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# Proline-Catalyzed, Asymmetric Mannich Reactions in the Synthesis of a DPP-IV Inhibitor

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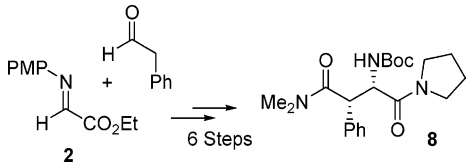
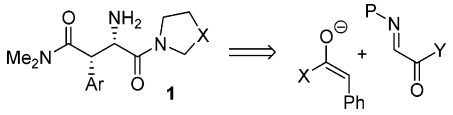



A highly stereoselective L-proline-catalyzed, asymmetric direct Mannich reaction between a glyoxalate-derived imine and phenyl acetaldehyde was employed for the formation of a syn substituted $\beta$-phenyl homoserine. This Mannich adduct was then readily elaborated to a functionalized $\beta$-phenyl aspartic acid derivative through a series of mild and efficient transformations.

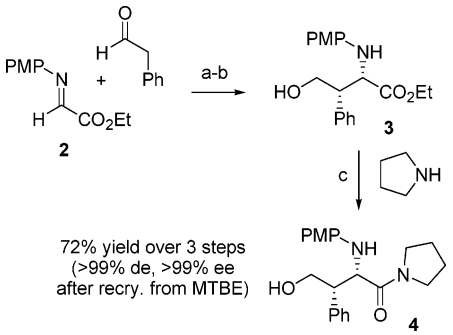
There has been intense research focused upon glucagon-like peptide 1 (GLP-1) and its potential for treating type 2 diabetes.[1] This hormone, released in the gut in response to food, stimulates insulin biosynthesis, while inhibiting the release of glucagon. In addition, GLP-1 regulates insulin in a glucose-dependent manner, thus reducing the risk of hypoglycemia. GLP-1 is readily degraded in vivo by dipeptidyl peptidase IV (DPP-IV), a serine protease. Identification of an orally available small molecule capable of inhibiting the DPP-IV enzyme and thereby increasing the amount of GLP-1 could yield a new and useful therapy for type 2 diabetes.[2] In that context, efforts by Merck medicinal chemists led to the identification of molecules with the general structure of **1** as novel inhibitors of DPP-IV.[3]

A retrosynthetic analysis of this challenging molecule revealed a possible Mannich reaction as a useful bond-forming reaction to set both stereocenters (Scheme 1). In particular, we were drawn to the proline-catalyzed direct Mannich reaction reported by List, Barbas, and co-workers as a potential way to address the stereochemistry and functionality of this molecule.[4,5] We report herein an efficient synthesis of a $\beta$-phenyl aspartic acid derivative **1**, which features a proline-catalyzed Mannich reaction.

**SCHEME 1. Key Mannich Disconnection**




**SCHEME 2. l-Proline-Catalyzed Mannich[a]**




[a] (a) 17 mol % L-Pro, THF, −5 °C, 20 h; (b) added 3 equiv of AcOH and then 1 equiv of $NaBH_4$; (c) 20 mol % $K_2CO_3$, THF 50 °C, 2 h.

To date, there are limited examples of the proline-catalyzed Mannich reaction as applied to aryl acetaldehydes.[5] This may be, in part, due to the difficulty in their synthesis and their inherent instability as they are quite prone to oxidation and polymerization to poly(styreneoxide). The reaction between a *p*-methoxyphenyl (PMP) protected imine derived from ethyl glyoxalate (**2**)[6] and phenylacetaldehyde catalyzed by 17 mol % L-proline provides the desired *syn*-$\beta$-phenyl-substituted homoserine with excellent levels of stereoselection (typically 92:8 syn/anti and >90% ee) after reduction of the crude aldehyde to the amino alcohol **3** (Scheme 2). Immediate reduction is necessary as the crude product aldehyde **5** is an unstable intermediate that slowly undergoes epimerization and/or polymerization upon standing at room temperature, thus necessitating reaction temperatures of −5 °C (Scheme 3). Reduction with $NaBH_4$ alone gave slow epimerization of alcohol **3** (~80:20 syn/anti) along with some lactonization (**6**). Upon workup with saturated aqueous $NaHCO_3$, lactone **6** could be obtained as the major product along with enhanced diastereomeric purity

(1) For a review of GLP-1, see: Knudsen, L. B. *J. Med. Chem.* **2004**, *47*, 4128−4134.

(2) For a review of DPP-IV mode of action and inhibitors, see: Weber, A. E. *J. Med. Chem.* **2004**, *47*, 4135−4141.

(3) Edmondson, S. D.; Mastracchio, A.; Duffy, J. L.; Eiermann, G. J.; He, H.; Ita, I.; Leiting, B.; Leone, J. F.; Lyons, K. A.; Makarewicz, A. M.; Patel, R. A.; Petrov, A.; Wu, J. K.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3048−3052.

(4) For proline cat. Mannich of *N*-PMP glyoxylate imines, see: (a) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507−2510. (b) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Synlett* **2003**, 1906−1909. (c) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624−9634. (d) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867. (e) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2003**, *44*, 1923−1926. (f) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843.

(5) For other proline cat. Mannich and aldol reactions, see: (a) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541−3544. (b) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208−11209. (c) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (d) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199−201. (e) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337.

(6) *N*-PMP imine **2** formed by slow addition of 1 equiv of ethyl glyoxylate to a stirring solution of 1 equiv of *p*-anisidine and 3 Å MS in toluene. The solution was stirred 1 day at room temperature (rt), with additional ethyl glyoxylate added as needed to consume *p*-anisidine. Treatment with $Na_2SO_4$ (s) followed by filtration gave >95% pure **2** in 89% yield.

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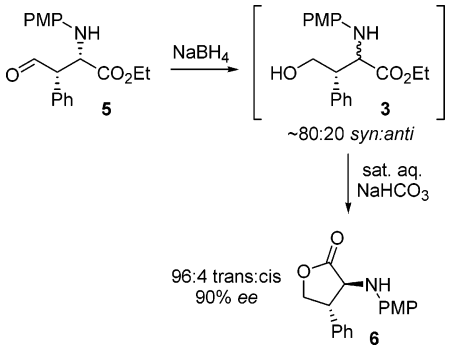
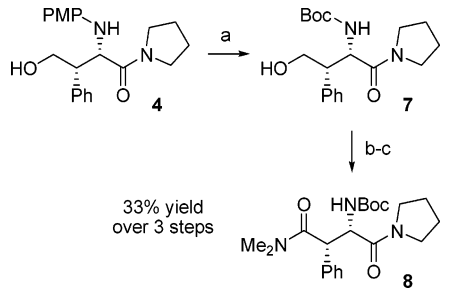
**SCHEME 3. Aldehyde Reduction and Lactonization**




**SCHEME 4. Amino Alcohol 4 Elaboration**[a]




[a] (a) 2 equiv of $PhI(OAc)_2$, *i*-PrOAc/pH 5.9 aqueous buffer workup with 2 equiv of $Boc_2O$, aqueous $Na_2CO_3$/THF; (b) 7 mol % TEMPO, 2 mol % NaOCl, 2 equiv of $NaClO_2$, $CH_3CN$/pH 6.7 aqueous buffer, 35 °C, 20 h; (c) 1.1 equiv of carbonyldiimidazole, 4 equiv of $Me_2NH$, THF, rt, 20 h.

due to epimerization to the more stable *trans*-lactone **6** (96:4 syn/anti). The optimal reductive workup conditions involved first treating the crude mixture with 3 equiv of AcOH followed by addition of 1 equiv of $NaBH_4$ (thereby generating $NaBH(OAc)_3$ in situ). This protocol provided consistent purity of amino alcohol **3** as the only product, with no lactone **6**. Without further purification, amino alcohol **3** was dissolved in THF and heated with pyrrolidine and catalytic $K_2CO_3$ to efficiently provide amide **4** in 72% yield over three steps from imine **2**. This material's optical purity was upgraded to >99% de and >99% ee by crystallization from MTBE. Presumably, this facile amidation of **3** proceeds through lactone **6** as samples of **3** with lower diastereomeric purity consistently provided amide **4** with high diastereomeric purity.

One potential drawback to this methodology is the use of PMP as a protecting group for the imine reaction partner. Typically, harsh oxidation conditions involving highly toxic reagents such as ceric ammonium nitrate are required to remove PMP from nitrogen. A recent alternative reported by Hoveyda and Snapper employs readily available $PhI(OAc)_2$ as the stoichiometric oxidant.[7] Thus, treatment of *N*-PMP amino alcohol **4** with $PhI(OAc)_2$ under buffered biphasic conditions followed by treatment with $Boc_2O$ gave *N*-Boc amino alcohol **7** in 51% yield (Scheme 4). Oxidation of alcohol **7** with catalytic TEMPO and bleach along with 2 equiv of $NaClO_2$ gave the crude acid.[8] This acid was then treated with carbonyldiimidazole followed by dimethylamine to give the desired diamide aspartic acid derivative **8** in 33% yield over three steps starting from amino alcohol **4**. The final coupling reaction with dimethylamine was >90% complete after 1 h, but allowing the reaction to run overnight gave some epimerization (83:17 syn/anti). A final recrystallization from MTBE gave material with >99% optical purity.

A concise, stereoselective synthesis of a diamide-functionalized $\beta$-phenyl aspartic acid derivative has been accomplished, highlighted by the use of a proline-catalyzed direct Mannich reaction. Also examined was the mild, selective removal of a PMP nitrogen-protecting group using $PhI(OAc)_2$. Despite limitations imposed by the nitrogen-protecting group and inherent instability of the aryl acetaldehyde starting materials and crude aldehyde products, this proline-catalyzed Mannich reaction represents a rapid and highly stereoselective method for the preparation of syn $\beta$-substituted α-amino acid derivatives.

## Experimental Section

**(2*S*,3*S*)-4-Hydroxy-2-(4-methoxyphenylamino)-3-phenyl-1-pyrrolidin-1-yl-butan-1-one (4).** To a stirring solution of imine **2** (7.11 g, 34.3 mmol, 1 equiv) in 100 mL of THF at −5 °C was added freshly distilled phenylacetaldehyde (3.99 mL, 35.7 mmol, 1.04 equiv) followed by l-proline (684 mg, 5.94 mmol, 0.17 equiv). The reaction was held at −5 °C for 24 h, then acetic acid was added (6.70 mL, 116 mmol, 3.4 equiv) followed by a portionwise addition of $NaBH_4$ (1.46 g, 38.6 mmol, 1.13 equiv). The reaction was allowed to slowly warm to room temperature over 3 h, after which time 50 mL of EtOAc was added along with 150 mL of saturated aqueous $NaHCO_3$. This biphasic mixture was stirred for 1 h at room temperature. The organic layer was then separated, washed with brine (~150 mL), dried with $Na_2SO_4$, filtered, and concentrated in vacuo giving crude alcohol **3**. To this crude material (**3**) dissolved in 60 mL of THF was added pyrrolidine (2.98 mL, 35.7 mmol, 1.04 equiv) and $Na_2CO_3$ (630 mg, 5.94 mmol, 0.17 equiv). This mixture was heated to 50 °C for 2 h. After cooling to room temperature, 50 mL of EtOAc was added. The organics were then washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine, dried with $Na_2SO_4$, filtered, and concentrated in vacuo giving 12.45 g of 70.6 wt % **4** (8.78 g of **4**, 72% yield from **1**, 96:4 syn/anti by HPLC). This material was upgraded to >99% optical purity after recrystallization from MTBE (6.93 g, 57% yield from **2**). mp 104.3−106.1 °C (MTBE); $[\alpha]^{25}_D$ +0.3 (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.35−7.25 (m, 5H), 6.77 (d, $J$ = 8.8 Hz, 2H), 6.66 (d, $J$ = 6.9 Hz, 2H), 4.52 (d, $J$ = 5.5 Hz, 1H), 4.11−4.02 (m, 2H), 3.75 (s, 3H), 3.52−3.40 (m, 2H), 3.38−3.31 (bm, 2H), 3.03−2.95 (bm, 1H), 1.84−1.67 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.3, 153.0, 141.5, 139.0, 128.9, 128.8, 127.6, 116.1, 115.1, 63.4, 59.9, 55.9, 49.9, 46.7, 46.3, 26.2, 24.2; Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.96; H, 7.48; N, 7.71.

**[(1*S*,2*S*)-3-Hydroxy-2-phenyl-1-(pyrrolidine-1-carbonyl)-propyl]-carbamic Acid *tert*-Butyl Ester (7).** To a biphasic mixture of amino alcohol **4** (425 mg, 1.20 mmol, 1 equiv) in 7.5 mL of *i*-PrOAc and 7.5 mL of pH 5.9 (*c* 0.05 M) aqueous phosphate buffer was added $PhI(OAc)_2$ (1.55 g, 4.81 mmol, 4 equiv). After being stirred for 2 h (HPLC indicates no **4**), the reaction mixture was diluted with 1 N HCl until acidic (pH ≈ 3) and organics were separated and discarded. To the aqueous acidic layer was added $Na_2CO_3$ (s) until pH = 9−10 followed by 10 mL of THF. To this mixture was added $Boc_2O$ (525 mg, 2.40 mmol, 2 equiv), and the reaction was stirred overnight at room temperature. The mixture was then diluted with 10 mL of EtOAc, the aqueous was separated, and the remaining organic layer was washed successively with 20 mL of 1 N $NaHSO_4$, 20 mL of water, and 20 mL of brine. The organics were dried with $Na_2SO_4$, filtered, and concentrated in vacuo giving 214 mg (51% yield) of crude **7**. This material may be used as is or can be further purified by recrystallization from MTBE.

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(8) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.

mp 149.3−152.5 °C (MTBE); $[\alpha]^{25}_D$ +36.4 (*c* 0.72, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.31−7.23 (m, 3H), 7.08 (dd, $J$ = 7.8, 1.7 Hz, 2H), 5.71 (d, $J$ = 7.9 Hz, 1H), 4.93 (dd, $J$ = 8.0, 4.0 Hz, 1H), 3.94 (dd, $J$ = 11.9, 10.1 Hz, 1H), 3.74 (dd, $J$ = 11.9, 4.9 Hz, 1H), 3.67−3.61 (m, 1H), 3.55−3.46 (m, 2H), 3.31 (ddd, $J$ = 12.7, 6.6, 6.6 Hz, 1H), 3.23 (ddd, $J$ = 9.4, 4.5, 2.9 Hz, 1H), 2.02−1.92 (m, 2H), 1.91−1.82 (m, 2H), 1.46 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 169.1, 157.1, 137.2, 128.7, 128.6, 127.8, 80.5, 62.8, 53.1, 49.9, 46.9, 46.2, 28.5, 26.3, 24.3; Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 64.84; H, 8.11; N, 7.71.

**[(*S*)-1-((*S*)-Dimethylcarbamoylphenylmethyl)-2-oxo-2-pyrrolidin-1-ylethyl]carbamic Acid *tert*-Butyl Ester (8).** To a mixture of alcohol **7** (103 mg, 0.296 mmol, 1 equiv) in 1.5 mL of $CH_3CN$ and 1.1 mL of pH 6.7 aqueous phosphate buffer (*c* 0.67 M) was added TEMPO (3.3 mg, 0.021 mmol, 0.07 equiv), $NaClO_2$ (53.3 mg, 0.592 mmol, 2 equiv) dissolved in 300 $\mu$L of water, and dilute (0.04 M) NaClO (150 $\mu$L, 0.0059 mmol, 0.02 equiv). The mixture was heated to 35 °C and stirred for 1 day. After cooling to room temperature, 2 mL of water was added, and the pH was adjusted to 8 with 2 N aqueous NaOH (∼400 $\mu$L). Next, a solution of $Na_2SO_3$ (90 mg in 1.5 mL of water) was added, and the reaction was allowed to stir 30 min, after which time 1.5 mL of MTBE was added. The organic layer was separated and discarded. To the aqueous layer was added 3 mL of MTBE, and the pH was adjusted to ∼4 with 2 N HCl (∼600 $\mu$L). The organic layer was separated and washed with water and brine, dried with $Na_2SO_4$, filtered, and concentrated in vacuo giving 79 mg (74% yield) of the crude acid. To 75 mg of the crude acid (0.207 mmol, 1 equiv) in 1 mL of dry THF was added CDI (carbonyldiimidazole) (37 mg, 0.228 mmol, 1.1 equiv). After being stirred for ∼30 min, dimethylamine was added (207 $\mu$L, 0.414 mmol, 2 equiv). HPLC indicates that the reaction was ∼90% complete after 1 h, but stirring was continued overnight after which time 1 mL of EtOAc was added and the organics were washed with ∼2 mL of 1 M $NaHSO_4$, water, and brine, dried with $Na_2SO_4$, filtered, and concentrated in vacuo giving 71 mg (88% yield) of the title compound **8**. HPLC indicates some epimerization had occurred (83:17 syn/anti), but optically pure *syn*-**8** could be isolated after recrystallization from MTBE. mp 191.6−192.8 °C (MTBE); $[\alpha]^{25}_D$ −157.1 (*c* 0.84, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCL_3$, ∼3.4:1 rotamer ratio at 300 K in $CD_3CN$): $\delta$ 7.37−7.29 (m, 5H), 5.15 (t, $J$ = 10.6 Hz, 1H), 4.70 (d, $J$ = 10.9 Hz, 1H), 4.23 (d, $J$ = 10.3 Hz, 1H), 4.02−3.96 (m, 1H), 3.70−3.65 (m, 1H), 3.50−3.40 (m, 2H), 2.91 (s, 3H), 2.87 (s, 3H), 2.03−1.82 (m, 4H), 1.16 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 172.6, 170.6, 156.0, 137.4, 130.4, 129.4, 128.3, 79.6, 56.2, 51.7, 47.2, 46.7, 37.5, 35.7, 28.4, 26.7, 25.0; Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.76; H, 8.02; N, 10.79. Found: C, 64.50; H, 8.03; N, 10.50.

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