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Stereoselective synthesis of 4-hydroxy-2-phenylproline framework

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Abstract—Highly diastereoselective (>20:1) bromo-lactonization of *N*-sulfonyl-2-allyl-2-phenylglycine methyl ester (**11**) was observed. Successive treatment of the chiral lactone with MeONa gave the desired (*2S,4R*)-4-hydroxy-2-phenylproline derivative in high yield without erosion of the diastereoselectivity. The starting chiral non-racemic compound (**5**) was prepared from the racemic 2-phenylglycine using a classical kinetic resolution (crystallization), an asymmetric phase transfer alkylation, and an enzyme-catalyzed kinetic resolution.

Proline is an important component of many bioactive natural compounds.[1] For the past few decades, highly functionalized proline derivatives have been used as chiral synthons for the development of pharmaceuticals.[2] In this regard, chiral 2-substituted prolines have not only been useful in the synthesis of new compounds with novel structures, but they have also been extensively used as ligands in synthetic organic chemistry.[3] Despite the well-developed stereoselective synthetic methods for the preparation of chiral proline derivatives,[4] the preparation of chiral 2-arylprolines has been limited, mainly due to the difficulty of simple S_N2 type substitution.[5]

During the course of our efforts toward the development of our drug candidate, a stereoselective synthesis of (*2S,4R*)-4-hydroxy-2-phenylproline framework (Fig. 1) was required as a core structure. Herein an efficient synthetic method for the preparation of this compound is described.

More than a decade ago, Ogasawara and co-workers reported a single-step synthesis of (*2S,4R*)-4-hydroxyproline from N-homoallylamide by an iodine-mediated consecutive cyclization.[6] Based on the reported methodology, a retrosynthetic approach, as outlined in Scheme 1, was envisioned. The extension of their chemistry to the quarternary amino acid derivative **2** was expected to maintain the chiral center and form compound **1**. Chiral compound **2** would be synthesized from racemic 2-phenylglycine methyl ester hydrochloride (**3**).

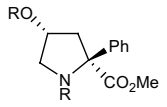

Figure 1.

For the preparation of (*S*)-2-allyl-2-phenylglycine ester (**5**, **8**), three different synthetic approaches, as outlined in Scheme 2, were initially explored. The racemic compound (**4**) was prepared by the published procedures[5b] and the screening of chiral resolution using a library of chiral acids was carried out. D-Tartaric acid was identified to obtain the diastereomeric salt with the desired (*S*)-isomer (**5**). Under the optimal conditions, D-tartaric acid salt of **5** could be obtained in over 95% ee and 33% isolated yield after a single crystallization.[7] Next, the enzyme-catalyzed hydrolysis of **4** was investigated. A library of hydrolytic enzymes were screened and several enzymes, including reported pig liver esterase (PLE), were identified as candidates.[5b] Among the identified enzyme catalysts, a microbial esterase from *Bacillus stearomorphilus* (BS3)[8] was discovered that hydrolyzed the ester to the desired acid enantiomer, and left behind the undesired ester enantiomer (97% ee with 49% yield).

Keywords: 4-Hydroxyproline; Optical resolution; Phase transfer reaction; Iodo cyclization; Halo lactonization.
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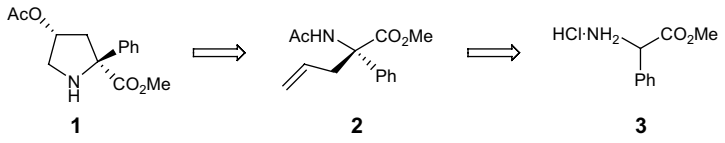
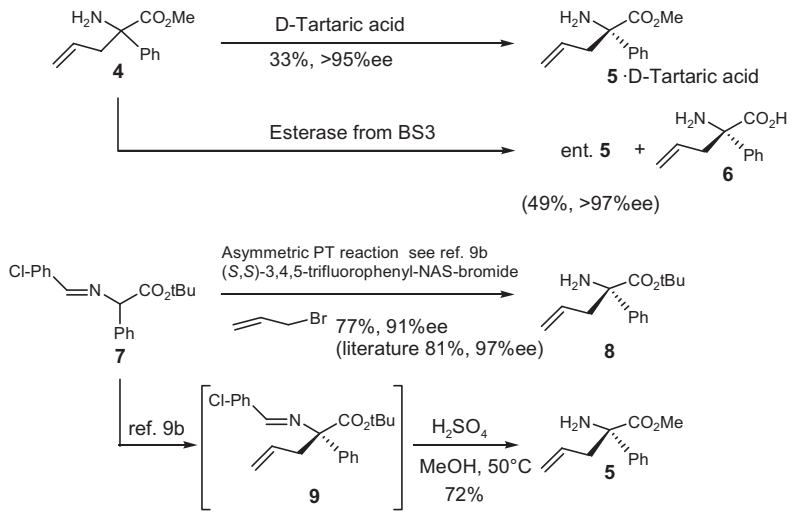
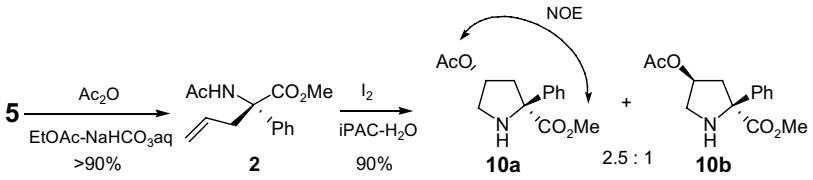


Scheme 1.



Scheme 2.



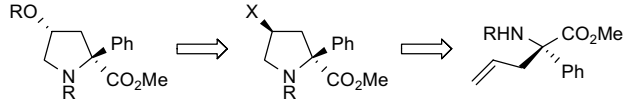
Scheme 3.

The third approach took advantage of the previously reported studies by Maruoka and co-workers.[9b,10] *tert*-Butyl ester derivative (**8**) was synthesized by the asymmetric phase transfer alkylation[9a] with their catalyst in high ee and yield. In the work-up sequence, both the hydrolysis and *trans*-esterification of benzylimine intermediate (**9**) occurred in one pot by the addition of H_2SO_4 in MeOH at 50 °C to afford the methyl ester (**5**).

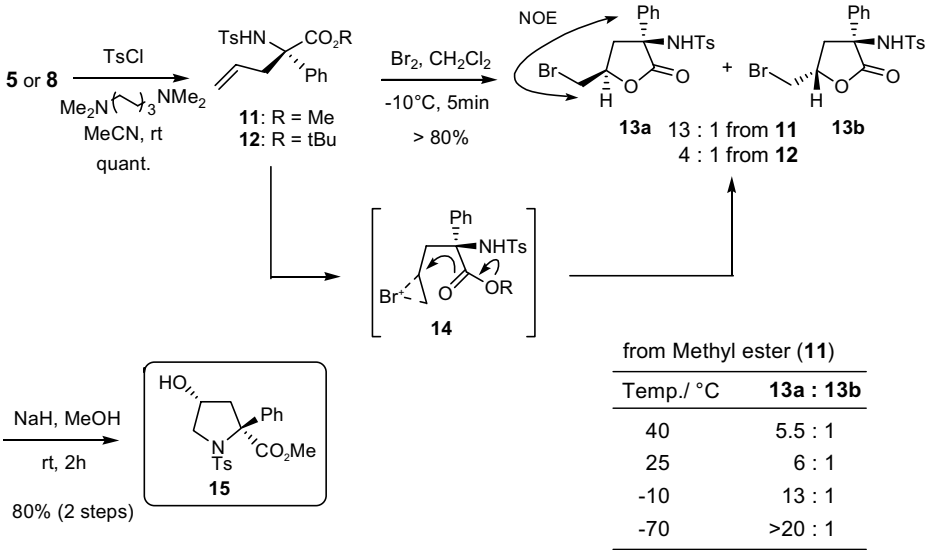
After acetylation of the resulting amine (**5**) with acetic anhydride, **2** was subjected to the iodine cyclization conditions (Scheme 3). The reaction was first attempted using in THF–H_2O as reported in the literature.[6a] While the reaction proceeded as expected, a number of impurities and intermediates were observed. A variety of conditions were then screened and the two phase reaction conditions (isopropyl acetate–H_2O) were observed to be the cleanest. The product was obtained as a diastereomeric mixture at the 4 position in a 2.5:1 ratio. The observed selectivity was not sufficient for the further manipulations. The stereochemistry and the ratio were determined by NOE experiment and HPLC, respectively.

Due to the above results, an alternative synthetic route was formulated. To date, electrophile, such as halogen and selenium, mediated 5-*endo* cyclization of the *C*-allylic secondary amine or amide has become a general tool to construct pyrrolidine skeleton.[11] Thus, this approach was adopted to construct the 4-halo-pyrrolidine framework (Scheme 4).

After making a sulfonamide from **5**,[12] the 5-*endo*-halocyclization was attempted. No reaction was observed by the treatment with either NIS or NBS. After several conditions and reagents were tried, we found that the reaction proceeded rapidly by the addition of Br_2 in CH_2Cl_2 at −10 °C. Unexpectedly, the resultant products appeared to be γ-lactones **13a** and **13b**, formed in high stereoselectivity instead of the predicted pyrrolidine (Scheme 5). The major isomer of the lactones possessed the desired stereochemistry. The stereochemistry and ratio were determined by NOE and ^1H NMR analysis.



Scheme 4.



from Methyl ester (**11**)

Temp./ °C	**13a : 13b**
40	5.5 : 1
25	6 : 1
-10	13 : 1
-70	>20 : 1

Scheme 5.

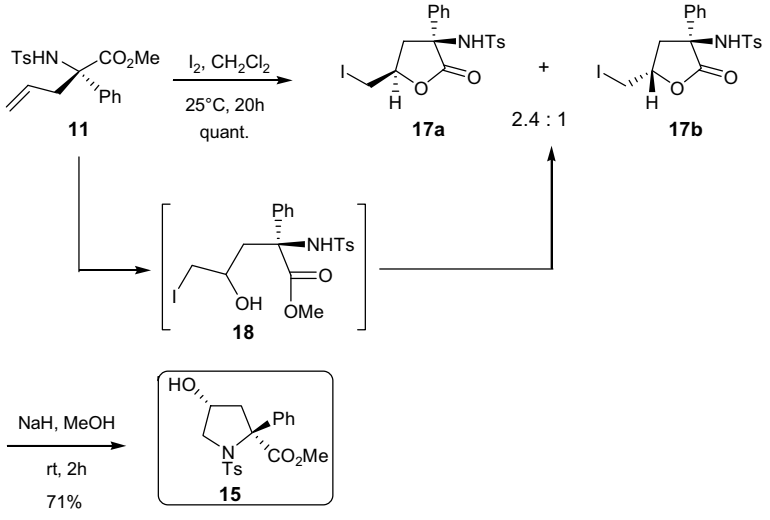
Although a halo-lactonization with carboxylic acid or amide in the presence of its secondary amide or carbamate has been well established,[13] there are few examples that the ester reacts with allyl cation rather than the secondary amide. The present unexpected results seem to come from the rigid and stabilized transition state caused by the tosyl amide and phenyl group, which would create a suitable conformation for the ester attack.[13b,14]

The obtained γ-lactones were readily transformed into the desired 4-hydroxyproline methyl ester by treatment with NaH in MeOH at room temperature without any by-products. During the reaction, no intermediates were detected in HPLC and TLC. We speculated that once the lactone was opened by methoxide, a successive ring-closure reaction would occur immediately. After silica gel purification, (*2S*,*4R*)-4-hydroly-2-phenylproline derivative (**15**) was isolated in 80% from **11**.

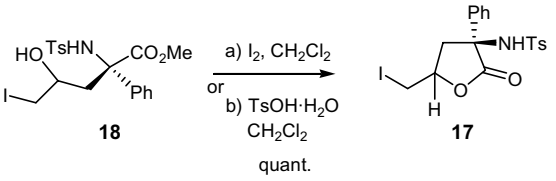
Next, the temperature effect of the bromo-cyclization was investigated. Under reflux conditions (40 °C) and 25 °C, the resultant lactone showed 5.5:1 and 6:1 selectivity, respectively, at γ-position, compared to 13:1 at −10 °C. At −70 °C, we observed selectivity of 20:1.[15]

The Br_2 cyclization was applied to *tert*-butyl ester derivative (**12**) under the exact same conditions. However, the ratio dropped to 4:1 as compared to 13:1 for the methyl ester (Scheme 5). The steric repulsion of the phenyl and *tert*-butyl groups apparently affected the transition state of the cyclization.[14]

The above lactonization was similarly carried out with iodine by aging for 20 h at room temperature (25 °C) and the resultant iodo-lactone was transformed to the desired hydroxy proline in the same manner as the bromo-lactone (Scheme 6). However, the observed selectivity was only 2.4:1, lower than that of



Scheme 6.



Scheme 7.

bromo-lactonization under the same conditions. Based on analysis of the reaction mixture by LC-MS, we observed a different intermediate than what had been predicted in the case of bromine. In this case, the reaction went through the iodohydrin intermediate (**18**). A trace amount of water in the solvent accelerated the reaction.[16] In order to provide more evidence for this mechanism, the iodohydrin (**18**) was isolated by a silica gel column chromatography and transformed to the iodo-lactones (**17**) under the original reaction conditions (Scheme 7). In addition, the isomer ratio of the iodohydrin was 2.4:1, identical to the ratio observed in the iodo-lactones (**17**). The lactonization was promoted by the treatment of $TsOH{\cdot}H_2O$ as well.

In conclusion, we report the highly stereoselective synthesis of (*2S*,*4R*)-4-hydroxy-2-phenylproline derivative achieved by developing chiral syntheses of 2-allyl-2-phenylglycine derivatives followed by stereoselective bromine-mediated cyclization. During the investigation, we revealed that the halo-lactonization of compound (**5**) proceeded via the different pathway depending on the halogen (Br_2 or I_2). A key finding of our studies was that the ester could react with an epi-bromonium cation much faster than the NH-Ts group under these particular conditions. Additionally, we observed a strong dependence of stereoselectivity with temperature, with >20:1 selectivity at −70 °C.

Acknowledgements

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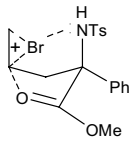
References and notes

1. (a) Cody, W. L.; Wilkes, B. C.; Muska, B. J.; Hruby, V. J.; Castrucci, A. M. D.; Hadley, M. E. *J. Med. Chem.* **1984**, *27*, 1186; (b) Prenner, E. J.; Lewis, R.; McElhaney, R. N. *Biochim. Biophys. Acta—Biomembr.* **1999**, *1462*, 201.
2. (a) Ondetti, M. A.; Cushman, D. W. *Science* **1977**, *196*, 441; (b) Shibata, T.; Iino, K.; Sugimura, Y. *Heterocycles* **1986**, *24*, 1331; (c) Renand, P.; Seebach, D. *Synthesis* **1986**, 424; (d) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; Deforrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, R.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W. *J. Med. Chem.* **1988**, *31*, 1148; (e) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *43*, 519–532; (f) Iso, Y.; Irie, T.; Nishino, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiotics* **1996**, *49*, 199–209; (g) Ohtake, N.; Okamoto, O.; Mitomo, R.; Kato, Y.; Yamamoto, K.; Haga, Y.; Fukatsu, H.; Nakagawa, S. *J. Antibiotics* **1997**, *50*, 598–613; (h) Kress, M. H.; Yang, C.; Yasuda, N.; Grabowski, E. J. J. *Tetrahedron Lett.* **1997**, *38*, 2633.
3. (a) Harrison, T.; Williams, B. J.; Swain, C. J. *BioMed. Chem. Lett.* **1994**, *4*, 2733; (b) Chatani, H.; Nakajima, H.; Kawasaki, H.; Koga, K. *Heterocycles* **1997**, *46*, 53.
4. (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390; (b) Seebach, D.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 155; (c) Noe, C. R.; Knollmuller, M.; Vollenkle, H.; Noe-letschnig, M.; Weigand, A.; Muhl, J. *Pharmazie* **1996**, *51*, 800; (d) Nagano, S.; Mizukami, M.; Akutsu, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209; (e) Sato, T.; Kawasaki, S.; Oda, N.; Yagi, S.; El Bialy, S. A. A.; Uenishi, J.; Yamauchi, M.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2623; (f) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001**, *3*, 2427.
5. (a) Semmelhack, M. F.; Hall, H. T.; Yoshifuji, M.; Clarck, G. *J. Am. Chem. Soc.* **1975**, *97*, 1247; (b) Betsbrugge, J. V.; Tourwe, D.; Kaptein, B.; Kierkels, H.; Broxterman, R. *Tetrahedron* **1997**, *53*, 9233.
6. (a) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1527; (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1861.
7. Enantiopurity was determined by chiral SFC analysis using Chiralpak OJ with MeOH–CO_2 as an eluent after acetylation of **5**. Its absolute configuration was determined by conversion of known *tert*-butyl ester (**7**) into its methyl ester as mentioned in Scheme 2 followed by comparison of the retention time of Chiral SFC analysis after acetylation.
8. The enzyme BS3 was obtained from Julich Fine Chemical, Julich, Germany.
9. (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446; (b) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, 1185.
10. Enantiopurity was determined by chiral SFC analysis using Chiralpak AS-H with MeOH–CO_2 as an eluent after tosylation of **7**, as mentioned in Scheme 3.
11. (a) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063; (b) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491; (c) Smaele, D. D.; Kimpe, N. D. *J. Chem. Soc., Chem. Commun.* **1995**, 2029; (d) Lee, W. S.; Jang, K. C.; Kim, J. H.; Park, K. H. *Chem. Commun.* **1999**, 251; (e) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874; (f) Outurquin, F.; Pannecoucke, X.; Berthe, B.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 1007; (g) McCormick, J. L.; Osterman, R.; Chan, T.; Das, P. R.; Pramanik, B. N.; Ganguly, A. K.; Girijavallabhan, V. M.; McPhail, A. T.; Saksena, A. K. *Tetrahedron Lett.* **2003**, *44*, 7997; (h) Kim, J. H.; Long, M. J. C.; Kim, J. Y.; Park, K. H. *Org. Lett.* **2004**, *6*, 2273.
12. Yoshida, Y.; Shimonishi, K.; Sakakura, Y.; Okada, S.; Aso, N.; Tanabe, Y. *Synthesis* **1999**, 1633.
13. (a) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307; (b) Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079; (c) Kitagawa, O.; Sato, T.; Taguchi, T. *Chem. Lett.* **1991**, 177; (d) Guillerm, D.; Guillerm, G. *Tetrahedron Lett.* **1992**, *33*, 5047; (e) Kitagawa, O.; Hanano, T.; Kikuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1993**, *34*, 2165; (f) Rousseau, G.; Robin, S. *Tetrahedron* **1998**, *54*, 13681; (g) Burger, K.; Mutze, K.; Osipov, S. N.; Tsouker, P.; Schier, A. *Monatshefte fur Chemie* **2003**, *134*, 69.

14. A plausible transition state. See Ref. 13b.



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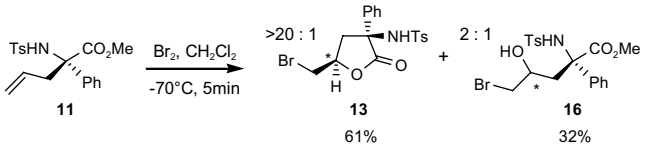
15. In this case, the bromohydrin (**16**) formed in 32% yield at the same time. Probably, the bromo-lactonization step might be competing with the attack of trace amount of water in the solvent to the bromonium cation intermediate (**14**) due to the relatively low reactivity of the ester at that temperature.



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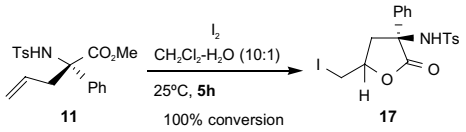
16. The iodo-lactonization completed more quickly in the presence of water.



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