

Synthesis of C_2 -Symmetric 1,3-Imidazolidin-2-ones as Bifunctional Chiral Auxiliaries from Industrial Chiral Waste

Chun Rim Oh, Choong Eui Song,* Eun Joo Roh, Sang-gi Lee, and Jong Hwa Jeong[†]

Division of Applied Science, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea

[†]Department of Chemistry, Kyungpook National University, Taegu 702-701, Korea

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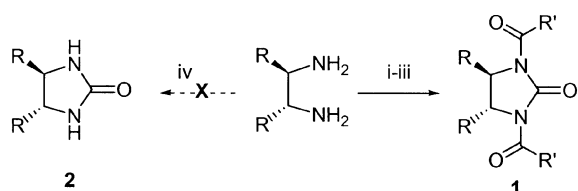
Unlike chiral catalysts, chiral auxiliaries are used stoichiometrically since they allow for asymmetric induction by modifying the structure of the substrate molecule. Thus not only the efficiency of auxiliary is important for the economics but also the molecular weight of the chiral auxiliary. A "bifunctional chiral auxiliary", in which a chiral auxiliary bearing two stereogenic centers is attached to two reactive side chains, will provide an elegant means for minimizing the amount of the auxiliary required. Recently Davies et al. reported¹⁻⁸ a novel series of highly effective bifunctional chiral auxiliaries, homochiral 1,3-diacylimidazolidin-2-ones **1**, which possess C_2 -symmetry and bifunctionality, reducing the effective molecular mass.⁹ The compounds **1** were synthesized by thionation of chiral diamines with CS_2 , followed by acylation and finally, by dethionation with mercury acetate (II), whereas the direct synthetic route to 1,3-imidazolidin-2-ones **2** by carbonylation of chiral diamines with phosgene or phosgen equivalents was failed (Scheme 1).⁷

In context with our study of the utilization of industrial waste material, we used the enantiomerically pure compound **3** for the synthesis of C_2 -symmetric 1,3-imidazolidin-

2-ones **2** as bifunctional chiral auxiliaries. The compound **3** could be obtained as a chiral waste material in the synthetic process of D-Biotin. We first determined the structure of **3** by spectroscopic and X-ray crystallographic analyses (Figure 1).

The following simple sequence (Scheme 2) was successfully employed to convert the waste material **3** into novel bifunctional chiral auxiliaries, 4,5-disubstituted-1,3-imidazolidin-2-ones **2a** and **2b**. The acid-alcohol **3** underwent esterification with CH_3OH -TMSCl to afford the ester-alcohol **4** in nearly quantitative yield. Reduction of ester-alcohol **4** with $LiBH_4$ afforded the diol **5** in 95% yield. Methylation of **5** gave 1,3-dibenzyl-4,5-bis(methoxymethyl)imidazolidin-2-one **6**, which was debenzylated with Na in NH_3 to afford 4,5-di(methoxymethyl)-1,3-imidazolidin-2-ones (**2a**) in 75% yield. 4,5-Dimethyl-1,3-imidazolidin-2-one (**2b**) was also easily prepared by the reaction of diol **5** with dimethylsulfamoyl chloride, and subsequent treatment with Na in NH_3 . The utility of 1,3-imidazolidin-2-ones **2a** and **2b** as efficient bifunctional chiral auxiliaries was already illustrated by Davies and coworkers in the asymmetric aldol and alkylation reactions.¹

In summary, we have synthesized novel bifunctional chiral auxiliaries **2a** and **2b** having low effective molecular mass



Scheme 1. Reagents and conditions: (i) CS_2 , H_3O^+ (ii) $R'COCl$, pyridine, DMAP (iii) $Hg(OAc)_2$, CH_2Cl_2 (iv) $COCl_2$.

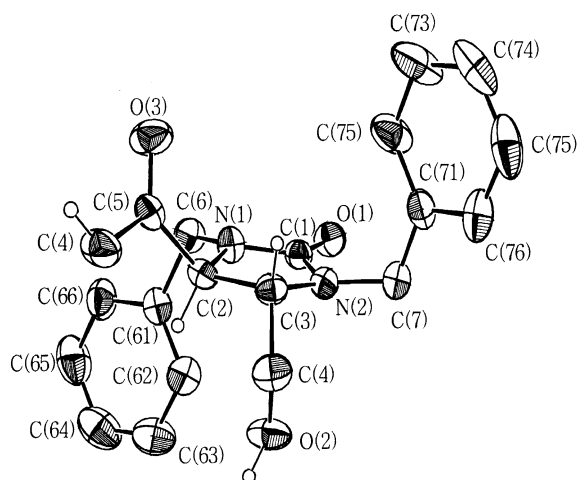
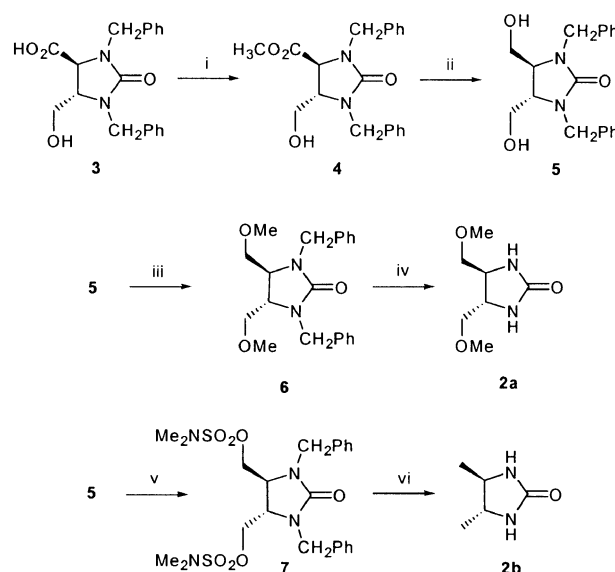


Figure 1. Crystal structure of **3**.



Scheme 2. Reagents and conditions: (i) TMSCl, MeOH, 95% (ii) $LiBH_4$, THF, 96% (iii) NaH, CH_3I , DMF, 96% (iv) Na/ NH_3 , THF, $-78^\circ C$, 71% (v) NaH, DMF, Me_2NSO_2Cl , 88% (vi) Na/ NH_3 , THF, $-78^\circ C$, 33%.

(EMM=87 and 57, respectively) in four steps starting from a chiral waste **3** which could be obtained as a by-product in the industrial synthetic process of D-biotin.

Experimental Section

General. Chromatographic purification of products was carried out using Merck silica gel 60 (230-400 mesh). Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. Optical rotation was measured on a AUTOPOL[®] III polarimeter (Rudolph Research). ¹H NMR (300 MHz) and ¹³C NMR (75.0 Hz) spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and main absorption frequencies were given in cm⁻¹. Elemental analyses were performed at Advanced Analytical Research Center in KIST using Perkin Elmer 240 C elemental analyzer.

(4S,5S)-1,3-Dibenzyl-5-(hydroxymethyl)-2-oxoimidazolidine-4-carboxylic acid 3. The homochiral compound **3**, which could be isolated as a by-product in the industrial synthetic process of D-Biotin, was generously gifted by I-Sung Chemical Co. in Korea. Single crystals suitable for X-ray crystallographic structure analysis were obtained by recrystallization from aqueous methanol.

m.p. 157 °C (MeOH-H₂O, 95 : 5); $[\alpha]_D^{16}$ -7.63 (*c* 1.016, EtOH); IR (KBr) 3346, 1704, 1674, 1468, 1265, 745, 696 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+DMSO-*d*₆) δ 7.4-7.2 (m, 10H), 5.07 (d, *J* = 15.3 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.18 (d, *J* = 12.4 Hz, 1H), 3.87 (d, *J* = 5.7 Hz, 1H), 3.65-3.49 (m, 3H); ¹³C NMR (75.0 MHz, CD₃OD) δ 173.74, 161.87, 138.10, 137.67, 129.75, 129.56, 129.22, 128.87, 128.69, 61.23, 59.18, 57.62, 47.42, 46.28. Anal. Calcd for C₁₉H₂₀N₂O₄·H₂O: C, 63.67; H, 6.18; N, 7.81. Found: C, 63.9; H, 6.30; N, 7.86.

Crystal data of 3. C₁₉H₂₂N₂O₅ (C₁₉H₂₀N₂O₄·H₂O), monoclinic, P2₁, *a* = 6.7925(8), *b* = 13.809(2), *c* = 10.174(2) Å, β = 107.48(1)°, *V* = 910.2(2) Å³, *Z* = 2, *D*_c = 1.308 g/cm³, *F*(000) = 380, (*MoK*_α) = 0.71073 Å. 1324 Independent reflections with *I*/*σ*(*I*) > 2.0 are used on the analysis. *R* = 0.036. Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4 diffractometer using Mo radiation and ω-2 scans in the range of θ: 2.10 < θ < 24.96. Structure was solved by direct methods and refined by least squares using the SHEL-X.

(4S,5S)-Methyl 1,3-dibenzyl-5-(hydroxymethyl)-2-oxoimidazolidine-4-carboxylate 4. To a stirred solution of **3** (1.0 g, 2.9 mmol) in MeOH (10 mL) was added TMSCl (1.10 mL, 8.7 mmol) at room temperature. After stirring for 24 hr at room temperature, the reaction was quenched by addition of water. The MeOH was removed *in vacuo* and the resulting residue was extracted with EtOAc (3×10 mL). The combined organic phase was dried over MgSO₄ and evaporated. The crude product was recrystallized from Et₂O to give **4** (0.98 g, 95%) as a white solid. m.p. 102 °C; $[\alpha]_D^{16}$ -23.72 (*c* 1.016, CHCl₃); IR (KBr) 3317, 1743, 1677, 1470,

1452, 1221, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.4-7.2 (m, 10H), 4.92 (d, *J* = 15.5 Hz, 1H), 4.69 (d, *J* = 15.5 Hz, 1H), 4.29 (d, *J* = 15.5 Hz, 1H), 4.22 (d, *J* = 15.5 Hz, 1H), 3.59 (s, 3H), 3.64-3.43 (m, 3H); ¹³C NMR (75.0 MHz, CDCl₃) δ 170.99, 160.02, 137.19, 136.25, 128.86, 128.65, 128.35, 127.88, 127.74, 127.64, 61.00 (m), 58.01 (m), 56.88, 56.48, 52.49 (m), 47.11 (m). Anal. Calcd for C₂₀H₂₂N₂O₄: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.7; H, 6.30; N, 7.86.

(4S,5S)-4,5-Bis(hydroxymethyl)-1,3-dibenzylimidazolidin-2-one 5. To a stirred mixture of LiBH₄ (0.08 g, 3.68 mmol) in THF (10 mL) was added a solution of **4** (0.87 g, 2.45 mmol) in THF (6 mL) at room temperature. The reaction mixture was refluxed for 12 hr, and the reaction was quenched at room temperature by addition of 3N HCl (2 mL) and water (5 mL), subsequently. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (3×10 mL). The combined organic phase was dried over MgSO₄ and evaporated *in vacuo*. Recrystallization of the crude product from Et₂O gave **5** (0.77 g, 96%) as a white solid. m.p. 142 °C; $[\alpha]_D^{25}$ +26.08 (*c* 0.460, EtOH); IR (KBr) 3391, 1636, 1507, 1436, 742, 702 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.4-7.2 (m, 10H), 4.83 (t, *J* = 5.1 Hz, 2H), 4.70 (d, *J* = 15.6 Hz, 2H), 4.14 (d, *J* = 15.6 Hz, 2H), 3.5-3.3 (m, 4H), 3.22 (m, 2H); ¹³C NMR (75.0 MHz, DMSO-*d*₆) δ 159.82, 137.90, 128.35, 127.53, 126.92, 60.73 (m), 56.03 (m), 44.80 (m). Anal. Calcd for C₁₉H₂₂N₂O₃: C, 69.91; H, 6.79; N, 8.58. Found: C, 69.7; H, 6.82; N, 8.53.

(4S,5S)-4,5-Bis(methoxymethyl)-1,3-dibenzylimidazolidin-2-one 6. Sodium hydride (60% dispersion in mineral oil) (0.32 g, 8.0 mmol) was added to a solution of **5** (0.65 g, 2.0 mmol) in DMF (10 mL) at room temperature and the reaction mixture was stirred for 1 hr. Iodomethane (1.00 mL, 16.0 mmol) was added at ambient temperature. After stirring for 4 hr, the reaction was quenched by addition of saturated aqueous ammonium chloride solution. The mixture was extracted with EtOAc (3×10 mL) and the combined organic layers were dried over MgSO₄. After evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel (hexane : EtOAc = 2 : 1) to give **6** (0.68 g, 96%) as a pale yellow oil. $[\alpha]_D^{27}$ +16.60 (*c* 0.747, CHCl₃); IR (neat) 2928, 2881, 1684, 1450 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.4-7.2 (m, 10H), 4.82 (d, *J* = 15.4 Hz, 2H), 4.23 (d, *J* = 15.4 Hz, 2H), 3.32-3.23 (m, 6H), 3.18 (s, 6H); ¹³C NMR (75.0 MHz, CDCl₃) δ 160.33, 137.82, 128.45, 128.13, 127.24, 73.24, 58.97, 55.34, 46.33 (m).

(4S,5S)-4,5-Bis(methoxymethyl)imidazolidin-2-one 2a. A solution of **6** (0.71 g, 2.0 mmol) in THF (20 mL) was added dropwise to a saturated solution of NH₃ in THF (15 mL) at -78 °C. Sodium metal (0.41 g, 18.0 mmol) was added and the reaction mixture was stirred until blue color disappeared. The reaction was quenched by addition of solid ammonium chloride (0.97 g, 18.1 mmol) and stirring continued for 2 hr. The excess of ammonia and THF were evaporated *in vacuo*. The white residue was extracted with methylene chloride by soxhlet extractor. After evaporation of solvent, the crude product was recrystallized from ethyl

ether/hexane = 1/1 to give **2a** (0.25 g, 71%) as a white solid. m.p. 103 °C; $[\alpha]_D^{16} +108.72$ (*c* 1.021, CHCl₃); IR (KBr) 3233, 1703, 1463, 1141, 1092 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.58 (sym.m, 2H), 3.40-3.30 (m, 4H), 3.37 (s, 6H); ¹³C NMR (75.0 MHz, CDCl₃) δ 163.18, 75.04, 59.12, 54.72. Anal. Calcd for C₇H₁₄N₂O₃: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.6; H, 8.11; N, 16.10.

(4S,5S)-4,5-Bis[(dimethylamino)sulfonyloxymethyl]-1,3-dibenzylimidazolidin-2-one 7. Sodium hydride (60% dispersion in mineral oil) (0.38 g, 9.5 mmol) was added to a solution of **3** (1.0 g, 3.06 mmol) in DMF (20 mL) at room temperature and allowed to stir for 1 hr. *N,N*-Dimethylsulfonyl chloride (0.99 mL, 9.19 mmol) was added at -5 °C and the reaction stirred for a further 4 hr before the reaction was quenched by addition of saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane : EtOAc = 2 : 1) to give **7** (1.45 g, 88%) as a pale yellow solid. m.p. 93 °C; $[\alpha]_D^{27} -2.59$ (*c* 1.003, CHCl₃); IR (KBr) 1675, 1477, 1374, 1173, 964, 813 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.4-7.2 (m, 10H), 4.91 (d, *J* = 15.4 Hz, 2H), 4.15 (d, *J* = 15.4 Hz, 2H), 4.06 (dd, *J* = 4.1, 11.0 Hz, 2H), 3.96 (dd, *J* = 2.6, 11.0 Hz, 2H), 3.54 (m, 2H), 2.73 (s, 12H); ¹³C NMR (75.0 MHz, CDCl₃) δ 159.38, 136.47, 128.92, 128.28, 127.86, 67.07 (m), 54.00 (m), 46.13, 45.87, 38.46 (m). Anal. Calcd for C₂₃H₃₂N₄O₇S₂: C, 51.09; H, 5.96; N, 10.36; S, 11.86. Found: C, 51.5; H, 6.04; N, 10.30; S, 11.60.

(4R,5R)-4,5-Dimethylimidazolidin-2-one 2b. A solution of **6** (1.0 g, 1.85 mmol) in THF (25 mL) was added dropwise to a saturated solution of NH₃ in THF (20 mL) at -78 °C. Sodium metal (2.27 g, 98.74 mmol) was added in small pieces and the mixture was stirred until blue color disappeared. The reaction mixture was quenched by addition of solid ammonium chloride (5.30 g, 99.12 mmol). The excess of ammonia and THF were evaporated *in vacuo*. To the resi-

due was added CH₂Cl₂ (20 mL) and the organic layer was separated. The aqueous phase was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (MeOH : CH₂Cl₂ : EtOAc : *n*-hexane = 7.5 : 42.5 : 40 : 10) to give **2b** (0.07 g, 33%) as a white solid. Purification of crude product was also accomplished by recrystallization from ethyl ether/ethyl acetate = 10/1. m.p. 177 °C; $[\alpha]_D^{16} 35.06$ (*c* 0.755, CHCl₃); IR (KBr) 3212, 1702 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.27 (sym.m, 2H), 1.12 (d, *J* = 5.3 Hz, 6H); ¹³C NMR (75.0 MHz, CDCl₃) δ 164.12, 56.20, 20.35. Anal. Calcd for C₅H₁₀N₂O: C, 52.61; H, 8.83; N, 24.54. Found: C, 52.8; H, 8.86; N, 23.70.

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