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Catalytic Asymmetric Synthesis of a Nitrogen Analogue of Dialkyl Tartrate by Direct Mannich Reaction under Phase-Transfer Conditions

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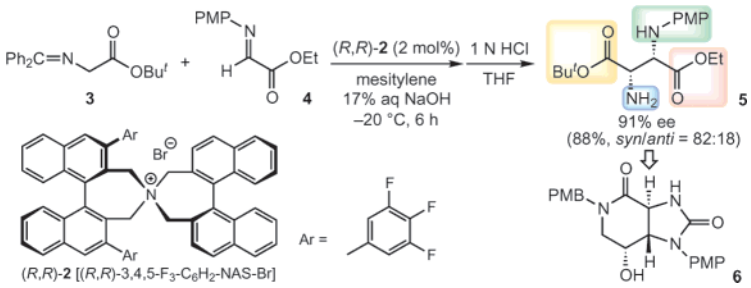
ABSTRACT



Phase-transfer-catalyzed direct Mannich reaction of glycinate Schiff base 3 with α-imino ester 4 has been accomplished with high enantioselectivity by the utilization of *N*-spiro C_2-symmetric chiral quaternary ammonium bromide 2 as a catalyst. This methodology enables the catalytic asymmetric synthesis of differentially protected 3-aminoaspartate, a nitrogen analogue of dialkyl tartrate. The product (*syn*-5) was converted into a precursor (6) of streptolidine lactam.

Natural and unnatural tartaric acids and their derivatives are undoubtedly one of the most familiar and readily available chiral molecular units, and during the past few decades, we have witnessed a dramatic increase in their fruitful applications, resulting in valuable contributions particularly in modern asymmetric synthesis.[1] Surprisingly, however, the corresponding nitrogen analogues **1**, 3-aminoaspartates, have received little attention despite their potential utility as C_2-symmetric chiral ligands for the design of new chemotherapeutic agents[2] as well as asymmetric catalysts.[3] Asymmetric syntheses of **1**, using stoichiometric amounts of chiral sources, have been reported.[4] The recently disclosed Mannich protocol using chiral Lewis acids from the Jørgensen group[5] and Yudin's stereoselective alkylation strategy with the $Pd(OAc)_2$/BINAP system[6] are the only examples of catalytic methods for the preparation of **1**. In this letter, we report catalytic asymmetric synthesis of nitrogen analogues of dialkyl tartrate by the highly enantioselective direct Mannich reaction of glycine derivative **3** with α-imino ester **4** under phase-transfer conditions (Scheme 1). The usefulness of this new method has been demonstrated in its application to the concise stereoselective construction of a precursor of Streptolidine lactam, taking full advantage of a differentially protected tartrate nitrogen analogue.

(1) For representative reviews, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley−VCH: New York, 2000; Chapter 6A, p 231. (b) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92.

(2) Reviews: (a) Sundquist, W. I.; Lippard, S. J. *Coord. Chem. Rev.* **1990**, *100*, 293. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2581. See also: (c) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barret, G. C., Ed.; Chapman and Hall: London, 1985; Chapter 4.

(3) Review: Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.

(4) (a) Fernández-Megía, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643. (b) Alvarez-Ibarra, C.; Csákÿ, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478.

(5) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583.

(6) Chen, Y.; Yudin, A. K. *Tetrahedron Lett.* **2003**, *44*, 4865.

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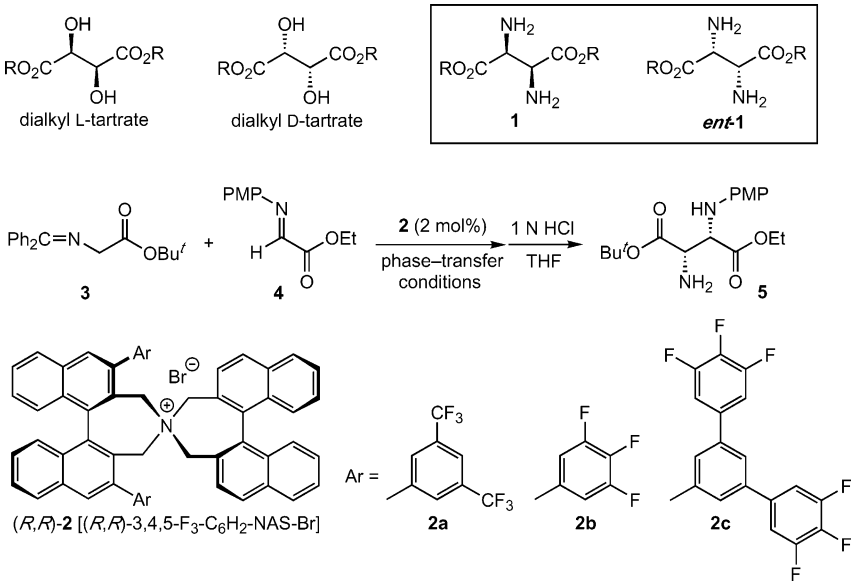
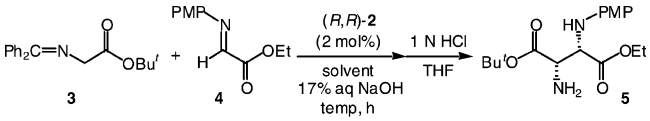
Scheme 1



Upon examining the direct Mannich reaction of the benzophenone Schiff base of *tert*-butyl glycinate **3** with α-imino ester **4** under phase-transfer conditions using chiral quaternary ammonium bromide of type **2** as a catalyst,[7] our initial concern was about the relative configuration of the Mannich adduct **5**, since only the syn isomer is optically active. Attempted reaction of **3** with **4** in the presence of **2a**[7c] (2 mol %) in toluene−1% aqueous NaOH at 0 °C showed almost no indication of product formation after stirring for 6 h (entry 1 in Table 1). Therefore, we screened various concentrations of aqueous NaOH and found that the use of 17% (5 N) aqueous NaOH under otherwise similar conditions resulted in the production of **5** in 41% yield.[8] Fortunately, preferential formation of the syn isomer (syn/anti = 74:26) was observed with 79% ee for product *syn*-**5** (entry 2). Here, we assumed that the low chemical yield was partly due to the instability of α-imino ester **4** under the reaction conditions. This was overcome by conducting the reaction at −20 °C to give Mannich adduct **5** in 73% yield (syn/anti = 79:21, 85% ee for *syn*-**5**) (entry 3). Switching to catalyst **2b**,[7d] which contains a 3,4,5-trifluorophenyl group, further enhanced the enantioselectivity, giving **5** in 79% yield (syn/anti = 76:24) with 87% ee (syn isomer) (entry 4). In contrast, catalyst **2c**, with radially extended 3,3′-aromatic substituents, significantly diminished both the chemical yield and the enantiomeric excess (entry 5). The use of mesitylene in place of toluene improved only the diastereoselectivity in the reaction with **2a** (entry 6). However, the solvent effect was found to be beneficial not only for the syn selectivity but also for the enantioselectivity under the influence of **2b**, leading to 91% ee of *syn*-**5** (88% yield, syn/anti = 82:18) (entry 7).

Table 1. Direct Catalytic Asymmetric Mannich Reaction of Glycine Derivative **3** with α-Imino Ester **4** under Phase-Transfer Conditions[a]



entry	catalyst	solvent	condition (°C, h)	% yield[b] (syn/anti)[c]	% ee[d] (configuration)[e]
1[f]	**2a**	toluene	0, 6	trace	
2	**2a**		0, 6	41 (74:26)	79
3	**2a**		−20, 6	73 (79:21)	85
4	**2b**		−20, 6	79 (76:24)	87
5	**2c**		−20, 6	49 (80:20)	50
6	**2a**	mesitylene	−20, 6	88 (82:18)	84
7	**2b**		−20, 6	88 (82:18)	91

[a] Unless otherwise specified, the reaction (0.2 mmol scale) was carried out with 2 equiv of **4** and 17% NaOH aqueous solution (0.6 mL) in the presence of 2 mol % of **2** under the given reaction conditions (2 mL of solvent). [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis. [d] Enantiopurity of *syn*-**5**, which was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane-2-propanol as a solvent. [e] For the assignment of the absolute configuration of the syn isomer, see Supporting Information. [f] Performed with 1% NaOH as an aqueous base.

The synthetic utility of the differentially protected tartaric acid nitrogen analogue, *syn*-**5**, was highlighted by its application to the facile asymmetric synthesis of an attractive precursor **6** of streptolidine lactam.[9] Streptolidine lactam constitutes the core structure of streptothricine antibiotics,[10] a family of potent antibiotics isolated from microbial sources.[11] As illustrated in Scheme 2, **5** (syn/anti mixture) was initially transformed to the cyclic urea **7** with triphos-

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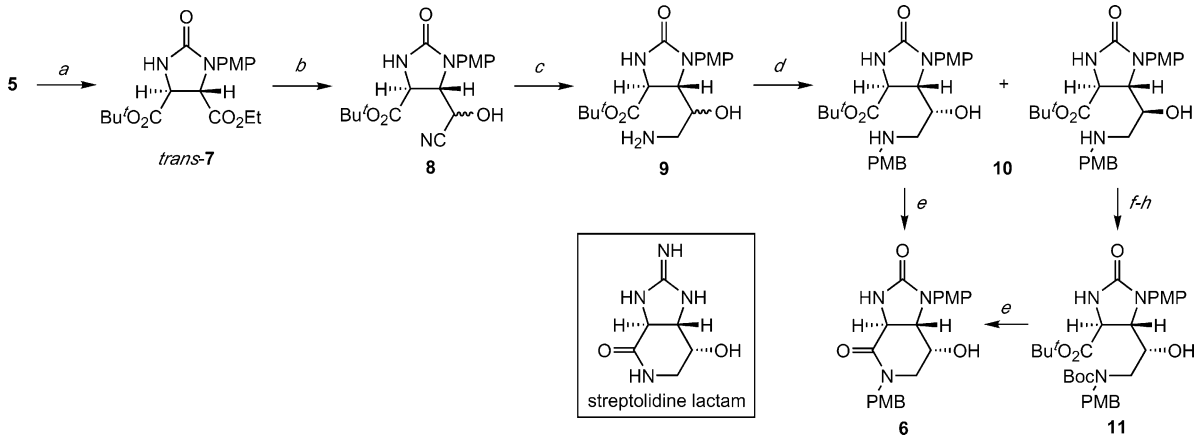
(8) Representative results of the Mannich reaction of **3** with NaOH aqueous solutions of different concentrations are as follows: 10% NaOH, 11% yield (syn/anti = 70:30), 77% ee (syn isomer); 25% NaOH, 43% yield (71:29), 78% ee; 50% NaOH, 81% yield (79:21), 6% ee.

Scheme 2 [a]



[a] Reaction conditions: (a) triphosgene, Et_3N, CH_2Cl_2, rt, 69%, 99% ee (*trans*-**7** after a single recrystallization); (b) DIBAH, ether−CH_2Cl_2, −78 °C, then Me_3SiCN, −78∼0 °C, 80% (dr = 1:1.5); (c) H_2, PtO_2, AcOH, rt, 90%; (d) anisaldehyde, Na_2SO_4, CH_2Cl_2, rt, then $NaBH_4$, EtOH, 0 °C, 71%; (e) HCO_2H, 60 °C, then DPPA, Et_3N, DMF, 65%; (f) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C∼rt, 98%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 97%; (h) $ZnBH_4$, ether, 0 °C, 53%.

gene, in which two diastereomers could be easily separated by simple chromatography and a single recrystallization provided essentially enantiopure *trans*-**7** in 69% yield (based on **5**). The subsequent selective reduction−cyanation of the ethyl ester moiety was achieved by the sequential treatment of *trans*-**7** with DIBAH and Me_3SiCN in ether−CH_2Cl_2, furnishing the desired cyanohydrin **8** in 80% yield as a mixture of two diastereomers. Hydrogenation of **8** gave the primary amine, which was protected with *p*-methoxybenzyl group by reductive amination. The requisite stereoisomer of the resulting amino alcohol **10** was then converted to **11** via acidic hydrolysis of the *tert*-butyl ester with formic acid and the consecutive intramolecular formation of amide linkage using diphenylphosphoryl azide (DPPA) in 65% yield. It is noted that the stereochemistry of the hydroxy-bearing carbon of the other isomer ***epi*-10** can be inverted, after the introduction of a *tert*-butoxycarbonyl group on the amino alcohol nitrogen, by Swern oxidation and reduction with $ZnBH_4$ to give **11**, an appropriate candidate for similar intramolecular condensation.

In summary, phase-transfer-catalyzed direct Mannich reaction of a glycine donor with α-imino ester has been accomplished with high enantioselectivity by the use of C_2-symmetric chiral quaternary ammonium bromide as a catalyst. This methodology enables the catalytic asymmetric synthesis of 3-aminoaspartate, a nitrogen analogue of dialkyl tartrate. Product **5**, with differentiated ester groups, was converted into **8**, a precursor of streptolidine lactam. The present finding should stimulate further research into utilization of this class of chiral compounds.

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Supporting Information Available: Detailed experimental procedure as well as spectroscopic characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For recent synthetic efforts using 3-aminoaspartate as a key intermediate, see: (a) Fernández-Megía, E.; Sardina, F. J. *Tetrahedron Lett.* **1997**, *38*, 673. (b) Fernández-Megía, E.; Iglesias-Pintos, J. M.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 4770. From carbohydrates: (c) Goto, T.; Ohgi, T. *Tetrahedron Lett.* **1974**, 1413. (d) Kusumoto, S.; Tsuji, S.; Shiba, T. *Tetrahedron Lett.* **1974**, 1417. (e) Kusumoto, S.; Tsuji, S.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2690. (f) Kusumoto, S.; Tsuji, S.; Shima, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3611.

(10) For the total synthesis of streptothricine, see: Kusumoto, S.; Imaoka, S.; Kambayashi, Y.; Shiba, T. *Tetrahedron Lett.* **1982**, *23*, 2961.

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