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Research paper

Synthesis of □-Hydroxy □-Proline: Potential for Organocatalysis Reactions

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Abstract

A chiral organic molecule, L-proline catalyzed an enantioselective transformation reaction has becoming interesting synthetic protocol especially in the area of organocatalysis. Herein, a synthetic approach towards □-hydroxy-□-proline starting from bicyclic lactone lactam is hereby described. The syntheses utilized dicarboxylation reaction of bicyclic lacton lactam, followed by ether hydrolysis of the bicyclic ether and oxidation reaction of the primary alcohol. The synthetic strategy disclosed here allows further the enantioselective synthesis of a variety of unnatural amino acids based on □-proline structure.

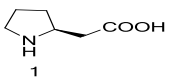
Keywords: *□-proline, organocatalysis, GABA transporter, Geissman Waiss Lactone*

1. Introduction

The use of organocatalysis in which a chiral organic molecule catalyzed an enantioselective transformation of drugs and drugs candidate has recently becoming attractive synthetic strategy for chemists and industries.[1] The prospect offered by using the organocatalysis rely on their role to minimize the toxic substances in conventional synthesis and the ability to catalyzed asymmetric synthesis of chiral and non-racemic drugs.[2] One of the established organocatalyst used are (*S*)-proline and (*R*)-proline. (*S*)-proline has been used to catalyzed the amination of indane carboxaldehyde[3] and intramolecular aldol reaction with high yields and excellent enantioselectivity. (*S*)-proline also could catalyzed the reaction of 2-phenylpropionaldehyde with diethylazodicarboxylate to give the corresponding oxazolidinones in 86% ee.[4] The preparation of chiral amino aldehyde utilizing (*S*)-proline catalyzed amination of aldehyde has been investigated.[5] Herein, we report the synthesis of □-hydroxy-□-proline starting from bicyclic lactone which can serve as potentials candidate for organocatalyst. Wanner [6] discovered that (*S*)- (*S*)-□□-proline **1** could inhibit the transporter of neurotransmitter (GABA transporter) with mGAT1 value 6.24 uM, whereas (*R*)-□-proline **2** give mGAT1 value 60 uM.

In addition, L-□-homohydroxyproline hydrochloride **3**, could be used as a starting material for the synthesis of tripeptide inhibitors of Hepatitis C Virus NS3 (HCV NS3). Hepatitis C Virus is the main cause of liver disease disorder and also the main indicator for liver transplant.[7]

Hence, studies around this aspect on the development of more efficient methodology are still wanting and significant, considering the seriousness of HCV infection on human health. As part of our continuing interest in the area of enantioselective proline based synthesis, we embarked on a new strategy starting from bicyclic lactone lactam **6** to prepare new derivatives of □-hydroxy-□-proline.



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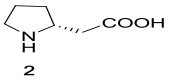

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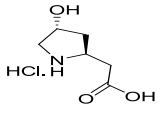

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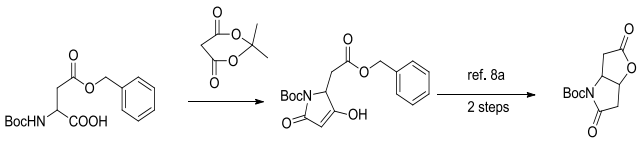
2. Results and Discussion

The synthesis of □-hydroxy-□-proline could be commenced with bicyclic lactone lactam **6** which could be derived from from NBoc-protected amino acid[8a] **4**, through a three steps reaction. (Scheme 1) Bicyclic lactone lactam **6** (with different chiralities) also could be synthesized from cyclohexene monoxide through three steps reaction. [8b,9]

In an afford towards the synthesis of □-hydroxy-□-proline, the carbonyl reduction near to amide and lactone functionality by borane dimethylsulfide gave 13% of compound **7**. Hydrolysis of ether ring of bicyclic compound **7** by $LiAlH_4$ in THF gave diol **8**, which was transformed into the desired □-hydroxy-□-proline, **9** by oxidation of primary alcohol utilizing Jones reagent in acetone. All the synthesized products are in the racemic form. Further reaction will be carried out in our lab to investigate the synthesized proline derivatives for catalyzing selected asymmetric reactions.



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Scheme 1: The synthesis of bicyclic lactone **6** from NBoc-protected amino acid, **4**

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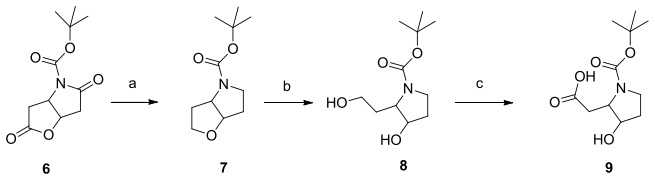

Reagent and conditions: (a) Borane-DMS (3 equiv.), 0 ^{o}C- rt, 17 h, 13%. (b) $LiAlH_4$ (3 equiv.), THF, 0 ^{o}C, 49 % (c) Jones reagent (2.5 M), acetone, 10 ^{o}C,15 min, 61%

Scheme 2: Synthesis of □-hydroxy-□-proline, **9**□

3. Experimental

***Tert*-butyltetrahydro-2H-furo[3,2-b]pyrrole-4(5H)-carboxylate (7)**

To a stirred solution of **6** (0.015mg, 0.068 mmol, 1 equiv.) in THF at 0 ^{o}C, under N_2 was added borane –DMS (0.12 ml, 1.24 mmol, 3 equiv.) dropwise, the mixture was stirred for 17 h under N_2 atmosphere, then MeOH was added until no evolutions of gas, then the solvent was removed, dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give crude product which was purified by column chromatography on silica gel (ethyl acetate/methanol, 4:6) to yield 13% of **7** as white solid.

R_f = 0.42 (SiO_2, hexane/ethylacetate 4:6); m.p. 83-85°C. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 4.28-4.36 (m, 1H, C*H*OCH$_2$), 3.85-3.92 (bs, 1H, C*H*NBoc), 3.55- 3.72 (m, 2H, CH_2O), 3.20-3.35 (m, 2H, CH_2NBoc), 3.55-2.02 (m, 4H, CH_2CHO, CH_2CH$_2$O), 1.38 (s, 9H, Boc); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 155.88 (C_{quart}, CO-Boc), 79.97 (*C*HO), 70.66 (C_{quart}, Boc-C), 59.00 (*C*HNBoc), 57.84 (*C*H$_2$O), 43.49 (*C*H$_2$NBoc), 31.06 (*C*H$_2$CHNBoc), 30.75 (*C*H$_2$CHO), 28.43 (Boc). **IR** (Film): $\tilde{\nu}$ = 2976, 2938, 2888, 1650, 1410, 1366, 1251, 1162, 1128, 1068, 1013, 980, 866, 770 cm^{-1}. **MS** [CI, NH_3] : m/z (%) = 213.1 [M^+].

***Tert*-butyl 3-hydroxy-2-(2-hydroxyethyl)pyrrolidine-1-carboxylate, (8)**

To a stirred solution of compound **7** in THF at 0°C, under N_2 was added with $LiAlH_4$ (0.2 mmol, 3 equiv.) Then the mixture was stirred over 30 min. The reaction mixture was quenched with 1 ml of EtOH and 0.5 ml of saturated NH_4Cl followed by filtration through celite. The crude product was purified by column chromatography on silica gel using ethyl acetate: petroleum ether (4:6) to yield **8**, (7.6 mg) 49% of the diol as colourless oil.

R_f = 0.21 (SiO_2, ethylacetate/methanol 4:6); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 4.43-4.32 (t, 2H, C*H*$_2$OH), 4.03-3.93 (m, 1H, C*H*NBoc), 3.89-3.37 (m, 1H, C*H*OH), 2.10-1.85 (m, 2H, C*H*$_2$NBoc), 1.77-1.1.68 (m, 2H, C*H*$_2$CH$_2$OH), 1.46 (s, 9H, Boc); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 158.8, 80.1, 77.5, 75.6, 56.3, 34.2, 312.8, 28.4..**MS** [CI, NH_3] : m/z (%) = 249.24; [M + NH_4^+].

2-(2*R*,3*R*)- 1-(*Tert*-butoxycarbonyl)-3- hydroxypyrrolidin-2-yl) acetic acid (9)

To a stirred solution of diol **8** (14.8 mg, 0.064 mmol, 1 equiv.) in acetone at 10°C, was added Jones reagent (2.5 M/ 0.24 ml) over 15 minutes. Then the mixture was stirred over 30 min while keeping the temperature between 10- 15°C. One drop of isopropanol was added to destroy any excess of oxidant. Subsequently 25 ml of H_2O was added to dissolve the precipitate salts. Acetone was then removed by reduce pressure and the product was recovered by extraction using ethyl acetate and petroleum ether (9:1), dried with $MgSO_4$ to afford **9** (9.21 mg) 61% as a white solid.
Rf = 0.61 (SiO_2, ethylacetate/methanol 9:1);. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 4.53-4.49 (m, 1H), 4.43-4.32 (m, 1H), 3.88-3.91 (m, 1H), 3.54-3.32 (m, 1H), 2.90-2.88 (m, 1H), 2.41-2.23 (m, 1H), 2.20-2.01 (m, 2H), 1.46 (s, 9H, BoC); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 176.2, 164.9, 83.5, 81.7, 58.3, 44.8, 36.9, 35.2, 29.4. **MS** [CI, NH_3] : m/z (%) = 246.1[M + H^+].

4. Conclusion

The synthesis of □-hydroxy -□-proline was successfully achieved from bicyclic lactone lactam with moderate yield. This type of proline derivative may have a potential as an organocatalyst candidate in an asymmetry synthesis.

Acknowledgement

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