Stereoselective Synthesis of (3*R*,5*R*)-*cis*-3-Hydroxy-5-phenylpyrrolidine

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Abstract: *Cis*-3-hydroxy-5-phenyl pyrrolidine could be synthesized stereoselectively from inexpensive starting materials, (*R*)-(+)-ethyl-4-chloro-3-hydroxybutanoate and (*R*)-(+)-4-chloro-3-hydroxybutyronitrile. Key feature involves face- and chemo-selective hydrogenation of cyclic imine **5** as the common key intermediate using Pt/C catalyst. Transformations described here will allow a practical synthesis of novel carbapenems, **1** and **2**.

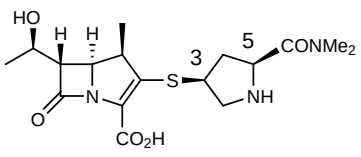
Key words: reductive amination, cyclic imine, hydrogenation, pyrrolidine, 1β-methylcarbapenem

1β-methylcarbapenem antibiotics having a (3*S*,5*S*)-cis-3-thio-5-substituted pyrrolidine ring as the C-2 side chain such as meropenem,[1] S-4661, [2] and BO-2727,[3] which have a broad gram-positive and -negative antibacterial spectrum, are widely known, and their syntheses have been well established. On the other hand, it has been recently reported that **1** and **2** possessing an unique (3*S*,5*R*)-*trans*-3-thio-5-substituted pyrrolidine ring C-2 side chain showed ultra-broad antibacterial activity even against MRSA (Figure).[4]

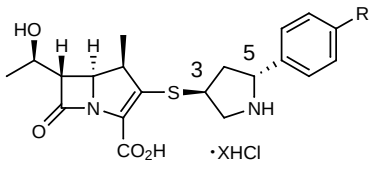
Although the (3*S*,5*R*)-trans-disubstituted pyrrolidine skeleton seems to be essential for appearance of these remarkable activities, development of an efficient synthesis has not been fully investigated.[5] Therefore, in the course of our studies toward a practical and large scale synthesis of **1** or **2**, a stereoselective synthesis of the thiol prototype **3** was extensively studied. Since the thiol group is preferably introduced by S_N2 fashion in a late stage of the synthesis, stereoselective construction of (3*R*,5*R*)-cis-3-hydroxy-5-phenyl pyrrolidine (**4**) is key for success of the synthesis. Herein we wish to report a general stereoselective synthesis of **4**.

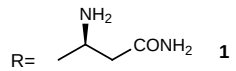
Our strategy for an efficient construction of **4** is outlined in Scheme 1. Diastereo and chemoselective reduction of the cyclic imine **5** would be one of most promising approaches to the desired pyrrolidine ring **4**. However, it has been known that **5** is quite unstable due to its liability to lose the silyloxy group to form the corresponding pyrrole.[6] This nature makes the synthesis more challenging although cyclic imines have been well recognized to be valuable intermediates for alkaloid synthesis.[6] In order to remove our apprehension, efficient generation of the cyclic imine **5** followed by spontaneous reduction under very mild condition would be key to the success. We envisioned that hydrogenation of azide **7** affords the desired pyrrolidine **4** via the reductive cyclization of the resulting aminoketone **6** in one operation.[7] This approach can provide a domino reaction to obviate the isolation of **5**. Azide **7** would be readily prepared from inexpensive (*R*)-(+)-ethyl-4-chloro-3-hydroxybutanoate (**8**).

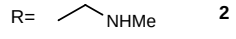
Azide **7** was prepared as shown in Scheme 2. The hydroxy group of **8** was protected as TBS ether. Conversion of ester **9** to Weinreb's amide **10** utilizing William's procedure,[8] followed by addition of phenyl Grignard reagent gave ketone **11** in good overall yield. Direct displacement of **11** with various metal azides was very sluggish even under forcing conditions and when bromo or iodo derivatives were used. These observations were probably due to the huge steric hindrance at the reactive site. In fact, azide group was introduced smoothly under the same conditions after removal of the TBS group. Finally, re-protecton of



Meropenem







Figure

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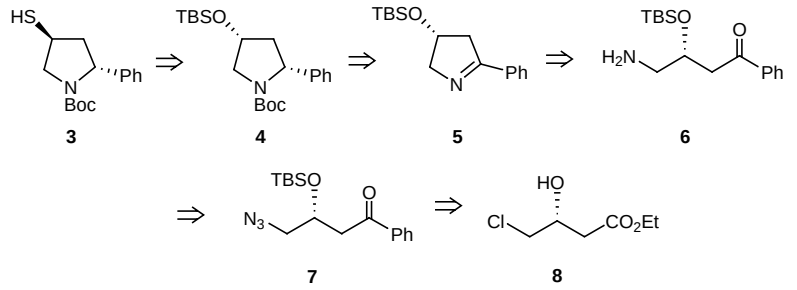
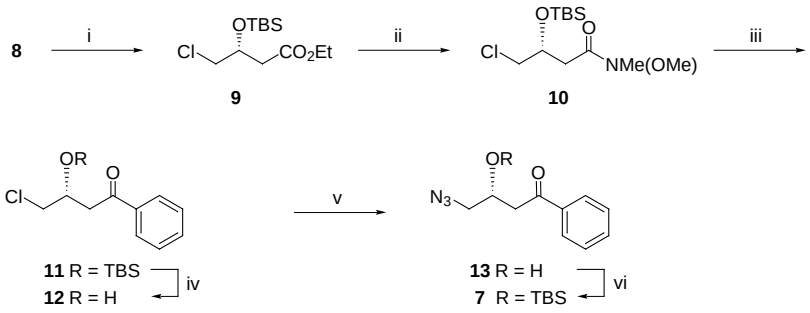


Scheme 1

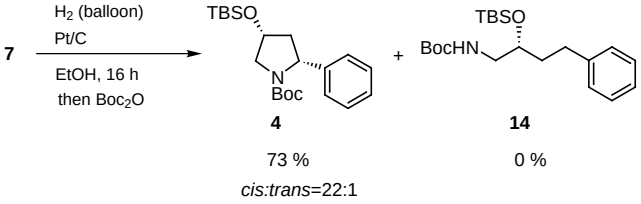


Scheme 2 Reagents and conditions: (i) TBSCl, Im, DMF, 89%; (ii) Me(MeO)NH·HCl, i-PrMgBr, THF, –20 °C, 98%; (iii) PhMgCl, THF, –20 °C to 0 °C, 99%; (iv) CSA, MeOH, 98%; (v) NaN_3, DMF, 80 °C, 74%; (vi) TBSCl, Im, DMF, 90%.

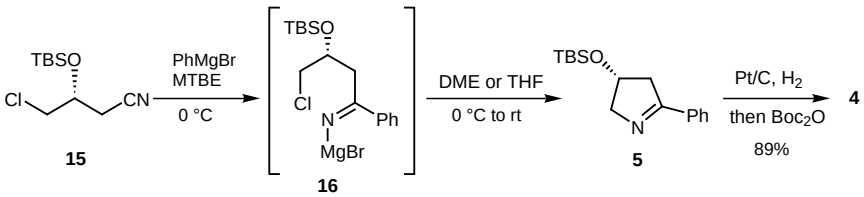
the hydroxyl group as TBS ether afforded the desired azide **7**.

With the desired azide in hand, we then tried the reductive domino cyclization of **7** under usual hydrogenation conditions. Hydrogenation of **7** using Pd/C at atmospheric pressure for 6 hours followed by direct addition of Boc_2O resulted in only the formation of the undesired open-chain product **14** in 85% overall yield. **14** would be probably formed via hydrogenolysis of the resulted pyrrolidine ring at the benzylic position before Boc protection. In contrast, platinum catalysts completely suppressed formation of the over-reduction product **14**. When Pt/C was used as a catalyst, the desired *cis*-pyrrolidine **4** could be stereoselectively produced in 73%[9] yield in ratio of 22:1 (*cis*:*trans*)[10] (Scheme 3). The steric bulkiness of the TBS ether would contribute to the stereoselectivity.[11]

Domino-cyclization of the azide **7** under the hydrogenation condition led to much success on diastereoselective construction of the desired pyrrolidine ring. However, transformation to **7** was tedious because it includes the deprotection/protection sequence for introduction of the azide function. Therefore, we re-investigated an alternative method to generate the cyclic imine. After several attempts,[12] finally we found that the desired cyclic imine **5** was smoothly generated from chloronitrile **15**, readily obtainable from TBS-protection of inexpensive (*R*)-(+)-4-chloro-3-hydroxybutyronitrile.[13] In this reaction, solvent effect was critical for controlling both of the Grignard addition and the cyclization. Non-polar solvent such as MTBE (metyl *t*-butyl ether)[14] was necessary for the addition reaction while neither THF nor DME was successful. Instead, either DME or THF was essential for the completion of the cyclization. Subsequent hydrogenation under the above conditions followed by Boc protection in one flask afforded the desired pyrrolidine **4** in 89% yield[15] (Scheme 4).[16]



Scheme 3



Scheme 4

In this way, we succeeded in the stereoselective synthesis of (3*R*,5*R*)-cis-3-hydroxy-5-phenyl pyrrolidine by highly selective reduction of the cyclic imine. These methods enable us to provide not only practical and large scale synthesis of new carbapenems, **1** and **2** but also a general method for construction of the *cis*-2,4-disubstituted pyrrolidine skeleton. The whole synthetic work will be described elsewhere as a full article.

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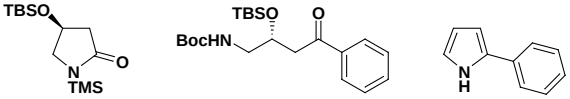
(9) 13% and 29% yield of the desired product(**4**)were obtained with PtO_2 and with Pt/Al_2O_3, respectively.
(10) The ratio was determined by HPLC analysis.
(11) Hydrogenation of **13** under the same conditions resulted in poor selectivity (*cis*:*trans* = 3.3:1, 70% yield).
(12) Aza-Wittig reaction of **4**, aza-Peterson reaction of **17** and acid promoted cyclic imination of *N*-Boc-amino ketone **18** were not successful. In most cases, the corresponding pyrrole **19** caused from elimination of the siloxy group was produced.



17 **18** **19**

(13) This approach using bromonitrile has been reported by Fry et al. See ref. 6.
(14) MTBE is the best solvent of toluene, benzene, hexane and MTBE.
(15) The *trans*-isomer was not seen in ^1H NMR analysis.
(16) Typical experimental procedure: To a solution of the chloronitrile **15** (1.80 g, 7.69 mmol) in MTBE (55 mL) at 0 °C was added drop wise phenyl MgBr (3.85 mL of 3.0 M solution in Et_2O, 11.54 mmol) and the mixture was allowed to reach room temperature. After 15 min, DME (10 mL) was added drop wise over 5 min followed by addition of EtOH (6.5 mL). To this reaction mixture was added 3.0 g of 5% Pt/C in one portion and stirred under H_2 atmosphere at room temperature for 18 h and then Boc_2O (3.58 mL, 15.6 mmol) was added. After 5 h, filtration followed by SiO_2 flash chromatography afforded the desired pyrrolidine **4** (2.58 g, 6.83 mmol) in 89% yield.