A Practical Formal Synthesis of D-(+)-Biotin from 4-Formylazetidin-2-one

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Abstract: A practical synthesis of (3*S*,6*R*)-1,3-dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione, an important intermediate in the synthesis of biotin, from 4-formyl-3-mesyloxyazetidin-2-one has been achieved. Acid-catalyzed azetidin-2-one ring opening followed by a one-pot conversion of diamine hydrochloride to a cyclic urea and hydroxymethylene to chloromethylene by triphosgene to obtain (4*S*,5*R*)-methyl-1,3-dibenzyl-5-chloromethyl-2-oxoimidazolidine-4-carboxylate is the key step in this synthesis.

Key words: β-lactams, cyclization, reduction, lactone, azetidin-2-one

Azetidin-2-ones, present as moieties in a variety of β-lactam antibiotics,[1–3] are being recognized as an important building block in the synthesis of variety of pharmaceutically useful products.[4] The strain energy associated with the four member azetidin-2-one ring makes it susceptible for the nucleophilic ring cleavage. The selective bond cleavage of the strained ring coupled with further interesting transformations render this fascinating molecule a powerful building block.[5] Efforts have been made in exploring such new aspects of β-lactam chemistry using enantiomerically pure β-lactams as a versatile synthon for the synthesis of many heterocyclic non-β-lactam structures,[6] aromatic β-amino acids and their derivatives,[7] and oligopeptides.[4c] One such synthetic intermediate, 4-formylazetidin-2-one, has found wide applications as a building block[5,6] in organic synthesis. This is mainly due to the fact that there are quite a few methods available for the preparation of enantiopure 4-formylazetidin-2-ones.[7] As a part of our ongoing research program on the synthesis and application of azetidin-2-ones as synthon,[8] we have also used 4-formylazetidin-2-ones as a building block for the synthesis of biologically useful organic molecules.[9] We herein report an application of 4-formylazetidin-2-one as a building block in the synthesis of (3*S*,6*R*)-1,3-dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (**1a**), which is a crucial intermediate in the synthesis D-(+)-biotin (**2**)[10] (Figure 1).

The biological and commercial importance of biotin has made it a fascinating target molecule for total synthesis for more than fifty years.[11] Although numerous synthetic approaches have been reported to date, the first synthesis of biotin described by Goldberg and Sternbach, and subsequent modifications is still one of the best syntheses.[11a] The potential of this approach depends upon the efficient method available for making optically active lactone **1a** or thiolactone **1b**. This is considered to be one of the most expedient approaches to the synthesis of biotin.[10] Most of the syntheses reported for the bicyclic lactone **1a** revolve around the desymmetrization of *meso* diacid **3**, diester **4**, cyclic anhydride **5** and bicyclic imide **6**, followed by further transformations. The conversion of *meso* diacid **3** to lactone **1a** via enzymatic resolution involved multi-step and also resulted in poor overall yield.[10h] Asymmetric hydrolysis of *meso* diester **4** using PLE (pig liver esterase) gave low enantioselectivity for hemiesters.[10i] The desymmetrization of cyclic anhydride[10k,l] **5** and cyclic imide[10c,m] **6** (Figure 1) by asymmetric reduction involved use of expensive chiral ligands in large quantities. A modified cinchona alkaloid was also reported as a catalyst for the desymmetrization of cyclic anhydride **5** to a hemiester.[10e] Apart from these methods a multi-step synthesis of lactone **1a** from L-aspartic acid in 11% overall yield was reported.[10f]

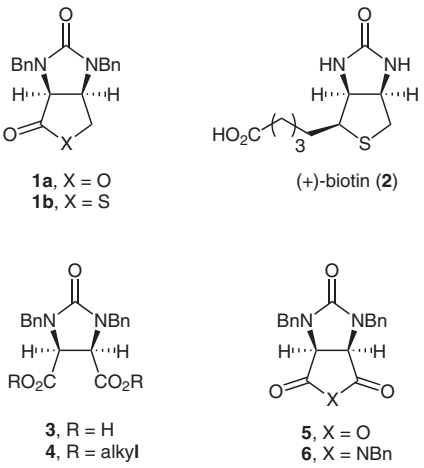

Figure 1 Compounds **1–6**

In spite of the biological significance and the commercial importance of biotin, there are very few practical methods available for the synthesis of enantiopure lactone **1a**, a key intermediate in the synthesis of D-(+)-biotin (**2**). Our experience in the β-lactam synthesis inspired us to design a retro-synthetic route (Scheme 1) for **1a**, from 4-formyl-β-lactam. We envisaged that the S_N2 substitution of mesyloxy group of 3-mesyloxy-4-hydroxymethyl-β-lactam (**8**) with an azido group would provide the *trans*-3-azido-4-

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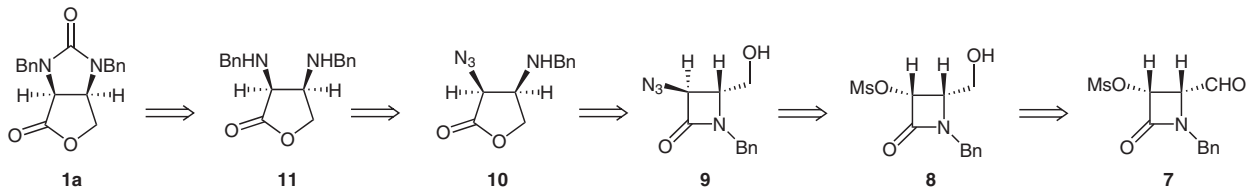
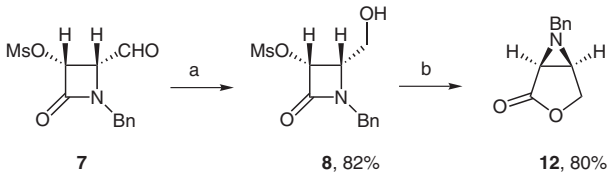


Scheme 1

hydroxymethyl-β-lactam (**9**) with the desired stereochemistry, which on ring-expansion would provide the azidolactone **10**. Further transformation of the azido group to NHBn and tying both the nitrogens with a carbonyl group would provide the target bicyclic lactone **1a**.

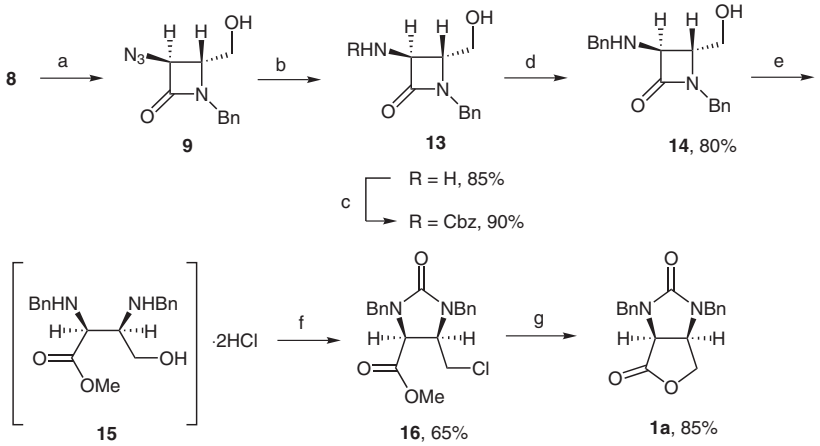
In our recent communication[9b] we have shown that aziridino-γ-lactone **12** can be obtained in excellent yield from 3-mesyloxy-4-formylazetidin-2-one (**7**) in two steps (Scheme 2). The same procedure was employed for the preparation of optically pure starting *N*-benzyl-4-formyl-3-mesyloxyazetidin-2-one and its reduction to *N*-benzyl-4-hydroxymethyl-3-mesyloxyazetidin-2-one by sodium borohydride. The displacement of the mesyloxy group with an azide was achieved by heating **8** with sodium azide in anhydrous DMF at 80 °C for 36 hours. The *trans*-azido-β-lactam **9** was obtained in very good yield with a complete inversion of the configuration at C3 of the azetidin-2-one ring. The azetidin-2-one ring expansion reaction of **9** with methanolic-HCl at room temperature resulted in very poor yield (20%) of the azidolactone **10**. All our efforts to improve the yield of **10** were unsuccessful. Moreover, the reduction of azido group by catalytic hydrogenation or transfer hydrogenation gave a complex mixture of products. The Staudinger reaction of azide **10** with *n*-tributylphosphine in the presence of benzyl bromide also did not give the desired product **11** (R = Bn).

Since all our efforts to improve the yield of azidolactone **10** and its further reduction to amino lactone failed, we de-



Scheme 2 *Reagents and conditions*: a) $NaBH_4$, MeOH, r.t., 3 h; b) HCl–MeOH (20%), reflux, 8 h.

cided to reduce azido-β-lactam **9** to the corresponding amino-β-lactam **13** (R = H). The reduction of azido-β-lactam **9** was successfully achieved by transfer hydrogenation using Pd/C and ammonium formate in methanol to afford amino-β-lactam **13** (R = H) in very good yield. The amino-β-lactam **13** (R = H) was further converted to the corresponding *N*-Cbz-derivative for the purpose of characterization. The amino-β-lactam **13** (R = H) was then transformed to *N*-benzyl derivative **14** in good yield by reacting with benzaldehyde followed by in situ reduction of the corresponding Schiff base with sodium borohydride. *N*-Benzylamino-β-lactam **14** was treated with methanolic HCl (20%) at room temperature to obtain the highly polar ring cleavage product, the dihydrochloride **15**. Our efforts to isolate the free base from the dihydrochloride **15** in pure form were unsuccessful. Therefore, the dihydrochloride **15** was directly reacted with triphosgene in the presence of triethylamine. Interestingly, a one-pot conversion of diamine to cyclic urea and hydroxymethylene to the corre-



Scheme 3 *Reagents and conditions*: a) NaN_3, DMF, 80 °C, 36 h; b) HCO_2NH_4, Pd/C (10%), MeOH, reflux, 45 min; c) CbzCl, $NaHCO_3$, acetone–H_2O (2:1), 1.5 h; d) i. PhCHO, $MgSO_4$, CH_2Cl_2, r.t., 12 h, ii. $NaBH_4$, MeOH, 0 °C to r.t., 2.5 h; e) HCl–MeOH (20%), r.t., 14 h; f) Et_3N, triphosgene, –20 °C, 2 h; g) aq KOH (2.5%), THF, 0 °C to r.t., 5 h.

sponding chloromethylene took place simultaneously to afford chloroester **16** in 65% yield (Scheme 3). The structure of **16** was established by spectral data and further confirmed by a single-crystal X-ray analyses (Figure 2). The conversion of the chloroester **16** to the desired (3*S*,6*R*)-1,3-dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (**1a**), was achieved by stirring with aqueous KOH (2.5%) in THF at room temperature for 5 h in 85% yield. The optical purity (ee >99%) was determined by chiral HPLC. The spectral data and the specific rotation were found to be identical with the reported values.[10e,n] The synthesis of D-(+)-biotin **2** from the lactone **1a** can be achieved by using a reported synthetic protocol.[11]

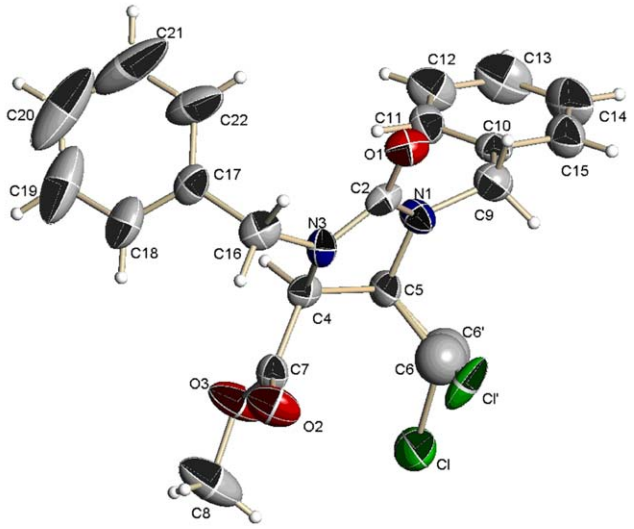


Figure 2 ORTEP diagram of **16**

In conclusion we have demonstrated the utility of azetidin-2-one as a synthon for the synthesis of the bicyclic lactone **1a**, an important intermediate in biotin synthesis. In this synthesis a crucial step is the azetidin-2-one ring opening followed by a one-pot conversion of diamine hydrochloride to cyclic urea and hydroxymehylene to chloromethylene by triphosgene to get the cyclic chloroester **16**. The starting β-lactam is also easily available in optically pure form and all the other steps of the synthesis are operationally simple and give very good yields.

^{1}H NMR and ^{13}C NMR Spectra were recorded in $CDCl_3$ solution on a Bruker AV 200 or Bruker AV 400 spectrometer and the chemical shifts are reported in ppm downfield from TMS for ^{1}H NMR spectra. IR spectra were recorded on Shimadzu FTIR-8400 using NaCl optics. Mass spectrometric measurements were carried out with electron spray ionization (ESI) on API QSTAR Pulsar mass spectrometer. Melting points were recorded on a Büchi Melting Point B 540 and were uncorrected. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 elemental analyzer. Petroleum ether (PE) used had boiling range 60–80 °C.

(3*R*,4*R*)-1-Benzyl-4-formyl-3-mesyloxyazetidin-2-one (7)
This compound was prepared by our earlier reported procedure;[9b] $[\alpha]_D^{30}$ +18 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1772, 1733 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.14 (s, 3 H), 4.20 (dd, *J* = 1.3, 5.4 Hz, 1 H), 4.31 (d, *J* = 14.7, 1 H), 4.70 (d, *J* = 14.7 Hz, 1 H), 5.66 (d, *J* = 5.3 Hz, 1 H), 7.12–7.31 (m, 5 H), 9.47 (d, *J* = 1.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 38.8, 46.1, 61.7, 78.4, 128.4, 128.8, 129.1, 133.4, 161.6, 195.6.

MS: *m*/*z* = 284 (M + 1).

Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94; S, 11.30. Found: C, 50.69; H, 4.56; N, 4.87; S, 11.19.

(3*R*,4*S*)-1-Benzyl-4-hydroxymethyl-3-mesyloxyazetidin-2-one (8)
To a cooled solution of **7**[9b] (1.43 g, 5.0 mmol) in MeOH (30 mL) at 0 °C, was added $NaBH_4$ (0.370 g, 10 mmol) portionwise under argon. The mixture was allowed to warm to r.t. and stirred for 3 h. After completion of the reaction (TLC), H_2O (10 mL) was added carefully and the mixture was further stirred for 1 h. MeOH was removed under reduced pressure and the residue was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography using acetone–PE (20:80) to afford alcohol **8** (1.18 g, 82%) as a white solid; mp 79–80 °C; $[\alpha]_D^{30}$ +7 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3458, 1751 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.90 (s, 1 H), 3.28 (s, 3 H), 3.81–3.91 (m, 3 H), 4.35 (d, *J* = 14.9 Hz, 1 H), 4.64 (d, *J* = 14.9 Hz, 1 H), 5.58 (d, *J* = 4.4 Hz, 1 H), 7.27–7.40 (m, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 38.9, 45.4, 57.9, 59.6, 78.5, 128.2, 128.3, 129.0, 134.6, 162.9.

MS: *m*/*z* = 286 (M + 1).

Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.51; H, 5.30; N, 4.92; S, 11.22. Found: C, 50.43; H, 5.17; N, 4.77; S, 11.04.

(3*S*,4*R*)-3-Azido-1-benzyl-4-hydroxymethylazetidin-2-one (9)
To a solution of **8** (0.6 g, 2 mmol) in anhyd DMF (20 mL) was added NaN_3 (0.650 g, 10 mmol) and stirred at 80 °C for 36 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The residue was diluted with EtOAc (200 mL) and washed with H_2O (4 × 20 mL) and brine (10 mL) successively. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography using acetone–PE (20:80) to afford 3-azido β-lactam **9** (0.380 g, 78%) as a white solid; mp 72–73 °C; $[\alpha]_D^{25.5}$ –228 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3392, 2102, 1731 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.79 (s, 1 H), 3.47–3.51 (m, 1 H), 3.67 (d, *J* = 3.3 Hz, 2 H), 4.33 (d, *J* = 15.2 Hz, 1 H), 4.52 (d, *J* = 14.9 Hz, 1 H), 4.56 (s, 1 H), 7.26–7.39 (m, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 44.7, 58.6, 60.2, 64.8, 128.0, 128.9, 134.5, 164.7.

MS: *m*/*z* = 233 (M + 1).

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.87; H, 5.21; N, 24.13. Found: C, 56.70; H, 5.17; N, 24.04.

(3*S*,4*R*)-3-Azido-4-(benzylamino)dihydrofuran-2(3*H*)-one (10)
3-Azido-4-hydroxymethyl azetidin-2-one (**9**; 0.5 g, 2.15 mmol) was dissolved in methanolic HCl (20%, 10 mL) and the mixture was stirred for 34 h at r.t. After the reaction was over (TLC), MeOH was removed under reduced pressure and sat. $NaHCO_3$ solution was added to the residue. It was then extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (10 mL). It was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residual thick oil was quickly purified by flash column chromatography using acetone–PE (20:80) as an eluent to furnish **10** (0.1 g, 20%) as a white solid; mp 143–144 °C (dec.); $[\alpha]_D^{30}$ –55.1 (*c* = 1.0, MeOH).

IR ($CHCl_3$): 3394, 2119, 1774 cm^{-1}.

^1H NMR (DMSO-d_6, 200 MHz): δ = 4.22–4.50 (m, 3 H), 4.53–4.80 (m, 1 H), 4.82 (d, *J* = 9.6 Hz, 1 H), 5.30 (d, *J* = 7.4 Hz, 1 H), 7.42–7.58 (m, 5 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 42.4, 49.5, 53.9, 69.8, 128.8, 128.9, 129.1, 130.4, 171.8.

MS: *m*/*z* = 233 (M + 1).

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.87; H, 5.21; N, 24.13. Found: C, 56.68; H, 5.14; N, 24.00.

(3*S*,4*R*)-3-Amino-1-benzyl-4-hydroxymethylazetidin-2-one (13, R = H)
A mixture of **9** (0.5 g, 2.16 mmol), ammonium formate (0.41 g, 6.47 mmol), 10% Pd/C (0.05 g) in MeOH (10 mL) was heated at reflux for 1 h. The mixture was filtered through a small pad of Celite and washed with EtOAc (2 × 10 mL). The solvent was removed under reduced pressure. The residue was diluted with EtOAc (50 mL) and washed with H_2O (2 × 5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford **13** (R = H) (0.34 g, 85%) as a white solid. The compound was unstable and the color changed to dark brown on keeping; mp 115–116 °C; $[\alpha]_D^{25}$ –60.28 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3332, 3271, 1739 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.10–2.22 (m, 3 H), 3.29 (br s, 1 H), 3.60 (d, *J* = 3.6 Hz, 2 H), 3.99 (br s, 1 H), 4.26 (d, *J* = 14.9 Hz, 1 H), 4.41 (d, *J* = 14.9 Hz, 1 H), 7.20–7.29 (m, 5 H).

MS: *m*/*z* = 207 (M + 1).

(3*S*,4*R*)-3-Amino(benzyloxycarbonyl)-4-hydroxymethylazetidin-2-one (13, R = Cbz)
To a solution of 3-amino azetidin-2-one **13** (R = H) (0.2 g, 0.97 mmol) in acetone–H_2O (8:2, 10 mL) was added $NaHCO_3$ (0.37 g, 3.88 mmol) portionwise. After complete addition, the mixture was stirred for 15 min and benzyl chloroformate (0.15 mL, 1.45 mmol) was slowly added. After completion of the reaction (1.5 h by TLC), acetone was removed under reduced pressure. The residue was dissolved in H_2O (5 mL), extracted with EtOAc (2 × 20 mL). The combined EtOAc extracts were washed with brine (5 mL). The organic layer was dried (Na_2SO_4) and the solvent was distilled off under reduced pressure to afford a crude product, which was purified by column chromatography using acetone–PE (20:80) to furnish pure **13** (R = Cbz) (0.27 g, 65%) as a colorless oil; $[\alpha]_D^{25.5}$ –14.47 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3415, 3332, 1747 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 3.48–3.63 (m, 3 H), 4.25 (d, *J* = 14.9 Hz, 1 H), 4.39–4.47 (m, 3 H), 5.63 (br s, 1 H), 4.99 (d, *J* = 12.2 Hz, 1 H), 5.06 (d, *J* = 12.2 Hz, 1 H), 7.19–7.26 (m, 10 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 45.0, 60.0, 60.5, 61.8, 67.3, 128.0, 128.1, 128.2, 128.5, 128.9, 135.2, 135.8, 156.2, 165.7.

MS: *m*/*z* = 341 (M + 1).

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.03; H, 5.93; N, 8.23. Found: C, 67.1; H, 5.83; N, 8.18.

(3*S*,4*R*)-3-Aminobenzyl-1-benzyl-4-hydroxymethylazetidin-2-one (14)
To a mixture of amine **13** (R = H) (0.38 g, 1.83 mmol) in anhyd CH_2Cl_2 (15 mL) was added activated $MgSO_4$ (0.4 g) and benzaldehyde (2.1 mL, 2.0 mmol) at 0 °C under argon. The mixture was then allowed to warm up to r.t. and stirred for another 10 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL) and $NaBH_4$ (0.08 g, 2.1 mmol) was added slowly at 0 °C with stirring. It was further stirred at the same temperature for 2.5 h. The mixture was poured into H_2O (5 mL) and extracted with EtOAc (2 × 20 mL). The organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to get the crude product, which was purified by silica gel column chromatography using EtOAc–PE (40:60) to afford pure **14** (0.46 g, 85%) as a colorless oil; $[\alpha]_D^{25}$ –57.56 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3404, 1737 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.95 (br s, 2 H), 3.37–3.43 (m, 1 H), 3.49–3.61 (m, 2 H), 3.84 (d, *J* = 13 Hz, 1 H), 3.94 (d, *J* = 13 Hz, 1 H), 4.02 (d, *J* = 1.9 Hz, 1 H), 4.36 (d, *J* = 15 Hz, 1 H), 4.48 (d, *J* = 15 Hz, 1 H), 7.27–7.38 (m, 10 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 44.8, 51.2, 60.4, 61.1, 66.6, 127.3, 127.9, 128.2, 128.3, 128.9, 129.1, 135.8, 139.0, 168.8.

MS: *m*/*z* = 297 (M + 1).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.81; N, 9.46. Found: C, 72.91; H, 6.78; N, 9.26.

(4*S*,5*R*)-1,3-Dibenzyl-5-chloromethyl-2-oxoimidazolidine-4-carboxylic Acid Methyl Ester (16)
A solution of methanolic HCl (20%, 12 mL) was added slowly to **14** (0.4 g, 1.18 mmol) and the mixture was stirred at r.t. for 14 h. The progress of the reaction was monitored by TLC. The solvent was completely removed under reduced pressure and the residue was taken up in anhyd THF (7 mL) and the suspension was cooled to –20 °C. Et_3N (0.86 mL, 6 mmol) was added to the mixture followed by a solution of triphosgene (0.361 g, 1.21 mmol) in anyhd THF (5 mL) over a period of 1 h. The mixture was then stirred further for 2 h at –20 °C. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (5 mL). It was extracted with EtOAc (2 × 10 mL) and washed with brine (5 mL). The organic layer was dried (Na_2SO_4) and the solvent was distilled off under reduced pressure to afford a crude product which was purified by column chromatography using EtOAc–PE (15:85) to furnish pure chloroester **16** (0.27 g, 65%) as a white crystalline solid; mp 85–86 °C; $[\alpha]_D^{25}$ +2.72 (*c* = 1.1, $CHCl_3$).

IR ($CHCl_3$): 1743, 1708 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 3.45–3.56 (m, 2 H), 3.66 (s, 3 H), 3.70–3.80 (m, 1 H), 3.91 (d, *J* = 11.1 Hz, 1 H), 3.95 (d, *J* = 14.9 Hz, 1 H), 4.12 (d, *J* = 15.7 Hz, 1 H), 4.79 (d, *J* = 15.7 Hz, 1 H), 4.97 (d, *J* = 14.9 Hz, 1 H), 7.13–7.30 (m, 10 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 40.51, 46.3, 46.6, 52.5, 55.8, 57.5, 127.8, 128.5, 128.8, 129.1, 136.0, 136.5, 159.8, 168.9.

MS: *m*/*z* = 373 (M + 1).

Anal. Calcd for $C_{20}H_{21}ClN_2O_3$: C, 64.49; H, 5.69; N, 7.55; Cl, 9.39. Found: C, 64.38; H, 5.49; N, 7.43; Cl, 9.21.

X-ray Crystal Data for 16
Single crystals of the compound were grown by slow evaporation of the solution mixture of CH_2Cl_2 and PE. Colorless needle of approximate size 0.40 × 0.09 × 0.04 mm, was used for data collection on

Bruker SMART APEX CCD diffractometer using MoK_α radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance 6.05 cm, 512 × 512 pixels/frame, multiscan data acquisition. Total scans = 5, total frames = 2142, oscillation/frame –0.3°, exposure/frame = 25.0 sec/frame, maximum detector swing angle = –30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.21 to 22.49°, completeness to θ of 22.49° is 99.8%. SADABS correction applied, $C_{20}H_{21}ClN_2O_3$, M = 372.84. Crystals belong to orthorhombic, space group $P2_12_12_1$, a = 5.7271(4), b = 13.1934(9), c = 25.7863(17) Å, V = 1948.4(2) Å^3, Z = 4, D_c = 1.271 mg m^{-3}, μ (MoKα) = 0.217 mm^{-1}, T = 293(2) K, 13315 reflections measured, 2553 unique [I > 2σ(I)], R value 0.0973, $wR2$ = 0.2043. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL)[12] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

X-ray crystal structure analysis revealed the stereochemistry of C4 and C5 carbon centers as 4*S* and 5*R*. The molecule has a disorder in the alkyl halide group attached to C5 carbon atom (Figure 2).

(3a*S*,6a*R*)-1,3-Dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (1a)

To a cooled solution of **16** (0.140 g, 0.393 mmol) in THF (4 mL) was added a solution of KOH (0.051 g, 0.78 mmol) in H_2O (2 mL). The mixture was stirred at r.t. for 5 h. The solvent was removed under reduced pressure and the residue was neutralized by adding aq HCl (20%) at 0 °C, stirred for 15 min and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by column chromatography using EtOAc–PE (15:85) to give lactone **1a** (0.107 g, 85%) as a white crystalline solid. The ee was determined to be 99.9% (HPLC conditions: Column: Daicel Chiralcel OD-H, 250 × 4.6 mm id; detector: UV set at λ = 254 nm; mobile phase: hexane: propan-2-ol, 7:3; flow rate: 0.5 mL/min; t_R: = 31.0 min); mp 118–119 °C (Lit.[10n] mp 120–121 °C); $[\alpha]_D^{25}$ +58.1 (c = 1.2, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ +58.2 (c = 1, benzene);[10n] $[\alpha]_D^{25}$ = +56.4 (c = 1.12, $CHCl_3$)[10e]].

IR ($CHCl_3$): 1782, 1703 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.84 (d, J = 8 Hz, 1 H), 4.02–4.07 (m, 3 H), 4.24 (d, J = 6.4 Hz, 1 H), 4.30 (d, J = 5.9 Hz, 1 H), 4.55 (d, J = 14.9 Hz, 1 H), 4.96 (d, J = 14.9 Hz, 1 H), 7.18–7.29 (m, 10 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 45.2, 46.9, 52.4, 54.4, 70.1, 127.8, 128.1, 128.2, 128.7, 128.8, 129.0, 135.9, 136.0, 158.2, 172.7.

MS: m/z = 323 (M + 1).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.68; H, 5.60; N, 8.59.

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