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Asymmetric synthesis of 3,4-dihydroxyglutamic acids via enantioselective reduction of cyclic *meso*-imide

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Abstract—Stereoselective synthesis of (3*S*,4*S*)- and (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids was investigated. The key reaction in this synthesis is asymmetric reduction of *meso*-imide derived from *meso*-tartaric acid. Lewis acid-promoted cyanation of the obtained optically active lactam via the acyliminium intermediate followed by standard deprotection procedure afforded the desired 3,4-dihydroxyglutamic acids.

1. Introduction

Much attention is being paid to the synthesis of non-proteinogenic as well as unusual amino acids of natural occurrence. 3,4-Dihydroxyglutamic acid is a natural glutamic acid derivative, which was isolated from the seeds of *Lepidum sativum* and the leaves of *Rheum rhaponticum* about 50 years ago.[1] However, nothing is known concerning the stereochemistry of the three consecutive chiral centers. Recently, two groups reported the stereoselective synthesis of (2*S*,3*S*,4*S*)- and (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid,[2,3] and the former compound was found to be a selective agonist of mGluR1. However, the methods require multistep synthesis from the commercially available compound and lack applicability to other diastereomers. Therefore, a simple and general approach to all stereoisomers of 3,4-dihydroxyglutamic acid must be explored.

We have previously reported a concise stereoselective synthesis of (2*S*,3*S*,4*R*)-, (2*R*,3*S*,4*R*)-, (2*S*,3*R*,4*S*)-, and (2*R*,3*R*,4*S*)-3,4-dihydroxyglutamic acid starting from L- or D-tartaric acid.[4] In order to obtain the corresponding (3*S*,4*S*)- and (3*R*,4*R*)-isomers, there are at least two ways including enantioselective symmetry breaking of *meso*-tartaric acid or utilization of a chiral starting material. Taking advantage of our previous work in this area, we planned to investigate enantioselective reduction of *meso*-imide derived from *meso*-tartaric acid. Such synthetic operation on the *meso*-imide can establish the absolute stereochemistry at three contiguous centers in a single step.

There are some reports on the enantioselective reduction of cyclic *meso*-imide.[5–8] Among them, optically active oxaborolidines mainly derived from L-amino acid have been widely used as a catalyst for borane reduction.[5] On the other hand, chiral BINAL-H is also recognized as an effective reducing agent for enantioselective desymmetrization of *meso*-imide;[6] however, reduction of *meso*-imide derived from *meso*-tartaric acid by the BINAL-H complex is not reported. In this paper, we examined the asymmetric synthesis of 3,4-dihydroxyglutamic acids via enantioselective reduction of cyclic *meso*-imide prepared from *meso*-tartaric acid with BINAL-H because both (*S*)-(−)- and (*R*)-(+)-binaphthol are commercially available.

2. Results and discussion

Scheme 1 shows the synthetic course of (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids. First of all, the enantioselective reduction of cyclic *meso*-imide **1**, derived from *meso*-tartaric acid, was carried out with 3 equiv. of (*R*)-BINAL-H reagent prepared in situ by mixing lithium aluminum hydride with equimolar amounts of (*R*)-(+)-binaphthol and ethanol in tetrahydrofuran.[9] The enantiomeric excess was assessed by HPLC analysis to be 83% ee using a chiral stationary column after conversion of the initially formed hydroxylactam into triacetoxylactam **2**. Among the simple alcohols such as methanol, 2-propanol, 2-methyl-2-propanol, and butanol tested as the additive,

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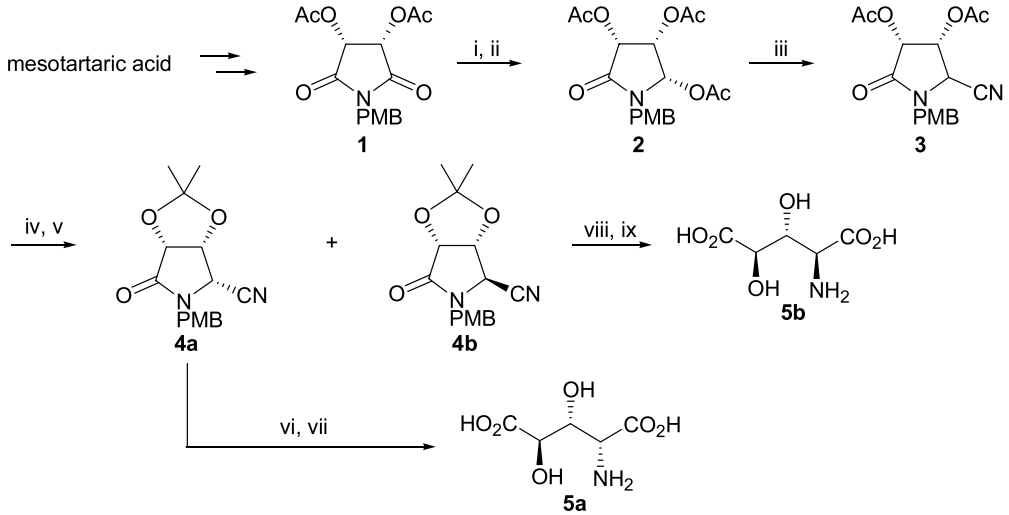
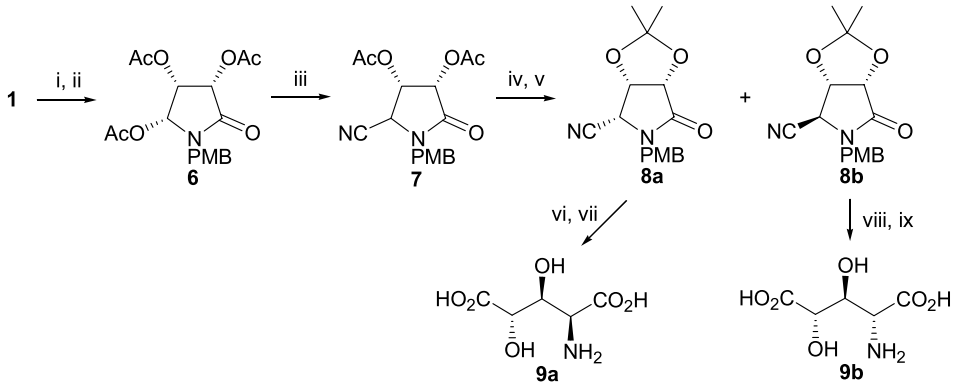


Scheme 1. (i) (*R*)-BINAL-H (EtOH), −78 °C; (ii) Ac_2O in pyridine, 61% (2 steps); (iii) BF_3–OEt_2, Me_3SiCN, toluene, 87%; (iv) AcCl, EtOH; (v) $Me_2C(OMe)_2$, *p*-toluenesulfonic acid, acetone, 36 and 60% yields for **4a** and **4b**, respectively (2 steps); (vi) $Ce(NH_4)_2(NO_3)_6$, acetonitrile–H_2O; (vii) 6 M HCl, reflux, 16 h, then Dowex 50W-X8, 75% (2 steps); (viii) as in vi; (ix) 1 M HCl, reflux, 3 h, then Dowex 50W-X8, 38% (2 steps).

ethanol afforded the best enantioselectivity. By comparing the sign of the specific rotation of the 3,4-dihydroxyglutamic acid **5a** formed from the triacetate **2** with that of known 3,4-dihydroxyglutamic acid, the (2*S*,3*S*,4*S*)-isomer,[2] the absolute configuration of the triacetate **2** was presumed as depicted in Scheme 1. The triacetate **2** was obtained as a single diastereomer and the stereochemical outcome suggests that the preferred trajectory of the (*R*)-BINAL-H reagent would be from the least hindered face of the carbonyl group attached to the *S* center of the cyclic *meso*-imide. Matsuki and co-workers reported that (*R*)-BINAL-H would attack the carbonyl carbon adjacent to the *R* center of the bicyclic *meso*-imide.[6] At the present stage, we cannot pinpoint the origin of enantioselective discrimination of the two enantiotopic imide carbonyl groups; however, the interaction of an acetoxy group with the (*R*)-BINAL-H reagent may be responsible for the observed reversal of the enantioselectivity.

The obtained triacetoxylactam **2** was then subjected to cyanation reaction. When a solution of triacetate **2** and trimethylsilyl cyanide (1.5 equiv.) in toluene was treated with boron trifluoride etherate (1.5 equiv.) at room temperature for 1 h, cyanolactam **3** was obtained in 87% yield as a 38:62 mixture of *syn* and *anti* adducts. The stereochemistry of the cyanolactam **3** was determined by comparison of the $J_{4,5}$ values, 5 and 1 Hz for the *syn* and *anti* adducts, respectively,[10] and was finally confirmed by transformation to 3,4-dihydroxyglutamic acid **5**. Several investigations were made on the diastereoselective cyanation; however, there was no improvement in diastereoselectivity.

Separation of the diastereomers was carried out after conversion of the diacetate **3** to the corresponding acetonide **4** because the diastereomeric mixture of **3** could not be separated by column chromatography. The cyanolactams **4a** and **4b** were isolated in 36 and 60% yields, respectively, and were independently treated with ammonium cerium (IV) nitrate followed by acidic hydrolysis to give novel (2*R*,3*R*,4*R*)- and (2*S*,3*R*,4*R*)-3,4-dihydroxyglutamic acid **5a** and **5b** in 75 and 38% yields, respectively. The transformation of the *anti* adduct **4b** to **5b** needed to be performed with care. The final acidic hydrolysis should be performed



Scheme 2. (i) (*S*)-BINAL-H (EtOH), −78 °C; (ii) Ac_2O in pyridine, 68% (2 steps); (iii) BF_3–OEt_2, Me_3SiCN, toluene, quant.; (iv) AcCl, EtOH; (v) $Me_2C(OMe)_2$, *p*-toluenesulfonic acid, acetone, 26 and 46% yields for **8a** and **8b**, respectively (2 steps); (vi) $Ce(NH_4)_2(NO_3)_6$, acetonitrile–H_2O; (vii) 6 M HCl, reflux, 16 h, then Dowex 50W-X8, 80% (2 steps); (viii) as in vi; (ix) 1 M HCl, reflux, 3 h, then Dowex 50W-X8, 63% (2 steps).

in refluxing 1 M HCl for 3 h. Refluxing in 6 M HCl overnight as in the synthesis of **5a** resulted in undesirable epimerization at the α-position.

3,4-Dihydroxyglutamic acids in another enantiomeric series, the (3*S*,4*S*)-isomers, were synthesized from a chiral triacetoxylactam **6** prepared by reduction of the *meso*-imide **1** with (*S*)-BINAL-H. The results are summarized in Scheme 2. Using the same procedure for the preparation of the corresponding (3*R*,4*R*)-isomers, the known (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid (**9a**)[2] and novel (2*R*,3*S*,4*S*)-isomer (**9b**) were obtained in good yields.

In conclusion, asymmetric synthesis of (3*S*,4*S*)- and (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids using enantioselective desymmetrization of *meso*-imide derived from *meso*-tartaric acid was achieved. Lewis acid-promoted cyanation of the obtained optically active lactam via the acyliminium intermediate followed by standard deprotection procedure afforded the 3,4-dihydroxyglutamic acids. Coupled with the results obtained in our previous work,[4] the present study provides a facile and versatile protocol for accessing all eight stereoisomers of 3,4-dihydroxyglutamic acids.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (δ_H 7.26), residual DMSO (δ_H 2.50), dioxane (δ_H 3.53 and δ_c 66.5), or the central peak of $CDCl_3$ (δ_c 77.0). High-resolution mass spectra (HRMS) were determined using perfluorokerosene as an internal standard. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. Enantiomeric excess was determined on an HPLC system (monitored at 254 nm) equipped with a chiral column (CHIRALPAK AS-H) using a mixture of hexane and ethanol (50:50) as an eluent.

3.1.1. (3*R,4*S**)-3,4-Diacetoxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione (1).** According to the procedure for the preparation of the corresponding *N*-benzyl derivative reported by Hiemstra and co-workers,[5] the title compound **1** was obtained as colorless needles (hexane–chloroform), mp 102–103 °C. ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6H), 3.77 (s, 3H), 4.66 (s, 2H), 5.53 (s, 2H), 6.83 (d, *J*=9 Hz, 2H), 7.31 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 19.95, 42.37, 55.23, 65.96, 114.08, 126.75, 130.49, 159.57, 168.99, 170.89. HRMS (EI, 70 eV) *m*/*z* 335.0970 (M^+, calcd for $C_{16}H_{17}NO_7$ 335.1005).

3.1.2. (3*R*,4*S*)-3,4,5-Triacetoxy-1-(4-methoxybenzyl)-2-pyrrolidinone (2). To a solution of (3*R**,4*S**)-3,4-diacetoxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione (**1**, 1.00 g, 3.00 mmol) in THF (90 mL) was added a solution of (*R*)-BINAL-H (EtOH) (9.00 mmol) in THF (25 mL) at −78 °C under an argon atmosphere. After it was stirred for 17 h, the reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to dryness to give a hydroxylactam. To a solution of the hydroxylactam in pyridine (60 mL) was added acetic anhydride (1.83 g, 18.0 mmol), and the reaction mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with 1 M HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel (hexane–ethyl acetate=50:50) to give the title compound **2** (690 mg, 61%) as an oil. ^{1}H NMR (DMSO-d_6) δ 1.91 (s, 3H), 1.97 (s, 3H), 2.07 (s, 3H), 3.70 (s, 3H), 4.20 (d, *J*=15 Hz, 1H), 4.49 (d, *J*=15 Hz, 1H), 5.45 (d, *J*=7 Hz, 1H), 5.50 (dd, *J*=7, 5 Hz, 1H), 6.11 (d, *J*=5 Hz, 1H), 6.87 (d, *J*=9 Hz, 2H), 7.15 (d, *J*=9 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 19.89, 20.08, 20.21, 43.03, 54.99, 64.78, 67.12, 79.49, 113.97, 126.97, 129.58, 159.21, 167.81, 168.87, 169.19, 169.52. HRMS (EI, 30 eV) *m*/*z* 379.1279 (M^+, calcd for $C_{18}H_{21}NO_8$ 379.1267).

3.1.3. (3*R*,4*R*)-3,4-Diacetoxy-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (3). To a solution of acetoxylactam **2** (3.03 g, 8.0 mmol) and trimethylsilyl cyanide (1.19 g, 12.0 mmol) in toluene (80 mL) was added a solution of boron trifluoride etherate (2.27 g, 12.0 mmol) in toluene (8 mL) at room temperature. After it was stirred for 1 h, the reaction mixture was quenched with saturated aqueous Na_2CO_3 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane–ethyl acetate=50:50) to give the title compound **3** (2.60 g, 87%) as a 62:38 mixture of diastereomers. HRMS (EI, 30 eV) *m*/*z* 346.1186 (M^+, calcd for $C_{17}H_{18}N_2O_6$ 346.1165). Major isomer: ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.17 (s, 3H), 3.80 (s, 3H), 3.98 (d, *J*=15 Hz, 1H), 4.07 (d, *J*=1 Hz, 1H), 5.12 (d, *J*=15 Hz, 1H), 5.61 (dd, *J*=6, 1 Hz, 1H), 5.63 (d, *J*=6 Hz, 1H), 6.98 (d, *J*=9 Hz, 2H), 7.19 (d, *J*=9 Hz, 2H). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.34 (s, 3H), 3.80 (s, 3H), 4.43 (d, *J*=15 Hz, 1H), 4.30 (d, *J*=5 Hz, 1H), 5.19 (d, *J*=15 Hz, 1H), 5.42 (d, *J*=5 Hz, 1H), 5.53 (dd, *J*=5, 5 Hz, 1H), 6.98 (d, *J*=9 Hz, 2H), 7.19 (d, *J*=9 Hz, 2H).

3.1.4. (3*R*,4*R*,5*S*)-3,4-*O*-Isopropylidene-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (4a) and (3*R*,4*R*,5*R*)-3,4-*O*-isopropylidene-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (4b). To a solution of cyanolactam **3** (3.42 g, 9.87 mmol) in ethanol (86 mL) was added acetyl chloride (2.02 g, 25.8 mmol), and the solution was stirred at 50 °C for 2.5 h. After evaporation of the solvent, the residue was dissolved in acetone (86 mL). To the solution was added 2,2-dimethoxypropane (4.47 g, 43.0 mmol) and *p*-toluenesulfonic acid (440 mg, 2.55 mmol), and the solution was stirred at 30 °C for 2 h. After removal of the solvent, the crude product was purified by column chromatography on silica gel (hexane–ethyl acetate=50:50) to give the title compound **4b** (1.80 g, 60%) as an oil, which solidified upon standing. Colorless powder (hexane–chloroform), mp 94–95 °C. ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.35 (s, 3H), 3.78 (s, 3H), 3.91 (d, *J*=15 Hz, 1H), 4.12 (s, 1H), 4.85 (s, 2H), 5.10 (d, *J*=15 Hz, 1H), 6.87 (d, *J*=9 Hz, 2H), 7.17 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 25.75, 26.84, 44.79, 51.24, 55.18, 74.81, 76.76, 113.92, 114.42, 114.93, 125.01, 139.88,

159.73, 169.69. HRMS (EI, 70 eV) *m/z* 302.1224 (M^+, calcd for $C_{16}H_{18}N_2O_4$ 302.1266).

Further elution with a mixture of hexane and ethyl acetate (50:50) gave the corresponding (3*R*,4*R*,5*S*)-isomer **4a** (1.09 g, 36%) as a pale yellow oil, which solidified upon standing. Colorless needles (hexane–chloroform), mp 174–175 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.52 (s, 3H), 3.78 (s, 3H), 3.95 (d, J=14 Hz, 1H), 4.30 (d, J=4 Hz, 1H), 4.70 (d, J=5 Hz, 1H), 4.77 (dd, J=5, 4 Hz, 1H), 5.18 (d, J=14 Hz, 1H), 6.86 (d, J=8 Hz, 2H), 7.22 (d, J=8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 25.79, 26.72, 44.89, 51.38, 55.19, 71.15, 76.90, 112.95, 114.06, 114.46, 125.63, 130.22, 159.76, 169.08. HRMS (EI, 70 eV) *m/z* 302.1273 (M^+, calcd for $C_{16}H_{18}N_2O_4$ 302.1266).

3.1.5. (2*R*,3*R*,4*R*)-3,4-Dihydroxyglutamic acid (5a). To a suspension of cyanolactam **4a** (302 mg, 1.00 mmol) and diammonium cerium (IV) nitrate (1.09 g, 2.00 mmol) in acetonitrile (15 mL) was added water (3 mL) at room temperature, and the resulting mixture was stirred for 4 h. The reaction mixture was then diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was hydrolyzed in refluxing 6 M HCl (20 mL) for 16 h. The cooled aqueous solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion exchange column chromatography on Dowex 50W-X8 to furnish the title compound **5a** (128 mg, 75%) as a colorless powder (EtOH–H_2O), mp 155–160 °C (dec). $[\alpha]_D^{25}=+0.7$ (c 1.0, H_2O). ^{1}H NMR (D_2O) δ 3.63 (d, J=0.4 Hz, 1H), 4.09 (d, J=3.5 Hz, 1H), 4.49 (dd, J=3.5, 0.4 Hz, 1H). ^{13}C NMR (D_2O) δ 56.96, 71.20, 76.21, 173.91, 178.33. HRMS (EI, 70 eV) *m/z* 135.0559 [$(M-CO_2)^+$, calcd for $C_4H_9NO_4$ 135.0532). MS (FAB) *m/z* 180 (MH^+).

3.1.6. (2*S*,3*R*,4*R*)-3,4-Dihydroxyglutamic acid (5b). To a suspension of cyanolactam **4b** (1.69 g, 5.60 mmol) and diammonium cerium (IV) nitrate (9.21 g, 16.8 mmol) in acetonitrile (56 mL) was added water (11 mL) at room temperature, and the resulting mixture was stirred for 4 h. The reaction mixture was then diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave deprotected cyanolactam (418 mg, 41%). The obtained crude cyanolactam (93.2 mg, 0.511 mmol) was hydrolyzed in refluxing 1 M HCl (30 mL) for 3 h. The cooled aqueous solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion exchange column chromatography on Dowex 50W-X8 to furnish the title compound **5b** (82.6 mg, 92%) as a colorless powder (EtOH–H_2O), mp 170–180 °C (dec). $[\alpha]_D^{25}=-1.6$ (c 1.0, H_2O). ^{1}H NMR (D_2O) δ 3.77 (d, J=4.4 Hz, 1H), 3.87 (d, J=3.7 Hz, 1H), 4.13 (dd, J=4.4, 3.7 Hz, 1H). ^{13}C NMR (D_2O) δ 56.96, 71.20, 72.82, 171.58, 177.46. HRMS (EI, 70 eV) *m/z* 135.0519 [$(M-CO_2)^+$, calcd for $C_4H_9NO_4$ 135.0532). MS (FAB) *m/z* 180 (MH^+).

3.1.7. (2*S*,3*S*,4*S*)-3,4-Dihydroxyglutamic acid (9a). According to the procedure for the preparation of compound **5a**, deprotection and hydrolysis of cyanolactam **8a** (532 mg, 1.76 mmol) gave the title compound **9a** (195 mg, 63%) as a white powder, $[\alpha]_D^{25}=-0.5$ (c 1.0, H_2O) (lit.[2] $[\alpha]_D^{28}=-0.8$ (c 1.0, H_2O)). The physical and spectral data of compound **9a** are identical with those of the compound **5a**.

3.1.8. (2*R*,3*S*,4*S*)-3,4-Dihydroxyglutamic acid (9b). According to the procedure for the preparation of compound **5b**, deprotection and hydrolysis of cyanolactam **8b** (958 mg, 3.17 mmol) gave the title compound **9b** (454 mg, 80%) as a white powder, $[\alpha]_D^{25}=+2.0$ (c 1.0, H_2O). The physical and spectral data of compound **9b** are identical with those of compound **5b**.

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10. In a similar system, the value of $J_{4,5}$ of the *syn* adduct is larger than that of the *anti* isomer. See Ref. 7.