

# The first stereospecific synthesis of L-tetrahydrodipicolinic acid †; a key intermediate of diaminopimelate metabolism

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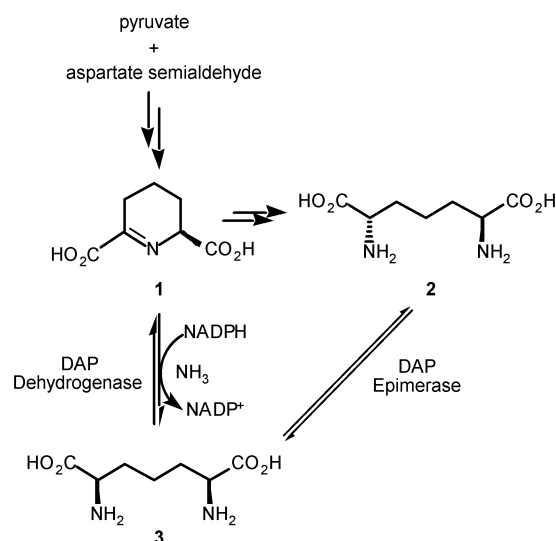
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L-Tetrahydrodipicolinic acid **1**, a key intermediate of diaminopimelate metabolism has been prepared in 6 steps and 23% overall yield from L-allylglycine **4**. The key step during this synthesis involves a base mediated cyclisation of dimethyl (2*RS*,6*S*)-2-[*N*-(benzyloxycarbonyl)-*N*-(*p*-tolylsulfonyl)amino]-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **8** to give (2*S*)-*N*-(benzyloxycarbonyl)-1,2,3,4-tetrahydropyridine-2,6-dicarboxylic acid **9**. <sup>1</sup>H NMR studies show this one pot transformation involves four steps; base elimination of toluene-*p*-sulfinic acid, intramolecular nucleophilic attack of the 6-benzyloxycarbonylamino group on the resulting imine, followed by hydrolysis of the esters and elimination of benzyl carbamate under acidic work-up to give the cyclic enamine **9**.

## Introduction

The recurring emergence of bacterial resistance to current antibiotics continues to stimulate strategies to disrupt microbial cell wall biosynthesis.<sup>1,2</sup> The peptidoglycan cell wall layer in bacterial cells provides numerous targets for further antibiotic development.<sup>3</sup> Crucially most bacteria require either lysine, or its biosynthetic precursor, *meso*-diaminopimelic acid (DAP), as the key cross-linking amino acid of the peptidoglycan cell wall layer. Since mammals lack the biosynthetic pathway to DAP and require L-lysine in their diet, there has been substantial interest in the specific inhibition of enzymes involved in this pathway.<sup>4</sup>

One of the key intermediates in the DAP biosynthetic pathway is L-tetrahydrodipicolinic acid (L-THDP) **1** which is formed in two steps from aspartate semialdehyde and pyruvate (Scheme 1). After formation of L-THDP **1** the pathway then



Scheme 1

splits into two main routes, both of which have been identified in different bacterial species.<sup>5</sup> The main route proceeds *via*

† The IUPAC name for tetrahydrodipicolinic acid is 2,3,4,5-tetrahydropyridine-2,6-dicarboxylic acid.

acylation of L-THDP **1**, followed by transamination and deacylation to give LL-DAP **2** which is then transformed to *meso*-DAP **3** using DAP epimerase. In the less common pathway, *meso*-DAP **3** is produced directly from L-THDP **1** by DAP dehydrogenase.

Although L-THDP **1** is a key intermediate in the DAP pathway, the only reliable source of this compound to date, is the oxidative deamination of *meso*-DAP **3** using DAP dehydrogenase.<sup>6</sup> Two synthetic methods have been reported for the synthesis of racemic THDP,<sup>7,8</sup> but there is as yet no reported stereoselective or stereospecific synthesis of L-THDP **1**.

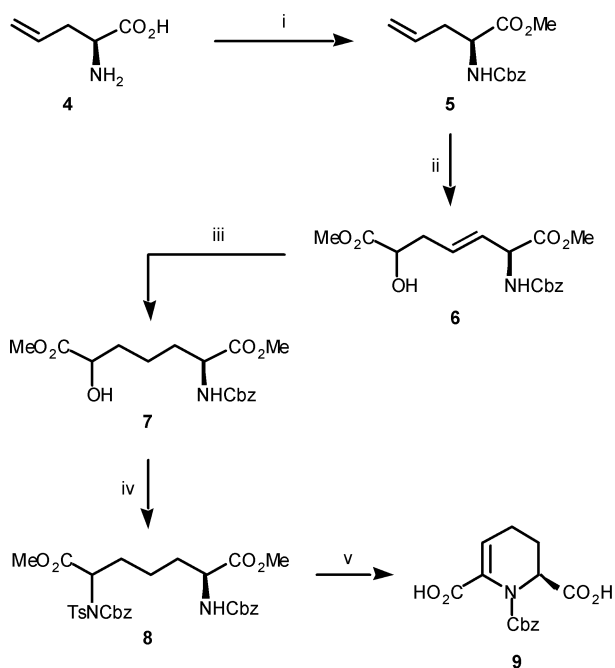
In the present study we report the first stereospecific synthesis of L-THDP **1** from L-allylglycine **4** in 6 steps and 23% overall yield. One of the key reactions during this synthesis involves an unusual one pot, four step formation of a tetrahydropyridine-2,6-dicarboxylate derivative. Examination of this reaction mechanism by <sup>1</sup>H NMR spectroscopy is also described.

## Results and discussion

The first stage of the synthesis required the efficient preparation of a fully protected diaminopimelic acid derivative. We sought to achieve this using an intramolecular ene reaction between a protected allylglycine and methyl glyoxylate,<sup>9</sup> followed by a Mitsunobu reaction using a nitrogen nucleophile.<sup>10</sup> Thus, commercially available L-allylglycine **4** was treated with chlorotrimethylsilane and methanol followed by triethylamine and benzyl chloroformate in a one pot process to give the protected derivative **5** in 91% yield (Scheme 2). Reaction of **5** with freshly distilled methyl glyoxylate (prepared by oxidation of dimethyl tartrate<sup>11</sup>) in the presence of tin tetrachloride at -78 °C afforded the ene adduct **6** as a 1 : 1 mixture of diastereomers in 79% yield.

Rhodium metal has been shown to catalyse the hydrogenation of double bonds without the hydrogenolysis observed with palladium.<sup>12</sup> Thus, ene adduct **6** was hydrogenated in the presence of a catalytic amount of 5% rhodium on carbon in ethyl acetate to give the saturated compound **7** in 86% yield (Scheme 2). Treatment of the saturated alcohol **7** with *N*-(benzyloxycarbonyl)toluene-*p*-sulfonamide<sup>13</sup> under standard Mitsunobu conditions gave the protected diaminopimelic acid derivative **8** in 75% yield.

The base mediated cyclisation of DAP derivative **8** was initially attempted using non-hydrolytic bases in an effort to

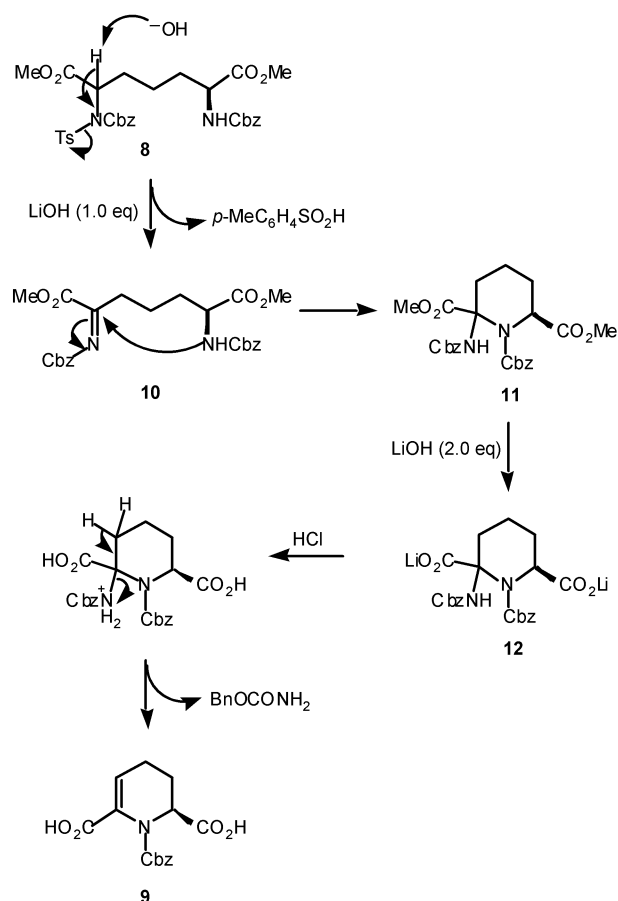


**Scheme 2** Reagents and conditions: i, a) TMSCl, MeOH, b) BnO-COCl, Et<sub>3</sub>N; ii, MeO<sub>2</sub>CCHO, SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; iii, H<sub>2</sub>, Rh/C, EtOAc; iv, TsNHCbz, DEAD, PPh<sub>3</sub>, THF; v, LiOH, MeCN, H<sub>2</sub>O.

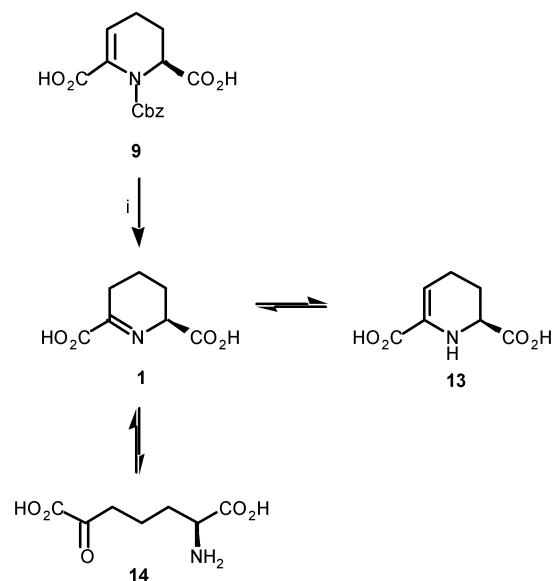
prepare the di-methyl ester analogue of **9**. It seemed that purification of such a compound might be more readily achieved than that of the corresponding di-acid derivative. However, attempted cyclisation using either diethylamine or sodium bis(trimethylsilyl)amide returned only starting material. Thus, DAP derivative **8** was treated with three equivalents of lithium hydroxide in aqueous acetonitrile. Purification of the reaction mixture by reversed phase HPLC gave the tetrahydropyridine-2,6-dicarboxylic acid derivative **9** in 76% yield (Scheme 2). The structure of this compound was confirmed by a HMQC NMR experiment, which showed coupling of the alkene proton signals (H-5) at 6.14 ppm to a carbon signal (C-5) at 123.9 ppm.

The success of this cyclisation reaction prompted an investigation of the mechanism by <sup>1</sup>H NMR spectroscopy. One equivalent of lithium hydroxide in D<sub>2</sub>O was added to a solution of the acyclic DAP derivative **8** in CD<sub>3</sub>CN and the reaction was monitored at specific intervals. After 1 hour, loss of the H-2 proton signals and the appearance of signals corresponding to toluene-*p*-sulfonic acid were observed. This suggested that the first step involved deprotonation of the H-2 proton by hydroxide followed by elimination of the tosyl group to give imine **10** (Scheme 3). This unstable *N*-acyl imine is then readily attacked by the 6-benzyloxycarbonylamino group to give the cyclic compound **11**. After 17 hours no further change was noted, hence a second equivalent of lithium hydroxide was added. This led to only partial hydrolysis of both esters and so the third equivalent of lithium hydroxide was added to yield the di-acid **12** after a further 6 hours. Subsequent exposure of the reaction mixture to a 20% solution of DCl in D<sub>2</sub>O resulted in the formation of benzyl carbamate and the cyclic enamine **9**. However, signals corresponding to the alkene proton (H-5) were not observed. This was attributed to deuterium exchange of the H-5 proton in the presence of the deuterated solvents. This was confirmed by repeating the reaction as described above, except that the deuterated solvents were removed before acidic work-up. As expected, the resulting <sup>1</sup>H NMR spectrum showed the presence of the H-5 signals at 6.14 ppm, demonstrating that elimination of benzyl carbamate to yield the cyclic enamine **9** is acid catalysed (Scheme 3).

The synthesis of L-THDP **1** was completed using a two step process as shown in Scheme 4. The di-lithium salt of cyclic enamine **9** was prepared using lithium hydroxide, which was



**Scheme 3**



**Scheme 4** Reagents and conditions: i, a) LiOH, MeOH, H<sub>2</sub>O, b) Li, NH<sub>3</sub> (l).

followed by reaction with lithium and liquid ammonia to give the target compound as an equilibrium mixture of tautomers in 66% yield after flash chromatography. The <sup>1</sup>H NMR spectrum showed the presence of L-THDP **1** along with its two equilibrium products,<sup>8</sup> enamine **13** and the acyclic keto acid **14** in a 1 : 1 : 1 mixture. The proton and carbon NMR signals of all three compounds were assigned using a combination of COSY, TOCSY, HMQC and HMBC NMR experiments.

The structure and stereochemistry of L-THDP **1** was further confirmed by incubation of the compound with NADPH and DAP dehydrogenase, which was isolated and purified from

the organism *Bacillus sphaericus* IFO 3525 as previously reported.<sup>6,14</sup> Monitoring of the reaction using a continuous spectrophotometric assay at 340 nm<sup>14</sup> showed consumption of the co-factor thus confirming that, as expected, the synthetic L-THDP **1** is a substrate for the enzyme and has the correct stereochemistry.

In summary, we have described the first stereospecific synthesis of L-THDP **1** in six steps from L-allylglycine **4**. This synthesis involves three key steps; an ene reaction using tin tetrachloride as the Lewis acid, a Mitsunobu reaction to insert the second nitrogen functionality and a lithium hydroxide mediated cyclisation. Deprotection of the resulting tetrahydropyridine-2,6-dicarboxylic acid **9**, gives the target compound **1** which is shown by <sup>1</sup>H NMR spectroscopy to be in equilibrium with the cyclic enamine **13** and the acyclic keto acid **14** as described by Robins and co-workers during their synthesis of racemic THDP.<sup>8</sup> The structure of the final product is confirmed by turnover of the DAP dehydrogenase enzyme using a UV spectrophotometric assay. Studies on the synthesis and interaction of other DAP analogues with enzymes in the pathway to L-lysine are currently in progress.

## Experimental

All reactions were done under dry Ar. All solvents were purified and distilled according to Perrin *et al.*<sup>15</sup> Progress of reactions was monitored by TLC on commercial silica gel plates (Merck 60F-254) using UV fluorescence, ninhydrin or potassium permanganate for visualization. Flash chromatography employed silica gel 60 (Silicycle, 230–420 mesh) and was performed according to the Still procedure.<sup>16</sup> HPLC separations were performed on a Beckman System equipped with a 166 variable wavelength UV detector and an Altex 210A injector. HPLC separations were monitored at a wavelength of 219 nm. Mps were determined on a Büchi apparatus using open-end capillary tubes and are uncorrected. NMR spectra were recorded on Inova Varian 300 and 500 MHz instruments. IR spectra were determined with a Nicolet Magna 750 FT-IR spectrometer. Mass spectra (MS) were recorded with either a Micromass ZabSpec Hybrid Sector-TOF instrument (electrospray ionization (ESI) or a MS-50 high resolution (HR) mass spectrometer (chemical ionization (CI) NH<sub>3</sub>). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 26 °C with a micro cell (100 mm; 0.9 cm<sup>3</sup>) or a standard cell (100 mm, 8 cm<sup>3</sup>) respectively. [ $\alpha$ ]<sub>D</sub> Values are given in units of 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. Microanalyses were completed at the University of Alberta Microanalytical Laboratory. All literature compounds had IR, <sup>1</sup>H NMR and mass spectra consistent with assigned structures. L-Allylglycine was purchased from Sigma-Aldrich and methyl glyoxylate was generated by standard literature procedures.<sup>11</sup>

### Methyl (2*S*)-2-[*N*-(benzyloxycarbonyl)amino]pent-4-enoate **5**

To a stirred suspension of L-allylglycine **4** (0.51 g, 4.35 mmol) in methanol (10 cm<sup>3</sup>) at 0 °C was added chlorotrimethylsilane (1.7 cm<sup>3</sup>, 13.05 mmol). After 2 h, the reaction mixture was warmed to room temperature and left stirring overnight. The reaction mixture was then cooled to 0 °C and triethylamine (2.5 cm<sup>3</sup>, 17.40 mmol) and benzyl chloroformate (0.91 g, 5.22 mmol) were added. After 3 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in 2 M hydrochloric acid (50 cm<sup>3</sup>) and extracted with ethyl acetate (2 × 40 cm<sup>3</sup>). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to leave a colourless oil. Purification by flash column chromatography, eluting with 30% ethyl acetate in hexane gave methyl (2*S*)-2-[*N*-(benzyloxycarbonyl)amino]pent-4-enoate **5** (1.06 g, 91%) as a colourless oil; [ $\alpha$ ]<sub>D</sub> +16.4 (*c* 4.0, CHCl<sub>3</sub>) [lit.<sup>14</sup> [ $\alpha$ ]<sub>D</sub> +15.3 (*c* 1.6, CHCl<sub>3</sub>)];  $\nu_{\max}$ (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3340 (NH), 1723 (ester C=O), 1525, 739, 698;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 2.38–2.62 (2H, m, 3-H<sub>2</sub>), 3.68 (3H, s, OMe), 4.45 (1H, dd, *J* 7.4

and 6.1 Hz, 2-H), 5.07–5.18 (4H, m, 5-H<sub>2</sub> and PhCH<sub>2</sub>), 5.32 (1H, d, *J* 8.0 Hz, NH), 5.67 (1H, m, 4-H), 7.22–7.39 (5H, m, Ph);  $\delta_{\text{C}}$  (75.5 MHz, CDCl<sub>3</sub>) 36.6 (C-3), 52.2 (OMe), 53.3 (C-2), 66.9 (PhCH<sub>2</sub>), 119.2 (C-5), 127.9, 128.1, 128.4 (aromatics), 132.0 (C-4), 136.2 (quaternary aromatic C), 155.7 (OCN), 172.1 (CO<sub>2</sub>Me); *m/z* (EI) 263.1155 (M<sup>+</sup>). C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> requires 263.1157.

### Dimethyl (2*RS*,6*S*)-2-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]hept-4-ene-1,7-dioate **6**

Tin tetrachloride (24.9 cm<sup>3</sup>, 212 mmol) was added to a solution of freshly distilled methyl glyoxylate (4.23 g, 47.9 mmol) in dichloromethane (65 cm<sup>3</sup>) at –55 °C. After 10 min, the reaction mixture was cooled to –78 °C and a solution of methyl (2*S*)-2-[*N*-(benzyloxycarbonyl)amino]pent-4-enoate **5** (5.23 g, 19.9 mmol) in dichloromethane (25 cm<sup>3</sup>) was added dropwise. The resulting white suspension was warmed to –25 °C and stirred for 5 h. The reaction mixture was then poured into 1 M hydrochloric acid (250 cm<sup>3</sup>) and extracted with dichloromethane (4 × 200 cm<sup>3</sup>). The combined organic layers were dried (NaSO<sub>4</sub>) and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography (40% ethyl acetate in hexane) to give the title compound **6** (5.5 g, 79%) as a colourless oil (Found: C, 57.75; H, 6.05; N, 3.85. C<sub>17</sub>H<sub>21</sub>NO<sub>7</sub> requires C, 58.1; H, 6.0; N, 4.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3355 (NH), 2953 (CH), 1738 (ester C=O), 1520, 1266;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 2.34–2.59 (2H, m, 3-H<sub>2</sub>), 3.72 (6H, s, 2 × OMe), 4.23 (1H, m, 2-H), 4.85 (1H, m, 6-H), 5.10 (2H, s, PhCH<sub>2</sub>), 5.60–5.65 (2H, m, NH and 5-H), 5.72–5.82 (1H, m, 4-H), 7.29–7.39 (5H, m, Ph);  $\delta_{\text{C}}$  (75.5 MHz, CDCl<sub>3</sub>) 36.9 (C-3), 52.5 (OMe), 52.7 (OMe), 55.5 (C-6), 67.0 (PhCH<sub>2</sub>), 69.8 (C-2), 128.0, 128.1, 128.5, 128.6 (C-4, C-5 and aromatics), 136.2 (quaternary aromatic C), 155.5 (OCN), 171.1, 174.4 (2 × CO<sub>2</sub>Me); *m/z* (EI) 351.1319 (M<sup>+</sup>). C<sub>17</sub>H<sub>21</sub>NO<sub>7</sub> requires 351.1318.

### Dimethyl (2*RS*,6*S*)-2-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **7**

A solution of dimethyl (2*RS*,6*S*)-2-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]hept-4-ene-1,7-dioate **6** (2.48 g, 7.07 mmol) in ethyl acetate (20 cm<sup>3</sup>) was treated with 5% rhodium on carbon (0.2 g) and stirred under hydrogen at atmospheric pressure for 2 d. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. Purification by flash column chromatography eluting with 40% ethyl acetate in hexane gave dimethyl (2*RS*,6*S*)-2-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **7** (2.15 g, 86%) as a colourless oil (Found: C, 57.8; H, 6.7; N, 3.95. C<sub>17</sub>H<sub>23</sub>NO<sub>7</sub> requires C, 57.8; H, 6.6; N, 4.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3354 (NH), 2953 (CH), 1737 (ester C=O), 1525, 740, 698;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.40–1.95 (6H, m, 3-H<sub>2</sub>, 4-H<sub>2</sub> and 5-H<sub>2</sub>), 2.75 (1H, br s, OH), 3.75 (3H, s, OMe), 3.76 (3H, s, OMe), 4.16 (1H, m, 2-H), 4.37 (1H, m, 6-H), 5.10 (2H, s, PhCH<sub>2</sub>), 5.36 (1H, br s, NH), 7.29–7.39 (5H, m, Ph);  $\delta_{\text{C}}$  (75.5 MHz, CDCl<sub>3</sub>) 20.6 (C-4), 32.3 (C-5), 33.6 (C-3), 52.4 (OMe), 52.6 (OMe), 53.7 (C-6), 67.1 (PhCH<sub>2</sub>), 70.1 (C-2), 128.1, 128.2, 128.6 (aromatics), 136.3 (quaternary aromatic C), 155.9 (OCN), 172.8, 175.4 (2 × CO<sub>2</sub>Me); *m/z* (EI) 353.1478 (MH<sup>+</sup>). C<sub>17</sub>H<sub>23</sub>NO<sub>7</sub> requires 353.1474.

### Dimethyl (2*RS*,6*S*)-2-[*N*-(benzyloxycarbonyl)-*N*-(*p*-tolylsulfonyl)amino]-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **8**

A solution of dimethyl (2*RS*,6*S*)-2-hydroxy-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **7** (2.17 g, 6.15 mmol) in THF (15 cm<sup>3</sup>) was added to a solution of triphenylphosphine (2.66 g, 10.1 mmol) and *N*-(benzyloxycarbonyl)toluene-*p*-sulfonamide (2.87 g, 9.4 mmol) in THF (25 cm<sup>3</sup>) at 0 °C. Diethyl azodicarboxylate (1.64 g, 9.4 mmol) was then added dropwise. After 5 h at room temperature, the reaction mixture was

concentrated *in vacuo*. The resulting residue was purified by flash column chromatography eluting with 25% ethyl acetate in hexane to give dimethyl (2*RS*,6*S*)-2-[*N*-(benzyloxycarbonyl)-*N*-(*p*-tolylsulfonyl)amino]-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **8** (2.95 g, 75%) as a colourless oil (Found: C, 59.6; H, 5.6; N, 4.3. C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>10</sub>S requires C, 60.0; H, 5.7; N, 4.4%);  $\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3360 (NH), 2952 (CH), 1735 (ester C=O), 1596, 1520, 1455, 1218;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.54 (2H, m, 4-H<sub>2</sub>), 1.82 (2H, m, 5-H<sub>2</sub>), 2.12 (2H, m, 3-H<sub>2</sub>), 2.35 (3H, s, CH<sub>3</sub>), 3.56 (3H, s, OMe), 3.74 (3H, s, OMe), 4.38 (1H, q, *J* 6.3 Hz, 6-H), 5.00–5.15 (5H, m, 2 × PhCH<sub>2</sub>O and 2-H), 5.40 (1H, br d, *J* 6.3 Hz, NH), 7.06–7.36 (12H, m, 2 × OCH<sub>2</sub>Ph, 3-CH and 3'-CH), 7.77 (2H, d, *J* 9.3 Hz, 2-CH and 2'-CH);  $\delta_{\text{C}}$  (75.5 MHz, CDCl<sub>3</sub>) 21.6 (CH<sub>3</sub>), 22.1 (C-4), 29.3 (C-5), 31.8 (C-3), 52.3 (OMe), 52.4 (OMe), 53.6 (C-6), 59.3 (C-2), 66.9, 69.1 (2 × OCH<sub>2</sub>Ph), 128.0, 128.4, 128.5, 128.9, 129.0 (aromatics), 134.2, 135.7, 136.3, 144.6 (4 × quaternary aromatic C), 151.3, 155.9 (2 × OCON), 169.9, 172.8 (2 × CO<sub>2</sub>Me); *m/z* (ES) 663.1993 (MNa<sup>+</sup>). C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>10</sub>SNa requires 663.1988.

### (2*S*)-*N*-(Benzyloxycarbonyl)-1,2,3,4-tetrahydropyridine-2,6-dicarboxylic acid **9**

A solution of lithium hydroxide monohydrate (0.21 g, 4.99 mmol) in water (5 cm<sup>3</sup>) was added to a solution of dimethyl (2*RS*,6*S*)-2-[*N*-(benzyloxycarbonyl)-*N*-(*p*-toluenesulfonyl)amino]-6-[*N*-(benzyloxycarbonyl)amino]heptane-1,7-dioate **8** (0.51 g, 1.61 mmol) in acetonitrile (10 cm<sup>3</sup>). After stirring for 8 h at room temperature, the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in water (10 cm<sup>3</sup>), extracted with ethyl acetate (2 × 15 cm<sup>3</sup>). The aqueous layer was acidified to pH 2 with 2 M hydrochloric acid (10 cm<sup>3</sup>) and extracted with ethyl acetate (2 × 15 cm<sup>3</sup>). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by reversed phase HPLC (C<sub>18</sub> Bondpak, gradient elution: 0–100% MeCN in water over 20 min) to afford (2*S*)-*N*-(benzyloxycarbonyl)-1,2,3,4-tetrahydropyridine-2,6-dicarboxylate **9** (0.18 g, 76%) as a white solid; mp 90–92 °C (from methanol);  $[\alpha]_{\text{D}}^{25}$  –66.7 (*c* 1.0, MeOH);  $\nu_{\max}$  (MeOH)/cm<sup>-1</sup> 3415 (OH), 2952 (CH), 1732 (C=O), 1716 (C=O), 1695 (C=C), 1455;  $\delta_{\text{H}}$  (300 MHz, CD<sub>3</sub>OD) 1.88–2.40 (4H, m, 3-H<sub>2</sub> and 4-H<sub>2</sub>), 5.00 (1H, dd, *J* 5.3, 2.7 Hz, 2-H), 5.11 (2H, 2 × d, *J* 12.8 Hz, PhCH<sub>2</sub>), 6.14 (1H, t, *J* 4.0 Hz, 5-H), 7.26–7.38 (5H, m, Ph);  $\delta_{\text{C}}$  (75.5 MHz, CD<sub>3</sub>OD) 21.4 (C-3), 27.2 (C-4), 58.1 (C-2), 69.1 (PhCH<sub>2</sub>), 123.9 (C-5), 128.7, 128.9, 129.0, 129.4 (aromatics), 135.1 (C-6), 137.3 (quaternary aromatic C), 155.9 (OCON), 170.0, 176.8 (CO<sub>2</sub>H); *m/z* (ES) 328.0793 (MNa<sup>+</sup>). C<sub>15</sub>H<sub>15</sub>NO<sub>6</sub>Na requires 328.0797.

### (2*S*)-2,3,4,5-Tetrahydrodipicolinic acid **1**

(2*S*)-*N*-(Benzyloxycarbonyl)-1,2,3,4-tetrahydropyridine-2,6-dicarboxylic acid **9** (0.088 g, 0.29 mmol) was dissolved in methanol (5 cm<sup>3</sup>) and a solution of lithium hydroxide monohydrate (0.024 g, 0.58 mmol) in water (1 cm<sup>3</sup>) was added. After 5 min, the reaction mixture was concentrated *in vacuo*. To the resulting residue was added predistilled liquid ammonia (15 cm<sup>3</sup>). The reaction mixture was then cooled to –78 °C and freshly cut lithium metal (0.025 g) was added until a blue colour persisted. After 15 min, water (3 cm<sup>3</sup>) was added and the reac-

tion mixture was warmed to room temperature. The reaction mixture was then acidified to pH 7 by the addition of 0.1 M hydrochloric acid (2 cm<sup>3</sup>) and concentrated *in vacuo*. The residue was then purified by flash column chromatography to remove trace impurities by eluting with 15% ammonia in isopropanol (propan-2-ol) to give the title compound **1** (0.033 g, 66%) as a white solid;  $\nu_{\max}$  (Nujol mull)/cm<sup>-1</sup> 3432 (NH), 2924 (CH), 2852 (OH), 1735 (C=O), 1641 (C=C), 1454, 1377, 1209;  $\delta_{\text{H}}$  (500 MHz, D<sub>2</sub>O) 1.70–1.88 (6H, m, 3-H<sub>2</sub> of imine, 4-H<sub>2</sub> of enamine, 4-H<sub>2</sub> of keto), 2.00–2.26 (6H, m, 4-H<sub>2</sub> of imine, 3-H<sub>2</sub> of enamine, 3-H<sub>2</sub> of keto), 2.42 (2H, m, 5-H<sub>2</sub> of imine), 2.55 (2H, t, *J* 7.4 Hz, 5-H<sub>2</sub> of keto), 4.10 (1H, dd, *J* 11.7, 3.1 Hz, 2-H of imine), 4.17 (1H, t, *J* 6.6 Hz, 2-H of keto), 4.46 (1H, dd, *J* 7.4, 5.1 Hz, 2-H of enamine);  $\delta_{\text{C}}$  (125 MHz, D<sub>2</sub>O) 21.6 (C-4 of enamine), 22.5 (C-3 of imine), 22.6 (C-4 of keto), 24.7 (C-4 of imine), 27.6 (C-3 of enamine), 27.8 (C-5 of imine), 31.9 (C-3 of keto), 35.8 (C-5 of keto), 55.6 (C-2 of keto), 57.5 (C-2 of enamine), 59.9 (C-2 of imine), 131.5 (C-5 of enamine), 149.3 (C-6 of enamine), 155.9 (C-6 of imine), 166.9, 169.3, 171.1, 174.2, 174.8, 180.5 (C=O), 204.1 (C-6 of keto); *m/z* (ES) 170.04467 (M – H). C<sub>7</sub>H<sub>8</sub>NO<sub>4</sub> requires 170.04478.

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