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A concise diastereoselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid

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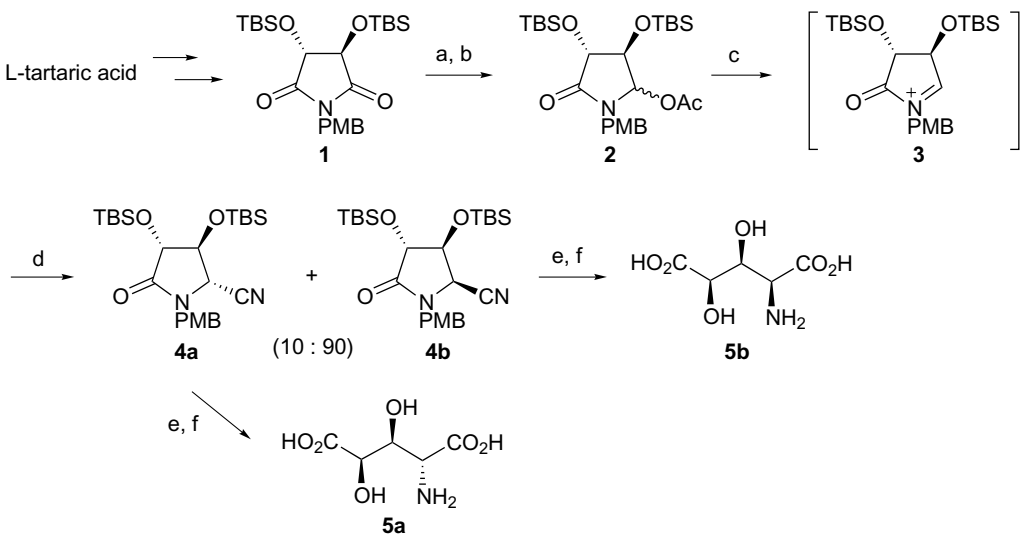
Abstract—A concise diastereoselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid, one of eight possible stereoisomers of 3,4-dihydroxyglutamic acids, is described. The key reaction in this synthesis is stereoselective cyanation of an optically active *N*-acyliminium intermediate derived from L-tartaric acid with tributyltin cyanide.

In the mammalian central nervous system, L-glutamic acid acts as an excitatory neurotransmitter through the ionotropic and metabotropic glutamate receptors. The glutamate receptors can be subdivided into three (NMDA, AMPA, and KA receptors) and eight subtypes (mGluR1–8), respectively. The development of subtype-specific agonists for glutamate receptors is indispensable for therapeutic purpose as well as investigating the physiological role of the receptors because of the implication of the receptors in brain ischemia, epilepsy and neurodegenerative syndromes such as Alzheimer's, Parkinson's and Huntington's diseases.[1] Hydroxylated glutamic acid derivatives are considered to be potent candidates for such subtype-selective ligands based on their additional ability of intra- and intermolecular hydrogen bonding. Although some methods for the preparation of 3- and 4-hydroxyglutamic acids have appeared in the literature,[2] the corresponding 3,4-dihydroxy derivatives have been less studied. Since the first isolation of the 3,4-dihydroxyglutamic acid from the seeds of *Lepidum sativum* and the leaves of *Rheum rhaponticum*,[3] this acidic amino acid was often found in several plants; however, the relative and absolute configurations of the three chiral centers



Scheme 1. (a) $NaBH_4$, 97%; (b) Ac_2O, pyridine, 85%; (c) BF_3–OEt_2; (d) Bu_3SnCN, 94%; (e) $Ce(NH_4)_2(NO_2)_6$; (f) 6 M HCl, 110°C, then Dowex 50W-X8, 54 and 73% yields for **5a** and **5b**, respectively (two steps).

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were unknown. Recently, two groups reported the stereoselective synthesis of (2*S*,3*S*,4*S*)- and (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acids,[4] and the former compound was found to be a selective agonist of mGluR1.[5] However, the methods are extremely tedious and lack applicability to other diastereomers. Therefore, a simple and general synthetic method of all diastereomers must be designed. We here disclose a concise diastereoselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid. In this synthesis (Scheme 1), we adopted L-tartaric acid as the starting material because the acid already contains the required two hydroxyl groups with established configurations.

The chiral imide **1**[6] derived from L-tartaric acid was reduced with sodium borohydride into hydroxylactam in 97% yield, which was then converted to acetoxylactam **2** in 85% yield. The hydroxylactam itself and the corresponding methoxylactam were inactive toward the subsequent cyanation reaction. The acetoxylactam **2** was then subjected to various cyanation conditions and the results are compiled in Table 1. When a solution of the lactam **2** (2.62 g, 5.00 mmol) and tributyltin cyanide[7] (2.37 g, 7.50 mmol) in toluene (20 ml) was treated with trifluoroborane etherate (1.42 g, 10.0 mmol) in toluene (5 ml), the expected cyanolactam **4**[8] was obtained in 94% yield as a 10/90 mixture of diastereomers (run 4). The choice of tributyltin cyanide over the silicon reagent and toluene over dichloromethane as the solvent proved to be advantageous for the selective cyanation. No significant improvement in the stereoselectivity was observed when the Lewis acid was changed, and lower temperature greatly retarded the reaction.

The stereochemistry of the newly created stereogenic center of **4a** and **4b** was assigned according to the observed vicinal coupling constants $J_{4,5}=4.4$ and 6.7 Hz, respectively.[9] There are some reports on the Lewis acid-promoted addition of tin and silicon nucleophiles to the *N*-acyliminium ion syn to the adjacent OTBS group,[9,10] revealing that this stereochemical outcome may be ruled by the Cieplak-type stereoelectronic effect.[11]

The diastereomers **4a** and **4b** could be easily separated by flash column chromatography on silica gel and the cyanolactam **4a** and **4b** were independently transformed into the 3,4-dihydroxyglutamic acids. The major isomer **4b** was then treated with cerium ammonium nitrate followed by 6 M HCl at 110°C. The crude product was purified by ion exchange column chromatography (Dowex 50W-X8) to furnish (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid (**5b**)[12] in 73% yield based on **4b**. The conversion of the minor isomer **4a** was also carried out and the diastereomeric (2*R*,3*S*,4*R*)-3,4-dihydroxyglutamic acid (**5a**),[13] a novel glutamic acid derivative, was obtained in 54% yield.

Table 1. Stereoselective cyanation of optically active acetoxylactam **2**

Run	Metal cyanide	Solvent	Selectivity (**4a**/**4b**)[a]	Yield (%)
1	Me_3SiCN	CH_2Cl_2	20/80	94
2	Me_3SiCN	Toluene	16/84	96
3	Bu_3SnCN	CH_2Cl_2	11/89	98
4	Bu_3SnCN	Toluene	10/90	94

[a] Determined by ^{1}H NMR spectroscopy.

In summary, we have demonstrated the concise diastereoselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid (**5b**) based on the stereoselective cyanation of the chiral *N*-acyliminium ion **3** derived from L-tartaric acid. In this synthesis, the (2*R*,3*S*,4*R*)-isomer **5a** was also obtained as a concomitant product. Although we have not employed D-tartaric acid as a starting material, we can see no reason why such reactions should not proceed with equally high diastereoselectivity to afford the corresponding (3*R*,4*S*)-isomers. The application of the present protocol to the synthesis of the (3*S*,4*S*)- and (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids is now under investigation.

References

1. Conn, P. J.; Pin, J. P. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205–237.
2. (a) Dell'Uomo, N.; Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Liebigs Ann. Chem.* **1994**, 641–644; (b) Gefflaut, T.; Bauer, U.; Airola, K.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **1996**, *7*, 3099–3102 and references cited therein.
3. Virtanen, A. I.; Ettala, T. *Soumen Kemistilehti.* **1956**, *B29*, 107–108.
4. (a) Dauban, P.; De Saint-Fuscien, C.; Dodd, R. H. *Tetrahedron* **1999**, *55*, 7589–7600; (b) Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 8801–8803.
5. Dauban, P.; De Saint-Fuscien, C.; Acher, F.; Prezeau, L.; Brabet, I.; Pin, J.-P.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 129–133.
6. (a) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455–1456; (b) Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621–623.
7. The enantioselective Strecker reaction of aldimine with tributyltin cyanide was reported: Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186–3188.
8. A closely related compound was prepared by a different method: Kim, Y. J.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 3423–3426.
9. (a) Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451–1454; (b) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290–295.
10. (a) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 753–764; (b) Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103–108; (c) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949–4952.
11. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552.
12. ^{1}H NMR (D_2O) δ 3.96 (d, $J=3$ Hz, 1H), 4.24 (d, $J=2$ Hz, 1H), 4.51 (dd, $J=3$ and 2 Hz, 1H); ^{13}C NMR (D_2O) δ 60.9, 72.4, 77.6, 175.4, 180.4; MS (FAB) m/z 180 (MH^+).
13. ^{1}H NMR (D_2O) δ 4.05 (d, $J=5$ Hz, 1H), 4.14 (d, $J=2$ Hz, 1H), 4.54 (dd, $J=5$ and 2 Hz, 1H); ^{13}C NMR (D_2O) δ 61.9, 71.4, 76.2, 174.5, 180.4; MS (FAB) m/z 180 (MH^+).