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Stereoselective Total Synthesis of (+)-Azimic Acid

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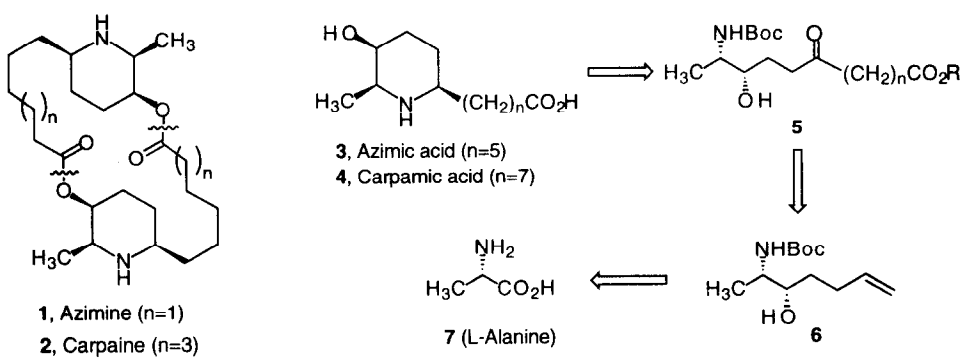
Abstract : An efficient synthesis of enantiopure (+)-azimic acid has been developed, utilizing easily available amino acid L-alanine as a chiral pool starting material.

Keywords : piperidine alkaloid; chiral pool; chelation control; stereoselection.

The piperidine alkaloids azimine (**1**)[1] and carpaine (**2**)[2] constitute a novel class of symmetrical macrocyclic dilactones, consisting of a pair of identical 2,3,6-trisubstituted piperidine moieties (Scheme 1). The structure and absolute configuration of **1** and **2** have been determined by spectroscopic and degradation studies.[1,2] The respective monomeric components, azimic acid (**3**) and carpamic acid (**4**) were thus found to be in an "all *cis*" (2*S*, 3*S*, 6*R*) absolute configuration. Besides the interesting structural features, these compounds and their synthetic analogues are also of pharmaceutical interest as they exhibit a wide range of biological activities.[3-5] Described herein is a chiral pool approach for the synthesis of (+)-azimic acid, starting from the amino acid L-alanine.[6]

Scheme 1



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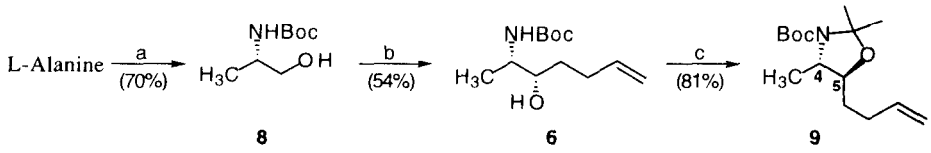
In recent studies from our laboratory we have demonstrated the versatility of chelation-controlled addition of various Grignard reagents to chiral α-amino aldehydes, toward stereoselective formation of the corresponding β-amino alcohols with high degree of *syn*-selection.[7] Thus, our retrosynthetic strategy for the present synthesis envisages initial building-up of the functionalized *syn*-1,2-amino alcohol fragment **6** with required stereochemistry, *via* chelation controlled addition of a suitable Grignard reagent to *N*-Boc-alaninal (Scheme 1). The strategically placed terminal alkene group of **6** can then be utilized towards formation of the pivotal ketoester intermediate **5**. Finally, intramolecular cyclodehydration involving the amine and the ketone functionalities followed by stereoselective hydrogenation of the resulting Δ^1-piperidine will complete the intended synthesis.

Results and Discussion

Accordingly, readily available amino acid L-alanine was converted to *N*-Boc-alaninol (**8**) by sequential reduction of the carboxylic group and Boc- protection of the amine (Scheme 2). Swern oxidation of **8** to the corresponding aldehyde and its *in-situ* reaction with (3-butenyl)magnesium bromide, following an established protocol,[7,8] afforded stereoselectively the *syn*-amino alcohol derivative **6** (*syn* : *anti* > 95 : 5). The high degree of *syn*-selectivity obtained is in accordance with the earlier observations and can be attributed to an effective chelation-controlled addition of the Grignard reagent to the aldehyde.[7,8] The assigned stereochemistry was further confirmed from the subsequent *N,O*-acetonide protected derivative **9**, where the observed coupling constant between the two ring protons ($J_{4,5}$ = 6.8 Hz) is indicative of their *trans*-relationship.

Scheme 2



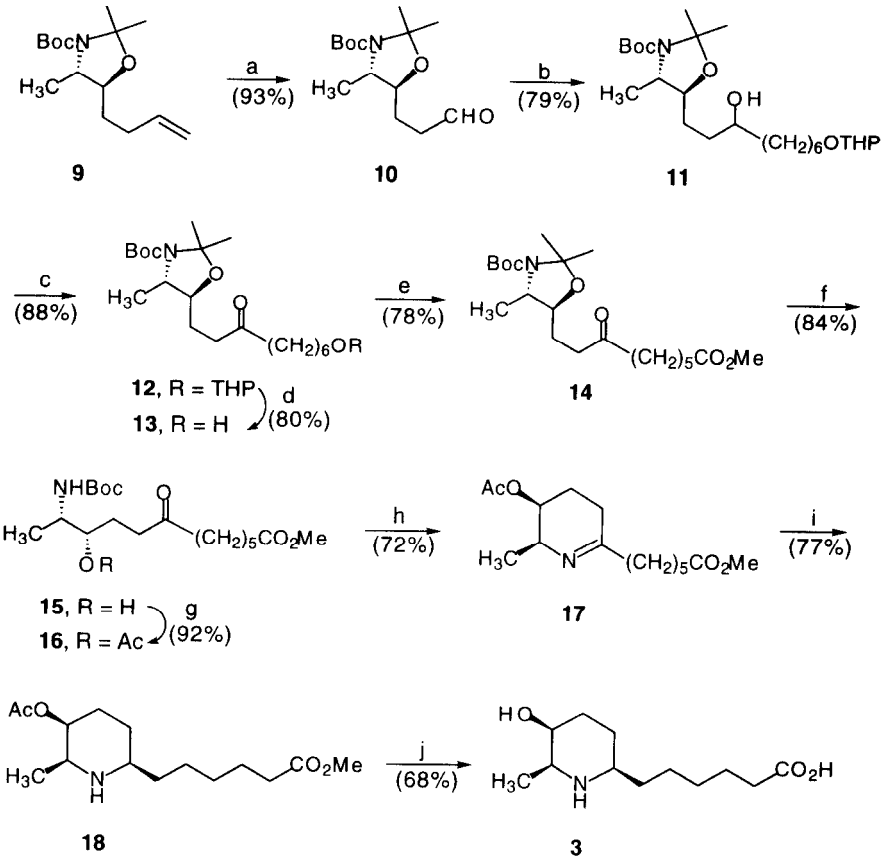
8 **6** **9**

a. $LiAlH_4$, THF then Boc_2O. **b.** Swern oxidn. then $H_2C{=}CH(CH_2)_2MgBr$. **c.** $Me_2C(OMe)_2$, PPTS.

Towards introducing the carboxylic acid side chain, oxidative degradation of the olefin moiety of **9** to the aldehyde **10** (Scheme 3) followed by its addition to the Grignard reagent derived from 6-bromo-1(2-tetrahydropyranyloxy)hexane cleanly afforded the adduct **11**. Oxidation of the resulting hydroxy group to the corresponding ketone **12** and removal of the THP-protecting group resulted in the hydroxy ketone **13**. Subsequent oxidation of the primary hydroxy group to carboxylic acid and its esterification with diazomethane under standard conditions led to the formation of the critical keto-ester derivative **14** in good overall yield. Unfortunately, attempted one-pot cyclization of **14** to the Δ^1-piperidine **17**, *via* simaltaneous deprotection of the acetonide and Boc- protecting groups and concomitant condensation involving the resulting free amine and ketone, afforded an intractable mixture of products. To circumvent this problem, in a step-wise sequence, initial hydrolysis of the acetonide and protection of the hydroxy group thus formed to its acetate derivative **16**, followed by unmasking of the amino group with 98% formic acid directly formed the expected Δ^1-piperidine derivative **17**. Catalytic

hydrogenation of **17** under standard conditions, afforded stereoselectively the saturated derivative **18** as the only product. The assigned stereochemistry at the newly created center was based on the assumption that hydrogenation

Scheme 3



a. OsO_4, NMO then $NaIO_4$ (impregnated on silica gel). **b.** $BrMg(CH_2)_6OTHP$. **c.** 2- Iodoxybenzoic acid. **d.** PTSA, EtOH. **e.** $RuCl_3.H_2O$, $NaIO_4$ then CH_2N_2, Et_2O. **f.** 80% AcOH-H_2O. **g.** Ac_2O, DMAP. **h.** HCO_2H, CH_2Cl_2. **i.** Pd-C, H_2. **j.** $N_2H_4.H_2O$, MeOH.

of the imine **17** will occur from the less hindered α-face of the molecule, resulting in the all *syn*- configuration.[6a] The above assumption was proved to be correct, when cleavage of the ester functionalities generated (+)-azimic acid (**3**), the specific rotation and spectral data of which were in good agreement with the reported values.

The above synthesis compares well with the earlier reported syntheses of enantiopure azimic acid[6] and offers an efficient alternative route to this novel class of piperidine alkaloids. The synthesis also corroborates the utility of chelation-controlled Grignard reactions on chiral α–amino aldehydes for the stereoselective formation of the structurally important *syn*-1,2-amino alcohol unit. The strategy and the approach described is of general

applicability and can be easily extended towards synthesizing carpamic acid (**4**),[11] and other related compounds[3] of structural and biological importance.[12]

Experimental Section

General. Reagents and solvents were obtained from commercial suppliers and used as received, unless otherwise noted. Moisture or air sensitive reactions were conducted under a nitrogen atmosphere in oven dried (120°C) glass apparatus. Diethyl ether and THF were distilled from sodium benzophenone ketyl prior to use. Toluene was dried over sodium, whereas dichloromethane and diisopropylethylamine were distilled from CaH_2 and stored over molecular sieves. All yields reported refer to isolated material judged to be homogeneous by tlc and NMR spectroscopy. Column chromatography was performed on silica gel 60 (60-120 mesh), using ethyl acetate/hexane mixture as eluent, unless specified otherwise. The NMR spectra were recorded in $CDCl_3$ on a 200 MHz spectrometer with TMS as the internal standard. Elemental analyses were carried out in the Indian Association for the Cultivation of Science, Jadavpur, Calcutta.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-propanol (8). L-Alanine (3.5 g, 39.3 mmol) was added in small portions to a suspension of lithium aluminium hydride (2.89 g, 76.26 mmol) in refluxing THF (125 mL) and refluxing continued for another 7 h. The reaction mixture was then cooled to 0°C (ice-bath) and excess reagent quenched by careful addition of an aqueous 15% NaOH solution (3 mL) and water (9 mL). After stirring at room temperature for 10 min, a solution of di-*tert*- butyl dicarbonate (8.31 g, 38.13 mmol) in CH_2Cl_2 (40 mL) was added to the mixture and stirred at 60°C for 6 h, cooled to room temperature, filtered through a pad of anhydrous Na_2SO_4 and the filtrate concentrated under vacuum. Purification of the oily residue by column chromatography (ethyl acetate/hexane = 1/3) afforded the pure *N*-Boc-amino alcohol **4** (4.8 g, 70%) as a white solid, similar in all respects to the commercially available sample (Aldrich Chemical Company, Inc.).

(5*S*, 6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-hydroxy-1-heptene (6). To a stirred solution of oxalyl chloride (3.2 mL, 36.86 mmol) in CH_2Cl_2 (50 mL) at -78°C under nitrogen atmosphere was added DMSO (3.5 mL, 49.14 mmol) dropwise. After stirring for 30 min, a solution of the amino alcohol **8** (4.3 g, 24.57 mmol) in CH_2Cl_2 (100 mL) was added to the reaction mixture over 30 min. The mixture was warmed to -35°C and stirred for 30 min at this temperature, followed by dropwise addition of diisopropylethyl amine (24.3 mL, 142.52 mmol) over 5 min. The reaction mixture was then warmed to 0°C in 15 min and transferred through a cannula to a room temperature solution of (3-butenyl)magnesium bromide [prepared from Mg (8.3 g, 345 g atom) and 4-bromobutene (23.3 g, 172 mmol) in ether (100 mL)] over 30 min. After stirring for 2 h at room temperature the reaction mixture was poured into aqueous saturated NH_4Cl solution (100 mL) and acidified to pH 4 by adding 10% aqueous HCl solution. The organic layer was separated, aqeous layer extracted with $CHCl_3$ (3x100 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4, solvent was removed under vacuum and the residue purified by flash column chromatography (ethyl acetate/hexane = 1/12) to yield the amino alcohol **6** (3.05 g, 54%) as a viscous semi solid: $[\alpha]_D$ = -10.2 (c=1, $CHCl_3$); IR (neat) 3405, 1691 cm^{-1}; ^1H NMR δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.45 (br s, 9H), 1.57 (m, 2H), 2.19 (m, 2H), 3.50 (m, 1H), 3.63 (m, 1H), 4.62 (br d, *J* = 8.2 Hz, 1H), 4.92-5.1 (m, 2H), 5.72-5.90 (m, 1H); ^{13}C NMR δ 158.2, 138.3, 114.8, 79.3, 74.1, 50.3,

33.2, 29.9, 28.3, 18.2; HRMS (FAB+) calcd. for $C_{12}H_{23}NO_3$: 229.1677 (M+); found 229.1684; Anal. Calcd for $C_{12}H_{23}NO_3$ (229.32): C, 62.85; H, 10.11; N, 6.11. Found: C, 63.07; H, 10.40; N, 6.28.

(4*S*, 5*S*)-2,2,4-Trimethyl-3-(*tert*-butoxycarbonyl)-5-(3-butenyl)-1,3-oxazolidine (9). A solution of **6** (1.25 g, 5.46 mmol), 2,2-dimethoxypropane (8.1 mL, 65.5 mmol) and a catalytic amount of pyridinium p-toluenesulfonate (30 mg) in toluene (25 mL) was stirred at 80°C for 4 h. Removal of solvent under vacuum and purification of the residue by column chromatography (ethyl acetate/hexane = 1/19) afforded the pure oxazolidine **9** (1.2 g, 81%) as a light yellow viscous liquid: $[\alpha]_D$ = +7.2 (c = 1, $CHCl_3$); IR (neat) 1698 cm^{-1}; ^1H NMR δ 1.25 (d, *J* = 6.4 Hz, 3H), 1.47 (br s, 9H), 1.55 (s, 6H), 1.66 (br q, *J* = 6.7 Hz, 2H), 2.0-2.3 (m, 2H), 3.35-3.58 (m, 1H), 3.63 (q, *J* = 6.8 Hz, 1H), 4.92-5.11 (m, 2H), 5.70-5.94 (m, 1H); ^{13}C NMR δ 152.3, 137.8, 114.8, 93.8, 80.7, 73.7, 57.8, 32.9, 28.8, 28.4, 26.6; HRMS (FAB+) calcd. for $C_{15}H_{27}NO_3$: 269.1990 (M+); found 269.1987.

(4*S*,5*S*)-5-(3-Hydroxy-9-tetrahydro-2H-2-pyranyloxynonyl)-2,2,4-trimethyl-3-(*tert*-butoxycarbonyl)-1,3-oxazolidine (11). To a stirred solution of the oxazolidine **9** (750 mg, 2.79 mmol) and N-methylmorpholine-N-oxide (60% aq. solution, 1.5 mL, 13.9 mmol) in acetone (5 mL) and water (1 mL) at room temperature was added a catalytic amount of OsO_4 solution in toluene (5% solution, 5 mol%). After stirring for 8 h, a saturated aqueous solution of Na_2SO_3 (5 mL) was added to the mixture and extracted with ethylacetate (3x50 mL). The combined extracts were dried over Na_2SO_4 and solvent removed thoroughly under vacuum affording the crude dihydroxylated compound (815 mg) which was dissolved in CH_2Cl_2 (15 mL) and added in one lot to a vigourously stirred suspension of $NaIO_4$ supported in silica gel (3.8 g, 20% $NaIO_4$)[9] in CH_2Cl_2 (15 mL) maintained at 0°C. After stirring at the same temperature for 1 h, the solid was removed by filtration, washed with $CHCl_3$ (3x25 mL), combined filtrate concentrated under vacuum and the residue filtered through a pad of silica gel column (ethyl acetate/hexane = 1/6) yielding the aldehyde **10** (712 mg, 93% two steps) as a viscous liquid. This aldehyde was found to decompose on storage and was used immediately for the next reaction.

To an ice-cooled solution of 1-[(tetrahydro-2H-pyran-2-yl)oxy]-6-hexylmagnesium bromide (4.96 mmol) {prepared from Mg (0.2 g, 8.3 g atom) and 2-[(6-bromohexyl)-oxy]-tetrahydro-2H-pyran (1.3 g, 4.96 mmol)}[10] in anhyd.THF (15 mL) was added dropwise over 15 min, a solution of the above aldehyde **10** (450 mg, 1.66 mmol) in THF (10 mL) under nitrogen atmosphere. The mixture was then stirred at room temperature for 2.5 h and poured into a saturated aqueous NH_4Cl solution (50 mL). The organic layer was separated, aqueous layer extracted with ethylacetate (2x50 mL), combined extracts washed with brine, dried (Na_2SO_4) and solvent removed under vacuum. The residue on chromatography (ethyl acetate/hexane = 1/7) afforded **11** (600 mg, 79%) as a colourless oil: IR (neat) 3405, 1686 cm^{-1}; ^1H NMR δ 1.29 (d, *J* = 6.8 Hz, 3H), 1.31-1.85 (m, 35H), 3.28-3.88 (m, 7H), 4.55 (br s, 1H); MS (FAB+) 480 (MNa^+), 456 (M^+-1).

(4*S*,5*S*)-5-(3-Oxo-9-tetrahydro-2H-2-pyranyloxynonyl)-2,2,4-trimethyl-3-(*tert*-butoxycarbonyl)-1,3-oxazolidine (12). To a room temperature solution of 2-iodoxybenzoic acid (1.8 g, 6.4 mmol) in DMSO (6 mL) was added a solution of the secondary alcohol **11** (1.2g, 2.57 mmol) in THF (10 mL) and stirred for 2 h. The reaction was quenched by addition of water (10 mL), the precipitated solid was filtered, filtrate extracted with ether (3x50 mL) and the combined extracts dried over Na_2SO_4. Evaporation of solvent and purification of the crude product by column chromatography (ethyl acetate/hexane = 1/8) afforded the pure ketone **12** (1.03 g , 88%) as a

colorless oily liquid: IR (neat) 1707, 1697 cm^{-1}; ^1H NMR δ 1.3 (d, J = 6.2 Hz, 3H), 1.35-1.42 (m, 4H), 1.45 (br s, 9H), 1.52-1.83 (m, 16H), 2.44 (t, J = 8.5 Hz, 2H), 2.52-2.62 (m, 2H), 3.30-3.56 (m, 4H), 3.61-3.90 (m, 4H), 4.58 (br s, 1H); MS (FAB+) 478 (MNa^+), 455 (M^+).

(4*S*, 5*S*)-(9-Hydroxy-3-oxynonyl)-2,2,4-trimethyl-3-(*tert*-butoxycarbonyl)-1,3-oxazolidine (13). To a room temperature solution of the ketone **12** (1.4 g, 3.07 mmol) in EtOH (20 mL), a catalytic amount of pyridinium p-toluenesulfonate (30 mg) was added and stirred for 12 h. To this mixture Et_3N (2 mL) was added, solvent removed under vacuum and the residue purified by column chromatography (ethyl acetate/hexane = 1/6) affording pure **13** (912 mg, 80%) as a viscous liquid: $[\alpha]_D$ = -3.4 (c = 1, $CHCl_3$); IR (neat) 3430, 1695 (br) cm^{-1}; ^1H NMR δ 1.28 (d, J = 6.1 Hz, 3H), 1.35 (m, 4H), 1.46 (br s, 9H), 1.50-1.64 (m, 10H), 1.71-1.98 (m, 2H), 2.42 (t, J = 7.1 Hz, 2H), 2.54 (m, 2H), 3.47 (m, 1H), 3.61 (t, J = 6.8 Hz, 2H), 3.89 (m, 1H) ; ^{13}C NMR δ 210.5, 152.0, 94.7, 80.3, 79.6, 62.4, 57.7, 55.3, 42.7, 38.4, 32.4, 28.9, 28.4, 26.9, 26.5, 25.5, 23.7; MS (FAB+) 372 (MH^+); Anal. Calcd for $C_{20}H_{37}NO_5$ (371.52): C, 64.66; H, 10.04; N, 3.77. Found: C, 64.28; H, 10.20; N, 4.12.

(4*S*, 5*S*)-(8-Methoxycarbonyl-3-oxooctyl)-2,2,4-trimethyl-3-(*tert*-butoxycarbonyl)-1,3-oxazolidine (14). A mixture of CCl_4 (4 mL), MeCN (4 mL), H_2O (6 mL) and $NaIO_4$ (2 g, 9.4 mmol) was stirred at room temperature for 15 min followed by addition of a catalytic amount of $RuCl_3.3H_2O$ (10 mg). The resulting solution was then added to the keto-alcohol **13** at 0°C and stirred for 1 h. After diluting with ether (25 mL), the precipitated solid was filtered, washed with ether (2x10 mL) and the filtrate extracted with ether (3x20 mL). The combined extract was dried (anhyd. Na_2SO_4) and concentrated thoroughly under vacuum. The residual acid was then dissolved into ether (10 mL) and subjected to esterification with excess diazomethane [prepared from NMU (2.3 g, 22.08 mmol), KOH (3.5 g in 7 mL of water)] in ether (30 mL) at -20°C. The mixture was allowed to attain room temperature and stirred for 4 h. Solvent was removed under vacuum and the residue column chromatographed (ethyl acetate/hexane = 1/6) affording the ester **14** (670 mg, 78%, two steps) as a colourless viscous liquid: $[\alpha]_D$ = +0.5 (c = 0.7, $CHCl_3$); IR (neat) 1740, 1695 cm^{-1}; ^1H NMR δ 1.28 (d, J = 6.2 Hz, 3H), 1.31 (m, 2H), 1.48 (br s, 12H), 1.49 (s, 3H), 1.51-1.74 (m, 5H), 1.82-2.0 (m, 1H), 2.29 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 6.7 Hz, 2H), 2.48-2.61 (m, 2H), 3.45 (br s, 1H), 3.62 (m, 1H), 3.68 (s, 3H); ^{13}C NMR δ 209.8, 173.8, 151.9, 93.9, 80.2, 79.4, 60.1, 57.6, 51.2, 42.4, 38.3, 28.4, 28.2, 26.9, 26.4, 24.4, 23.1; HRMS (FAB+) calcd. for $C_{21}H_{38}NO_6$: 400.2699 (MH^+); found 400.2672.

(10*S*, 11*S*)-Methyl-11-(*tert*-butoxycarbonylamino)-10-hydroxy-7-oxododecanoate (15). A solution of **14** (350 mg, 0.88 mmol) in 80% aqueous AcOH (12 mL) was stirred at room temperature for 18 h. Excess acetic acid was then removed under vacuum, the residue diluted with CH_2Cl_2 (25 mL), cooled to 0°C and neutralized to pH 7 by adding aqueous saturated $NaHCO_3$ solution. The layers were then separated, aqueous layer extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4 and removal of solvent under vacuum, the residue was column chromatographed (ethyl acetate/hexane = 1/3) to afford the pure amino alcohol **15** (264 mg, 84%) as a colorless liquid: $[\alpha]_D$ = -8.6 (c = 1, $CHCl_3$); IR (neat) 3440, 1740, 1711, 1695 cm^{-1}; ^1H NMR δ 1.16 (d, J = 7 Hz, 3H), 1.25-1.40 (m, 2H), 1.42 (br s, 9H), 1.52-1.76 (m, 6H), 2.31 (t, J = 7.3 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.50-2.65 (m, 2H), 3.09 (br s, 1H, exchangeable with D_2O), 3.43 (m, 1H), 3.58 (m, 1H), 3.65 (s, 3H), 4.75 (br d, J = 9.2 Hz, 1H, exchangeable with

D_2O); MS (FAB+) 359 (MH^+); Anal. Calcd for $C_{18}H_{33}NO_6$ (359.47): C, 60.14; H, 9.25; N, 3.89. Found: C, 60.33; H, 9.52; N, 4.07.

(10*S*, 11*S*)-Methyl-10-acetoxy-11-(*tert*-butoxycarbonylamino)-7-oxododecanoate (16). To an ice-cooled solution of **15** (230 mg, 0.64 mmol) in pyridine (2 mL), acetic anhydride (0.5 mL, 4.5 mmol) and a catalytic amount of DMAP (10 mg) was added followed by stirring at room temperature for 2 h. The reaction was quenched by addition of water (15 mL) and extracted with EtOAc (3x25 mL). Combined extracts were washed with brine, dried over Na_2SO_4 and solvent removed under vacuum. Column chromatography of the crude product (ethyl acetate/hexane = 1/7) afforded **16** (235 mg, 92%) as a colourless oil : $[\alpha]_D$ = -16.3 (c = 1, $CHCl_3$); IR (neat) 1738, 1710, 1697 cm^{-1}; ^1H NMR δ 1.10 (d, *J* = 7 Hz, 3H), 1.25-1.35 (m, 2H), 1.43 (br s, 9H), 1.52-1.61 (m, 4H), 1.72-1.93 (m, 2H), 2.06 (s, 3H), 2.31-2.48 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H), 3.65 (s, 3H), 3.85 (m, 1H), 4.48 (br d, *J* = 8.9 Hz, 1H), , 4.78 (m, 1H); MS (FAB+) 402 (MH^+).

Methyl 6-[(2*S*, 3*S*)-3-acetoxy-2-methyl-2,3,4,5-tetrahydro-6-pyridinyl]hexanoate (17). A solution of **16** (245 mg, 0.61 mmol) in CH_2Cl_2 (2 mL) was treated with 98% formic acid (2 mL) at 0°C, followed by stirring at room temperature for 6 h. Excess acid was removed under vacuum, the residue diluted with CH_2Cl_2 (25 mL), cooled to 0°C and neutralized to pH 7 by adding aqueous saturated $NaHCO_3$ solution. The layers were then separated, aqueous layer extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic extracts were washed with brine. After drying over Na_2SO_4 and removal of solvent under vacuum, the residue was column chromatographed (ethyl acetate/hexane = 1/2) to afford pure **17** (124 mg, 72%) as a viscous liquid: $[\alpha]_D$ = -18 (c = 1, $CHCl_3$); IR (neat) 1736, 1660 cm^{-1}; ^1H NMR δ 1.23 (t, *J* = 6.8 Hz, 3H), 1.39 (m, 2H), 1.51-1.75 (m, 4H), 2.06 (s, 3H), 2.22-2.35 (m, 6H), 2.72-2.95 (m, 2H), 3.65-3.78 (br s, 4H), 4.97-5.09 (m, 1H); ^{13}C NMR δ 173.8, 171.9, 170.3, 68.2, 54.1, 51.2, 39.6, 33.6, 28.5, 26.2, 25.2, 24.4, 22.7, 20.7, 17.3; CIMS 284 (MH^+); Anal. Calcd for $C_{15}H_{25}NO_4$ (283.38): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.21; H, 8.72; N, 5.24.

Methyl 6-[(2*S*, 3*S*, 6*R*)-5-acetoxy-2-methyl-6-piperipyridinyl]hexanoate (18). To a room temperature solution of the imine **17** (110 mg, 0.39 mmol) in MeOH (2 mL), 10% Pd-C (10 mg) was added and the mixture stirred under H_2 atmosphere for 6 h. The reaction mixture was filtered, the solid washed with MeOH (3x10 mL) and the combined filtrate concentrated under vacuum. The oily residue was column chromatographed (ethyl acetate) to afford pure piperidine **18** (86 mg, 77%) as a light yellow solid : mp = 117°-118°C; $[\alpha]_D$ = +17.2 (c = 1, MeOH); IR (neat) 3440, 1737 cm^{-1}; ^1H NMR δ 1.19 (d, *J* = 6.8 Hz, 3H), 1.26-1.45 (m, 4H), 1.53-1.72 (m, 7H), 2.01-2.11 (m, 1H), 2.19 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.91-3.08 (m, 1H), 3.24-3.36 (m, 1H), 3.58 (s, 3H), 4.54 (br s, 1H, exchangeable with D_2O), 4.98 (br s, 1H); ^{13}C NMR δ 173.9, 170.3, 68.5, 57.1, 54.7, 51.4, 33.8, 28.8, 28.1, 25.0; CIMS 286 (MH^+); Anal. Calcd for $C_{15}H_{27}NO_4$ (285.4): C, 63.13; H, 9.53; N, 4.91. Found: C, 63.47; H, 9.80; N, 5.25d.

(+)-Azimic acid (3). To a stirred solution of the piperidine **18** (60 mg, 0.21 mmol) in MeOH (3 mL) at room temperature was added hydrazine hydrate (3 mL) and stirring continued for 30 min. Solvent was removed under vacuum and the residue purified by column chromatography (MeOH/ethyl acetate = 1/24) to afford **3** (33 mg, 68%) as a light yellow solid : mp = 209°-211°C (dec) [lit.[6a] mp = 214-215°C]; $[\alpha]_D$ = +7.9 (c = 1.0, MeOH) [lit.[6a]

$[\alpha]_D$= +8 (MeOH)}]; IR (neat) 3410, 3250, 1657 cm^{-1}; ^1H NMR (CD_3OD) δ 1.26 (d,*J* = 6.5 Hz, 3H), 1.50-1.88 (m, 8H), 1.92-2.02 (m, 4H), 2.17 (br t, *J* = 6.7 Hz, 2H), 3.02 (br s, 1H), 3.18-3.28 (m, 1H), 3.82 (br s, 1H); ^{13}C NMR (CD_3OD) δ 169.3, 65.8, 58.5, 57.5, 34.4, 30.9, 29.7, 25.9, 23.5, 15.9; FABMS 229 (M+); Anal. Calcd for $C_{12}H_{23}NO_3$ (229.32): C, 62.85 ; H, 10.11; N, 6.11. Found: C, 63.12; H, 9.95; N, 6.38.

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References and Notes

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