 h. **(k)** CAN, CH_3CN-H_2O (3 : 1), 23 °C, 2 h.

Scheme 2



PMB β-lactone (30.0 mg, 55%) as a colorless oil. $[\alpha]_D^{23}$ +27 (*c* = 0.75, EtOAc); FTIR (film) ν_{max}: 1031, 1248, 1394, 1515, 1686, 1836, 2969, 3414 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.67 & 0.79 (each d, 3 H, *J* = 6.8 Hz, $(CH_3)_2CH$), 1.38 (d, 3 H, *J* = 8.0 Hz, CH_3CHCON), 1.40 (br m, 1 H, $CH(CH_3)_2$), 2.60 (d, 1 H, *J* = 6.0 Hz, CHO*H*), 2.91 (q, 1 H, *J* = 8.0 Hz, $CHCH_3$), 3.78 (s, 3 H, CH_3O), 4.07 (dd, 1 H, *J* = 2.5; 5.8 Hz, CHC*H*OH), 4.41 & 4.59 (each d, 1 H, *J* = 15.0 Hz, CH_2Ph), 4.96 (s, 1 H, CHOCO), 6.83 & 7.24 (each d, 2 H, *J* = 8.6 Hz, ArH) *ppm*; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 15.5; 14.3; 20.6; 28.0; 41.6; 45.5; 55.3; 69.9; 75.9; 83.8; 114.2; 128.4; 130.0; 130.1; 168.9; 176.6 *ppm*; HRMS (FAB, 3-NBA+NaI) *m/z* calcd for $C_{18}H_{23}NO_5Na$ 356.1474; found for $[M+Na]^+$ 356.1483.

A stirred mixture of the above *N*-PMB β-lactone (22.0 mg, 0.066 mmol) in CH_3CN / H_2O (*v/v*, 3 : 1, 0.8 mL) was treated with ceric ammonium nitrate (CAN, 160.0 mg, 0.29 mmol). The resulting mixture was stirred for 2 h at 23 °C, quenched with sat. aqueous $NaHCO_3$ (1.0 mL) and extracted with EtOAc (5 x 4 mL). The combined extracts were washed with brine and dried. After evaporation of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel to give β-lactone **15** (9.0 mg, 65%) as white solids. mp. 160 °C, $[\alpha]_D^{23}$ +57 (*c* = 0.25, EtOAc); FTIR (film) ν_{max}: 1706, 1832, 3358 cm^{-1}; ^{1}H-NMR (500 MHz, Py-d_5) δ 1.13 & 1.16 (each d, 3 H, *J* = 6.8 Hz, $(CH_3)_2CH$), 1.42 (d, 3 H, *J* = 7.9 Hz, CH_3CHCON), 2.12 (m, 1 H, $CH(CH_3)_2$), 3.04 (q, 1 H, *J* = 7.9 Hz, CHOCO), 4.18 (t, 1 H, *J* = 7.4 Hz, CHOH), 5.30 (s, 1 H, CHOCO), 7.71 (d, 1 H, *J* = 7.4 Hz, CHO*H*), 10.44 (br s, 1 H, NH) *ppm*; ^{13}C-NMR (125 MHz, Py-d_5) δ 14.4; 18.0; 20.4; 30.4; 42.3; 71.8; 79.9; 81.7; 171.7; 178.8 *ppm*; HRMS (CI, NH_3) *m/z* calcd for $C_{10}H_{19}N_2O_4$ 231.1345; found for $[M+NH_4]^+$ 231.1438.

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15. (a) X-ray data for **9**: $C_{24}H_{33}NO_7$; monoclinic; $P2_1/n$, a = 11.2181(2) Å; b = 10.717 Å; c = 20.0778(3) Å; α = 90°, β = 94.0690(10)°, γ = 90°; Z = 4; $R_1[I>2\sigma(I)]$ = 0.0750. (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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17. X-ray data for β-lactone **3**: $C_{10}H_{15}NO_4$; orthorhombic; $P2_12_12_1$, a = 7.5008(9) Å; b = 8.3057(11) Å; c = 17.965(2) Å; α = β = γ = 90°; Z = 2; $R_1[I>2\sigma(I)]$ = 0.0674.