Note

Synthesis of *N*-Butanoylhomoserine Lactone

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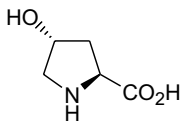
Synthesis of *N*-butanoylhomoserine lactone has been achieved from *trans*-(2*S*,4*R*)-4-hydroxyproline via the key regioselective Baeyer-Villiger reaction.

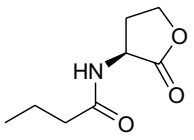
Keywords: *trans*-(2*S*,4*R*)-4-Hydroxyproline; *N*-Butanoylhomoserine lactone; Regioselective Baeyer-Villiger reaction.

INTRODUCTION

The structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline shows that it possesses three functional groups that can be easily modified, and these are 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents a significant feature for producing a series of different carbon frameworks using an efficient modification technique.[2] Recently we have introduced a straightforward approach toward anisomycin,[2h] epibatidine,[2i] pancracine,[2j] and streptorubin B core[2k] employing *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) as the starting material. To explore a new application, synthetic studies toward *N*-butanoylhomoserine lactone (**2**) were investigated.



trans-(2*S*,4*R*)-4-hydroxyproline (**1**)



N-butanoylhomoserine lactone (**2**)

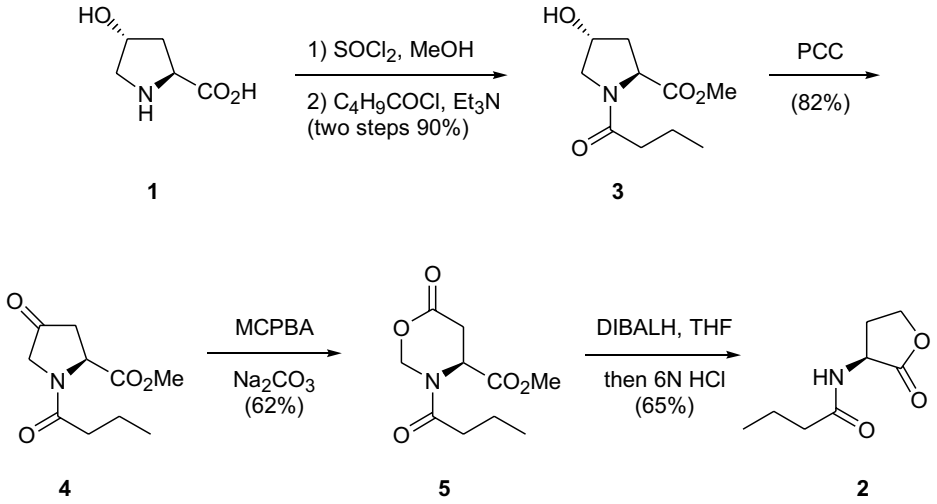
Pseudomonas aeruginosa is an opportunistic pathogen that causes a wide range of acute and chronic infections, including sepsis and wound and pulmonary infections.[3a-b] It predominately produces two small diffusible autoinducers, *N*-3-oxododecanoylhomoserine lactone (3-oxo-C_{12}-HSL) and *N*-butanoylhomoserine lactone (C_4-HSL).[3c-d] Bioassays revealed that L-isomers were essential as the autoinducers in quorum sensing, while no effect was observed with D-isomers. The scaffold of *N*-acyl homoserine lactones is common in certain biological analogs including anti-allergy, asthma, immunosuppressant, and antineoplastic agents.[4] For the preparation of C_4-HSL (**2**) and its analogs, one-step acylation reaction of commercially available L-homoserine lactone[4f,5] with acid chloride has been generally employed. Therefore, we envisioned that there is a continuing need for other chiral materials to synthesize C_4-HSL (**2**) and related derivatives. In continuing the previous investigations and building upon these observations on *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) as the chiral material, we are interested in developing a new method to C_4-HSL (**2**) via the key regioselective Baeyer-Villiger reaction.

RESULTS AND DISCUSSION

As shown in Scheme I, compound **3** was prepared by the standard protocol operation via esterification with thionyl chloride and methanol at -78 °C and acylation with triethylamine and *n*-butanoyl chloride in dichloromethane at 0 °C. Oxidation of compound **3** was treated with pyridinium chlorochromate and Celite to yield ketone **4** in dichloromethane at rt. Regioselective Baeyer-Villiger reaction of ketone **4** with *m*-chloroperoxybenzoic acid[6] yielded sole tetrahydro-1,3-oxazin-6-one **5**. During the process, other ring-expanded frameworks were not observed. While poring over the related literature of Baeyer-Villiger ring expansion reactions, we found that Young and co-workers had developed a copper(II) acetate-mediated ring expansion of 4-ketoprolines with *m*-chloroperoxybenzoic acid in modest yield. The most likely explanation would be that it is controlled by involvement of the nitrogen lone pair on substituted pyrrolidin-4-one.[6]

Finally, C_4-HSL (**2**) was afforded by the regioselective reduction with diisobutylaluminum hydride and fol-

Scheme I Synthesis of *N*-butanoylhomoserine lactone (C_4-HSL, **2**)



lowed acidification.[7] Although the synthetic efficiency of C_4-HSL (**2**) is decreased in comparison with the literature reports, we believe the rather lengthy route will be valuable to report and the present work is complementary to existing methodology. In summary, we succeeded in accomplishing the synthesis of C_4-HSL (**2**) from the chiral starting material *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) via the key regioselective Baeyer-Villiger reaction. Currently studies are in progress in this direction.

EXPERIMENTAL SECTION

(2*S*,4*R*)-1-Butyryl-4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester (3)

Thionyl chloride (2.5 g, 21.0 mmol) was added to a stirred solution of *trans*-4-hydroxyproline (**1**) (1.31 g, 10.0 mmol) in methanol (20 mL) at -78 °C for 10 min. The mixture was stirred in an ice bath for 30 min then at rt for 30 min, followed by reflux for 3 h. Concentration *in vacuo* followed by azotropic removal of water using benzene (50 mL) gave methyl 4-hydroxyproline hydrochloride (1.81 g, 100%). Triethylamine (3.1 g, 30.6 mmol) and *n*-butanoyl chloride (1.07 g, 10.0 mmol) were added to a solution of the resulting product in dichloromethane (40 mL) at 0 °C. After stirring at the same temperature for 10 h, the reaction mixture was concentrated. Ethyl acetate (40 mL) was added to the residue, and the solution was washed with hydrogen chloride solution (0.1 N, 10 mL), saturated sodium bicarbonate solution and brine, dried, filtered and evaporated to afford crude product. Recrystallization from hexane and ethyl acetate (approx. 4:1) yielded compound **3** (1.94 g, 90%). $[\alpha]_D^{22}$ -81.12° (*c* 0.04, $CHCl_3$); IR ($CHCl_3$) 3400, 2961, 1742, 1655, 1436, 1200, 1084 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{10}H_{18}NO_4$ 216.1236, found 216.1240; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58-4.55 (m, 2H), 3.77-3.72 (m, 1H), 3.73 (s, 3H), 3.53 (d, *J* = 10.5 Hz, 1H), 2.83 (br s, 1H), 2.32-2.26 (m, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.10-2.04 (m, 1H), 1.70-1.62 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.99, 172.53, 70.27, 57.47, 55.12, 52.27, 37.74, 36.33, 18.05, 13.75; Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.98; H, 8.21; N, 6.72.

(2*S*)-1-Butyryl-4-oxo-pyrrolidine-2-carboxylic acid methyl ester (4)

A solution of compound **3** (1.1 g, 5.1 mmol) in dichloromethane (10 mL) was added to a mixture of pyridinium chlorochromate (2.2 g, 10.2 mmol) and Celite (2.0 g) in dichloromethane (20 mL) at rt. After being stirred at rt for 10 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 5/1) yielded compound **4** (900 mg, 82%). $[\alpha]_D^{22}$ +8.33° (*c* 0.04, $CHCl_3$); IR ($CHCl_3$) 1750, 1656, 1651, 1435, 1418, 1196 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{10}H_{16}NO_4$ 214.1079, found 214.1081; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 2.7, 10.5 Hz, 1H), 4.50 (d, *J* = 17.7 Hz, 1H), 3.97 (d, *J* = 17.7 Hz, 1H), 3.76 (s, 3H), 2.92 (dd, *J* = 10.5, 18.9 Hz, 1H), 2.61 (dd, *J* = 2.7, 18.9 Hz, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.74-

1.67 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.53, 172.99, 172.13, 55.32, 53.21, 52.93, 40.36, 36.82, 18.06, 13.94; Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.69; H, 6.77; N, 6.96.

(2*S*)-3-Butyryl-6-oxo-[1,3]oxazinane-4-carboxylic acid methyl ester (5)

To a solution of *m*-chloroperoxybenzoic acid (6.0 g, 75%, 26.1 mmol) in dichloromethane (30 mL) was added a solution of compound **4** (2.2 g, 10.3 mmol) and sodium carbonate (4.3 g, 40.6 mmol) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at rt for 20 h. Saturated sodium carbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate = 4/1~2/1) afforded lactone compound **5** (1.47 g, 62%) as the rotamers. HRMS (ESI, M^++1) calcd for $C_{10}H_{16}NO_5$ 230.1029, found 230.1026; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, J = 10.5 Hz, 1H), 5.38 (d, J = 10.5 Hz, 1H), 4.91-4.82 (m, 1H), 3.74 (s, 3H), 3.09 (dd, J = 10.5, 18.9 Hz, 1H), 2.64 (dd, J = 2.7, 18.9 Hz, 1H), 2.25 (t, J = 7.5 Hz, 2H), 1.76-1.61 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.69; H, 6.72; N, 6.36.

***N*-Butanoylhomoserine lactone (C_4-HSL, 2)**

A solution of diisobutylaluminum hydride (12.0 mL, 1.0 M in hexane, 12.0 mmol) was added to a solution of compound **5** (1.15 g, 5.0 mmol) in tetrahydrofuran (10 mL) at -78 °C. After 1.5 h, hydrogen chloride solution (6N, 10 mL) was added to the reaction mixture. After 20 min, the reaction was warmed slowly to 0 °C and the solvent was concentrated. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate = 2/1) afforded compound **2** (560 mg, 65%). IR ($CHCl_3$) 3288, 1769, 1651, 1537, 1179 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_8H_{14}NO_3$ 172.0974, found 172.0977; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (br s, 1H), 4.60-4.51 (m, 1H), 4.47 (t, J = 9.0 Hz, 1H), 4.28 (ddd, J = 6.0, 9.0, 11.4 Hz, 1H), 2.91-2.80 (m, 1H), 2.23 (t, J = 6.9 Hz, 2H), 2.23-2.05 (m, 1H), 1.73-1.62 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.76, 173.82, 66.33, 49.47, 38.26, 30.87, 19.09, 13.89.

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