Practical Synthesis of a Key Intermediate for Lactacystin from (*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl Acetate

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A practical synthesis of a key intermediate for the proteasome inhibitor lactacystin from (*R*)-4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate was established. (*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate is a useful chiral building block for the synthesis of biologically active compounds containing α-substituted α-amino acid moieties.

Key words lactacystin; formal synthesis; α-substituted α-amino acid; chiral building block; proteasome inhibitor

Natural products containing highly functionalized α-substituted α-amino acid moieties have recently been isolated and shown to display interesting biological activity.[2—5)] Lactacystin, isolated from the culture broth of *Streptomyces* sp. OM-6519 by Ōmura *et al.* in 1991, is an α-substituted α-amino acid derivative which first attracted interest given its ability to inhibit cell proliferation and induce nerve outgrowth in mouse neuroblastoma cells.[6,7)] Given that the cellular target of lactacystin is the 20S proteasome, lactacystin has been used as a tool in the study of proteasome function.[8—16)] Numerous attempts have been made to achieve the total synthesis of lactacystin given its structural features and potential biological significance. Since the first total synthesis of lactacystin was reported by Corey and Reichard in 1992,[17)] a lot of total and formal syntheses of lactacystin have been reported.[17—38)]

The authors recently reported on the development of a useful new chiral building block **1**, (*R*)-4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate, employed in the synthesis of α-substituted α-amino acid derivatives using lipase-catalyzed asymmetrization of prochiral diol. Chiral building block **1** was efficiently converted to (*R*)-2-(hydroxymethyl)glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine.[39)] In this paper, the authors report on the efficient formal synthesis of lactacystin using chiral building block **1**.

Results and Discussion

Our strategy outlining the synthesis of lactacystin is presented in Chart 1. Kang and coworkers reported on the synthesis of lactacystin by introduction of an isopropyl unit to lactam ester **2**.[25)] Therefore, the authors synthesize lactam ester **2**, Kang's synthetic intermediate, from chiral building block **1**. Lactam ester **2** is likely to be converted from dihydrooxazole **A** through hydrolysis of the dihydrooxazole moiety and formation of a lactam ring. Dihydrooxazole **A** is synthesized by diastereoselective introduction of a propionyl unit to chiral building block **1** at the C-6 position.[40)]

Introduction of a propionyl unit at the C-6 position in **1** was achieved using α,β-unsaturated ester **3** (Chart 2). Chiral building block **1** (>99% ee) was converted to (*E*)-α,β-unsaturated ester **3** by Swern oxidation, followed by a Horner–Wadsworth–Emmons reaction and subsequent ethanolysis of the acetate.[39)] The enantiomeric excess of α,β-unsaturated ester **3** was confirmed to be >99% ee, as determined by HPLC analysis using the chiral column CHIRALPAK AS® (hexane : 2-propanol=93 : 7). The primary hydroxy group in **3** was protected as a *tert*-butyldimethylsilyl (TBS) ether followed by diisobutylaluminium hydride (DIBAL-H) reduction in the presence of $BF_3 \cdot OEt_2$[41)] to afford allylic alcohol **4**.

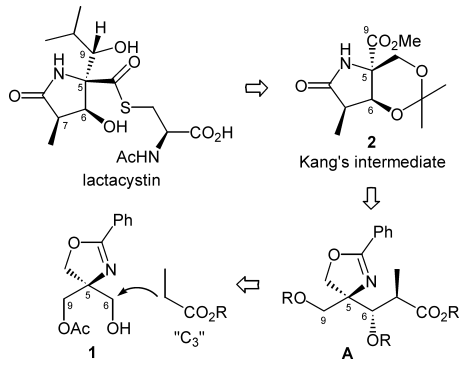
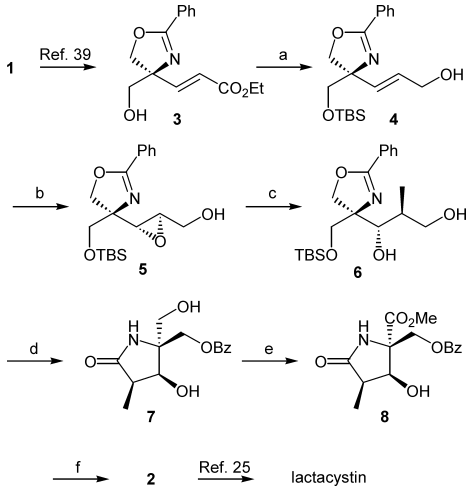


Chart 1. Synthetic Strategy for Lactacystin



Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, rt, 98%, (ii) DIBAL-H, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C to rt, 74%; (b) TBHP, D-(−)-DET, $Ti(O^iPr)_4$, MS, CH_2Cl_2, −20 °C, 93%; (c) Me_2CuLi, Et_2O, −20 °C, 99%; (d) (i) TEMPO, NaClO, KBr, $NaHCO_3$, acetone, 0 °C, (ii) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, ^tBuOH–H_2O, 0 °C, (iii) 1 M HCl, EtOH, 80 °C, 58% (three steps); (e) (i) TEMPO, BAIB, H_2O–CH_2Cl_2, rt, (ii) CH_2N_2, THF, 0 °C, 67% (two steps); (f) (i) K_2CO_3, MeOH, rt, (ii) TsOH, acetone, rt, 60% (two steps).

Chart 2

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DIBAL-H reduction of α,β-unsaturated ester **3** in the absence of $BF_3\cdot OEt_2$ resulted in a mixture comprising allylic alcohol **4** and the reduced alcohol derived from reduction of the carbon–carbon double bond in **4**. Asymmetric epoxidation of allylic alcohol **4** according to Sharpless' procedure[42] gave epoxyalcohol **5**. The diastereomer of epoxyalcohol **5** was not obtained. Epoxyalcohol **5** was treated with Me_2CuLi in Et_2O to give 1,3-diol **6** as the sole product. The high regioselectivity of epoxide-opening methylation was facilitated by steric hindrance due to the dihydrooxazole ring. Given the successful introduction of a C_3 unit at the C-6 position, formation of the lactam was then considered.

Selective oxidation of the primary hydroxy group in 1,3-diol **6** was achieved by treatment with 2,2,6,6-tetramethyl-1-piperodinyloxyl (TEMPO) and NaClO to give the aldehyde.[43] The aldehyde was then oxidized with $NaClO_2$ to give the carboxylic acid, and subsequent hydrolysis of the dihydrooxazole ring by treatment with 1 M HCl afforded lactam **7**. The primary hydroxy group in lactam **7** was oxidized by TEMPO and bis(acetoxy)iodobenzene (BAIB) to give the carboxylic acid,[44] and subsequent esterification of the carboxylic acid by treatment with CH_2N_2 afforded methyl ester **8**. Methanolysis of the benzoate in **8** with K_2CO_3 in MeOH gave the diol, which was then subjected to acetonization using TsOH in acetone to give lactam ester **2**, $[\alpha]_D^{25}$ +10.2° (c=0.38, $CHCl_3$) [lit.[32] $[\alpha]_D^{25}$ +9.1° (c=1.08, $CHCl_3$)], which is Kang's intermediate[25,32] for the synthesis of lactacystin.

The formal synthesis of lactacystin from chiral building block **1**, (*R*)-4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate, was successfully achieved. Chiral building block **1** can potentially be used in a broad range of applications directed towards the synthesis of biologically active chiral compounds containing α-substituted α-amino acid moieties.

Experimental

General Melting points (mp) were measured using a Yazawa melting point apparatus BY-2 and are uncorrected. Optical rotations were measured using a Jasco P-1030 polarimeter or a Jasco DIP-360 polarimeter. IR spectra were recorded using a Jasco FT-IR/620 spectrometer. UV spectra were recorded using a Jasco V-550 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-400 spectrometer. Chemical shifts are given on the δ (ppm) scale using tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad). ESI-MS and high resolution ESI-MS (HR-ESI-MS) spectra were obtained using a Micromass LCT spectrometer. Elemental analysis data were obtained using an Elemental Vavio EL. Flash column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, neutral) 40—50 μm.

(*R*,*E*)-3-[4-(*tert*-Butyldimethylsilanyloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]prop-2-en-1-ol (4) To a solution of alcohol **3**[39] (214 mg, 777 μmol) and imidazole (68.8 mg, 1.01 mmol) in DMF (780 μl) was added TBSCl (129 mg, 855 μmol) and the mixture was stirred for 30 min at rt. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=3 : 1) to give the TBS ether (296 mg, 98% yield) as a colorless oil: $[\alpha]_D^{25}$ −45.9° (c=1.05, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2857, 1721, 1648, 1580, 1496; UV λ_{max} (EtOH) nm (ε): 241 (14830); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.96 (2H, m), 7.49 (1H, m), 7.41 (2H, m), 7.16 (1H, d, J=15.8 Hz), 6.11 (1H, d, J=15.8 Hz), 4.61 (1H, d, J=8.4 Hz), 4.20 (2H, q, J=7.1 Hz), 4.19 (1H, d, J=8.4 Hz), 3.77 (1H, d, J=9.9 Hz), 3.71 (1H, d, J=9.9 Hz), 1.28 (3H, t, J=7.1 Hz) 0.84 (9H, s), 0.06 (3H, s), 0.01 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.4, 164.7, 148.1, 131.6, 128.4, 128.3, 127.5, 121.9, 75.9, 74.0, 67.6, 60.4, 25.7, 18.2, 14.2, −5.4, −5.5; ESI-MS m/z: 390 (M^++H, 100); HR-ESI-MS m/z: 390.2078 (Calcd for $C_{21}H_{32}NO_4Si$: M^++H, 390.2101); *Anal.* Calcd for $C_{21}H_{31}NO_4Si$: C, 64.75; H, 8.02; N, 3.60. Found: C, 64.76; H, 7.98; N, 3.70.

To a cold (−78 °C) solution of the above TBS ether (331 mg, 849 μmol) in CH_2Cl_2 (4.25 ml) was added $BF_3\cdot OEt_2$ (139 μl, 1.10 mmol) and the mixture was stirred for 30 min at the same temperature. DIBAL-H (2.19 ml, 2.12 mmol, 0.97 M in hexane) was added at −78 °C and the reaction mixture was warmed to rt over 2 h. MeOH was added, the mixture was diluted with Et_2O and then an excess of $Na_2SO_4\cdot 10H_2O$ was added. After stirring at rt for 8 h, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=2 : 1) to give allylic alcohol **4** (217 mg, 74% yield) as a colorless oil: $[\alpha]_D^{25}$ −36.4° (c=1.30, $CHCl_3$); IR (neat) cm^{-1}: 3304, 2953, 2929, 2856, 1646, 1580, 1496; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.95 (2H, m), 7.47 (1H, m), 7.40 (2H, m), 5.95 (2H, m), 4.58 (1H, d, J=8.1 Hz), 4.18 (2H, m), 4.17 (1H, d, J=8.1 Hz), 3.70 (2H, t, J=10.3 Hz), 1.52 (1H, br t, J=5.9 Hz), 0.82 (9H, s), 0.05 (3H, s), −0.01 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.1, 132.5, 131.3, 130.2, 128.3, 128.2, 127.8, 75.5, 74.4, 68.0, 63.3, 25.7, 18.1, −5.3, −5.4; ESI-MS m/z: 348 (M^++H, 100); HR-ESI-MS m/z: 348.1969 (Calcd for $C_{19}H_{30}NO_3Si$: M^++H, 348.1995); *Anal.* Calcd for $C_{19}H_{29}NO_3Si$: C, 65.67; H, 8.41; N, 4.03. Found: C, 65.64; H, 8.42; N, 4.01.

{(2*R*,3*R*)-3-[(4*R*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]oxiranyl}methanol (5) To a cold (−20 °C) suspension of 4A molecular sieves (3.60 g) in CH_2Cl_2 (64.1 ml) was added D-(−)-DET (450 μl, 2.63 mmol), $Ti(O^iPr)_4$ (560 μl, 1.88 mmol) and TBHP (4.98 ml, 56.4 mmol, 11.34 M in CH_2Cl_2). After stirring for 10 min at the same temperature, a solution of allylic alcohol **4** (6.54 g, 18.8 mmol) in CH_2Cl_2 (30.0 ml) was added over 30 min. Following stirring at −20 °C for 5 h, NaOH (3.01 ml, 30% in saturated aqueous NaCl) was added. The mixture was diluted with Et_2O, warmed to rt and stirred for 10 min. $MgSO_4$ (2.68 g) and Celite (334 mg) were then added and after stirring for 15 min the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=2 : 1) to give epoxyalcohol **5** (6.33 g, 93% yield) as a colorless oil: $[\alpha]_D^{25}$ +18.4° (c=1.05, $CHCl_3$); IR (neat) cm^{-1}: 3366, 2953, 2929, 2857, 1646, 1580, 1496; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.90 (2H, m), 7.47 (1H, m), 7.38 (2H, m), 4.45 (1H, d, J=8.7 Hz), 4.30 (1H, d, J=8.7 Hz), 3.95 (1H, ddd, J=2.4, 5.3, 12.7 Hz), 3.85 (1H, d, J=10.1 Hz), 3.74 (1H, d, J=10.1 Hz), 3.67 (1H, ddd, J=4.1, 7.5, 12.7 Hz), 3.45 (1H, m), 3.32 (1H, d, J=2.1 Hz), 1.91, (1H, m), 0.86 (9H, s), 0.08 (3H, s), 0.04 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.2, 131.5, 128.4, 128.2, 127.5, 74.1, 71.6, 66.8, 61.2, 57.3, 55.2, 25.7, 18.2, −5.4, −5.5; ESI-MS m/z: 364 (M^++H, 100); HR-ESI-MS m/z: 364.1959 (Calcd for $C_{19}H_{30}NO_4Si$: M^++H, 364.1944); *Anal.* Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.72; H, 8.04; N, 3.94.

(1*S*,2*S*)-1-[(4*R*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]-2-methylpropane-1,3-diol (6) To a cold (−20 °C) suspension of CuI (5.51 g, 28.9 mmol) in Et_2O (200 ml) was added dropwise methyllithium (50.7 ml, 57.9 mmol, 1.14 M in Et_2O). After stirring at −20 °C for 30 min, a solution of epoxyalcohol **5** (4.03 g, 11.1 mmol) in Et_2O (22.0 ml) was added. Following stirring at −20 °C for 1 h, a mixture of saturated aqueous NH_4Cl and 28% aqueous NH_3 (9 : 1) was added. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=2 : 1) to give diol **6** (4.16 g, 99% yield) as colorless crystals: mp: 70—72 °C; $[\alpha]_D^{25}$ +8.7° (c=1.15, $CHCl_3$); IR (KBr) cm^{-1}: 3388, 2954, 2929, 2856, 1652, 1582, 1497; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.91 (2H, m), 7.51 (1H, m), 7.41 (2H, m), 6.00 (1H, br s), 4.57 (2H, s), 3.92 (1H, d, J=10.1 Hz), 3.74 (1H, d, J=10.1 Hz), 3.71 (1H, m), 3.64 (1H, dd, J=9.3, 12.3 Hz), 3.46 (1H, br d, J=12.3 Hz), 2.18 (1H, m), 1.94 (1H, d, J=9.8 Hz), 1.00 (3H, d, J=7.1 Hz), 0.84 (9H, s), 0.06 (3H, s), 0.02 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.3, 132.1, 128.6, 128.5, 126.6, 77.7, 76.8, 74.1, 66.0, 62.3, 36.7, 25.6, 18.0, 16.9, −5.5 (×2); ESI-MS m/z: 380 (M^++H, 100); HR-ESI-MS m/z: 380.2264 (Calcd for $C_{20}H_{34}NO_4Si$: M^++H, 380.2257); *Anal.* Calcd for $C_{20}H_{33}NO_4Si$: C, 63.29; H, 8.76; N, 3.69. Found: C, 63.24; H, 8.79; N, 3.50.

(2*S*,3*S*,4*R*)-3-Hydroxy-2-hydroxymethyl-4-methyl-5-oxopyrrolidin-2-ylmethyl Benzoate (7) To a cold (0 °C) solution of diol **6** (691 mg, 1.79 mmol) in acetone (13.1 ml) was added $NaHCO_3$ (4.82 ml, 2.87 mmol, 5% aqueous solution), KBr (21.3 mg, 179 μmol), TEMPO (28.0 mg, 179 μmol) and NaClO (4.14 ml, 3.23 mmol, 0.78 M aqueous solution). After stirring at 0 °C for 30 min, $NaHCO_3$ (6.00 ml, 5% aqueous solution) was

added. The mixture was diluted with AcOEt and then washed with water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude aldehyde, which was used for the next reaction without further purification.

To a cold (0 °C) solution of the above crude aldehyde in ^tBuOH–H_2O (2 : 1, 27.0 ml) was added $NaH_2PO_4 \cdot 2H_2O$ (924 mg, 5.92 mmol), 2-methylbut-2-ene (950 μl, 8.97 mmol) and $NaClO_2$ (406 mg, 4.49 mmol). After stirring at 0 °C for 30 min, Na_2SO_3 was added. The mixture was diluted with AcOEt and then washed with 1 M HCl, water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude carboxylic acid, which was used for the next reaction without further purification.

To a solution of the above crude carboxylic acid in EtOH (17.9 ml) was added 1 M HCl (5.98 ml). After stirring at 80 °C for 1.5 h, the reaction mixture was filtered through filter paper. The filtrate was diluted with AcOEt and then washed with saturated aqueous $NaHCO_3$, water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : acetone = 1 : 2) to give lactam **7** (288 mg, 58% yield, three steps) as a colorless oil: $[\alpha]_D^{25}$ −23.0° (c = 1.31, $CHCl_3$); IR (neat) cm^{-1}: 3346, 2938, 1691, 1602, 1451; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (2H, m), 7.57 (1H, m), 7.42 (2H, m), 6.75 (1H, br s), 4.75 (1H, d, J = 11.7 Hz), 4.50 (1H, d, J = 11.7 Hz), 4.38 (1H, t, J = 6.4 Hz), 3.61 (2H, s), 3.60 (1H, m), 3.06 (1H, m), 2.80 (1H, m), 1.17 (3H, d, J = 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 179.1, 167.2, 133.6, 129.8, 129.2, 128.6, 72.2, 65.2, 64.0, 63.5, 41.1, 8.3; ESI-MS m/z: 280 (M^++H, 100); HR-ESI-MS m/z: 280.1209 (Calcd for $C_{14}H_{18}NO_5$: M^++H, 280.1185); *Anal.* Calcd for $C_{14}H_{17}NO_5$+1/2H_2O: C, 58.33; H, 6.29; N, 4.86. Found: C, 58.60; H, 6.49; N, 4.89.

Methyl (2*S*,3*S*,4*R*)-2-Benzoyloxymethyl-3-hydroxy-4-methyl-5-oxopyrrolidine-2-carboxylate (8) To a solution of alcohol **7** (33.4 mg, 120 μmol) in H_2O–CH_2Cl_2 (2 : 1, 600 μl) was added TEMPO (5.6 mg, 36.0 μmol) and BAIB (116 mg, 360 μmol). After stirring at rt for 10 h the reaction mixture was diluted with AcOEt and then washed with saturated aqueous $Na_2S_2O_3$, water and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude carboxylic acid, which was used for the next reaction without further purification.

To a cold (0 °C) solution of the above crude carboxylic acid in THF (1.20 ml) was added a solution of CH_2N_2 in Et_2O until the color of the mixture turned yellow. After stirring at 0 °C for 5 min, the reaction mixture was warmed to rt, stirred for 50 min and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 3) to give methyl ester **8** (24.6 mg, 67% yield, two steps) as colorless crystals: mp: 191—193 °C; $[\alpha]_D^{25}$ −17.4° (c = 1.04, MeOH); IR (KBr) cm^{-1}: 3383, 3318, 2961, 1737, 1701, 1452; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (2H, m), 7.58 (1H, m), 7.42 (2H, m), 6.33 (1H, br s), 4.93 (1H, d, J = 11.5 Hz), 4.70 (1H, m), 4.62 (1H, d, J = 11.5 Hz), 3.77 (3H, s), 2.73 (1H, d, J = 6.9 Hz), 2.62 (1H, dq, J = 6.0, 7.4 Hz), 1.55 (3H, s), 1.23 (3H, d, J = 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 177.3, 171.3, 166.2, 133.6, 129.7, 129.0, 128.6, 74.0, 68.6, 66.4, 53.2, 41.0, 8.0; ESI-MS m/z: 308 (M^++H, 52), 317 (100); HR-ESI-MS m/z: 308.1130 (Calcd for $C_{15}H_{18}NO_6$: M^++H, 308.1134); *Anal.* Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.42; H, 5.66; N, 4.58.

Methyl (4a*S*,7*R*,7a*S*)-2,2,7-Trimethyl-6-oxo[1,3]dioxino[5,4-b]pyrrole-4a-carboxylate (2) To methyl ester **8** (10.1 mg, 32.9 μmol) was added K_2CO_3 (0.5 g/l in MeOH, 330 μl). After stirring at rt for 2.5 h, the reaction mixture was diluted with AcOEt and then washed with saturated aqueous NH_4Cl, water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude diol, which was used for the next reaction without further purification.

To a solution of the above crude diol in acetone (330 μl) was added $TsOH \cdot H_2O$ (0.6 mg, 3.29 μmol). After stirring at rt for 15 h, the reaction mixture was diluted with AcOEt and then washed with saturated aqueous $NaHCO_3$, water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 4) to give acetonide **2**[25,32] (4.8 mg, 60% yield, two steps) as colorless crystals: mp: 155—157 °C; $[\alpha]_D^{25}$ +10.2° (c = 0.38, $CHCl_3$); IR (KBr) cm^{-1}: 3260, 2921, 2852, 1740, 1718, 1678, 1434; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.13 (1H, br s), 4.62 (1H, dd, J = 1.0, 5.1 Hz), 4.26 (1H, d, J = 12.4 Hz), 3.78 (3H, s), 3.75 (1H, d, J = 12.4 Hz), 2.63 (1H, dq, J = 5.1, 7.2 Hz), 1.49 (3H, s), 1.37 (3H, s), 1.14 (3H, d, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 178.4, 171.5, 98.9, 71.4, 63.2, 61.8, 53.1, 40.3, 26.8, 20.5, 7.3; ESI-MS m/z: 244 (M^++H, 100); HR-ESI-MS m/z: 244.1188 (Calcd for $C_{11}H_{18}NO_5$: M^++H, 244.1185); *Anal.* Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.62; H, 7.10; N, 5.77.

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