Asymmetric Synthesis of (*S*)-4-Oxopipecolic Acid by a 3+3 Atom-Unit Assembly Strategy

Karolin Partogyan-Halim,[a] Laure Besson,[a] David J. Aitken,*[a,b] and Henri-Philippe Husson[a]

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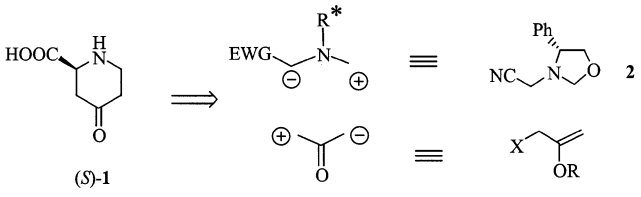
(*S*)-4-Oxopipecolic acid has been prepared in enantiomerically pure form from two readily accessible starting materials, (*R*)-*N*-(cyanomethyl)-4-phenyloxazolidine (**2**) and 2-(methoxymethoxy)allyl chloride, (**3**, MOM-allyl chloride). This strategy exploits the complementary electrophile/nucleophile reactivity at each end of this pair of 3-atom unit building blocks. Thus, alkylation of the anion of **2** with **3** (creation of the piperidine C-2–C-3 bond) followed by Lewis acid induced cyclisation (creation of the C-5–C-6 bond), leads principally to a bicyclic intermediate **5** which incorporates a protected form of the title compound. Subsequent chemical transformations lead to the target molecule in an overall yield of 20% for the five-step sequence.

Introduction

4-Oxopipecolic acid (**1**) is an unusual non-proteinogenic α-amino acid, present as its (*S*)-enantiomer in some naturally occurring cyclic depsipeptide antibiotics isolated from *streptomyces* strains.[1] Recently, it has also been used as an intermediate in the synthesis of protein tyrosine phosphatase modulators,[2] NMDA receptor antagonists,[3] and thrombin inhibitors.[4] As a consequence of its increasing biological interest and its close structural and synthetic relationships with the equally important 4-hydroxypipecolic acid[5] and other ring-substituted derivatives,[6] a number of synthetic strategies have been investigated for the racemic[7,8] and enantioselective[8–15] preparation of **1** in free or protected form. Some preparations of enantiomerically pure **1** have been achieved through chemical or enzymatic resolution of derivatives of the racemate.[8,9] Asymmetric synthesis strategies have included the use of nonracemic chiral auxiliaries in olefin/iminium cyclisations,[3b] nucleophilic additions to 1-acylpyridinium salts,[5a] [2+3] cycloadditions between methylenecyclopropane and a nitrone followed by thermal rearrangement of the resulting isoxazolidine,[10] or the construction of the piperidine ring from acyclic building blocks derived from the chiral pool.[11–14] However, satisfactory stereocontrolled construction of the 4-oxopipecolate skeleton remains a contemporary challenge.

We became interested in an unusual route to **1**, based on a 3+3 atom-unit assembly. This is not an obvious retrosynthetic analysis of pipecolic acid derivatives,[15] or indeed piperidines in general,[16] whether the planned synthesis be enantioselective or not; however, the approach seemed particularly well adapted for **1**, as Scheme 1 illustrates. Differential nucleophile/electrophile activity on either side of a chiral nitrogen synthon − effectively a chiral azomethine ylide − required complementary reactivity for each of the α-carbon atoms of an acetone equivalent. Previous work from our laboratory on chiral nonracemic *N*-(cyanomethyl)oxazolidines[17] suggested that compound **2** would be a useful candidate for the former fragment,[18] while an enol ether of an α-haloacetone appeared to be a convenient synthetic equivalent of the latter fragment. Encouraged by some preliminary studies on the use of such reagents for entry to piperidine derivatives,[19–21] we undertook the asymmetric synthesis of (*S*)-4-oxopipecolic acid [(*S*)-**1**] according to this strategy.



Scheme 1

[a] Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université René Descartes, Faculté des Sciences Pharmaceutiques et Biologiques,
4 avenue de l'Observatoire, 75270 Paris cedex 06, France
Fax: (internat.) + 33/(0)143291403
E-mail: husson@pharmacie.univ-paris5.fr
[b] Laboratoire SEESIB − CNRS UMR 6504, Département de Chimie, Université Blaise Pascal − Clermont-Ferrand II,
24 avenue des Landais 63177 Aubière cedex, France
Fax: (internat.) + 33/(0)473407717
E-mail: aitken@chisg1.univ-bpclermont.fr

Results and Discussion

A summary of the synthesis is presented in Scheme 2. After some reflection, we selected 2-(methoxymethoxy)allyl chloride (MOM-allyl chloride, **3**) as the acetone equivalent in the synthesis. Reagent **3** was prepared conveniently in high yield by using the literature procedure.[22] Deprotonation of *N*-(cyanomethyl)-4-phenyloxazolidine (**2**)[23] with LDA/HMPA at low temperature, and treatment of the resulting anion with **3**, gave a mixture of the two diastereoisomers **4a** and **4b** in a 71:29 ratio with an overall yield of 79%. All known previous alkylations of **2** by using this procedure[18,23−25] were known to give preferentially the (*S*) configuration at the new chiral centre and we assumed, for the time being, that this would also be the case for the major isomer **4a**. There was some circumstantial support for this assumption, in that the ^{1}H NMR spectrum of **4a** displayed a vicinal coupling constant of 2.5 Hz for the nonequivalent oxazolidine ring C-2 protons; this phenomenon had previously been observed for (*S*)-alkylated derivatives of **2**, while (*R*) isomers generally display a coupling constant of around 4.5 Hz.[23,24] Major isomer **4a** therefore possessed the correct configuration for the target molecule, and was separated from **4b** by standard chromatography before being used in the next step. In this respect, compound **3** was a more useful acetone equivalent than 2-methoxyallyl bromide, which leads to inseparable diastereomeric alkylation products in the alkylation of **2**.[19]

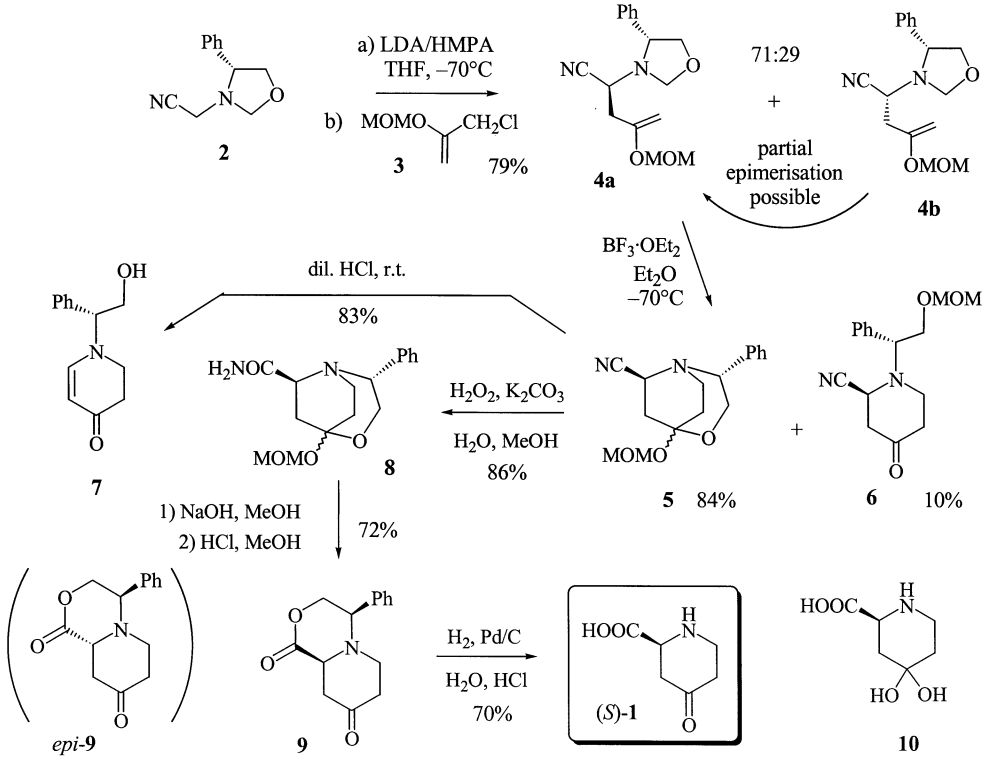
Although we did not exploit the minor isomer **4b** further in this work, it is interesting to note that it could be epimerised to an approximately 50:50 mixture of **4a/4b** by simple treatment with LDA/HMPA in THF at low temperature followed by a proton quench with ammonium chloride solution, with virtually quantitative recovery (Scheme 2). Thus, **4b** may be considered as material for potential recycling in this synthesis.

Cyclisation of **4a** required the generation of an iminium ion from the oxazolidine system, for which an oxophilic Lewis acid such as $BF_3{\cdot}Et_2O$ seemed appropriate. In the event, following low-temperature treatment of **4a** with this reagent, two piperidine-containing structures **5** and **6** were obtained, in yields which varied depending on the conditions. These results are presented in Table 1. The transformation was sluggish and starting material **4a** was partially recovered if the Lewis acid was not present in at least stoichiometric amounts, while a significant excess of the reagent increased the formation of **6**. Optimum formation of **5** was observed with 1.5 equiv. of the Lewis acid, and was slightly better in diethyl ether than in THF.

Table 1. Lewis acid mediated cyclisation of compound **4a**

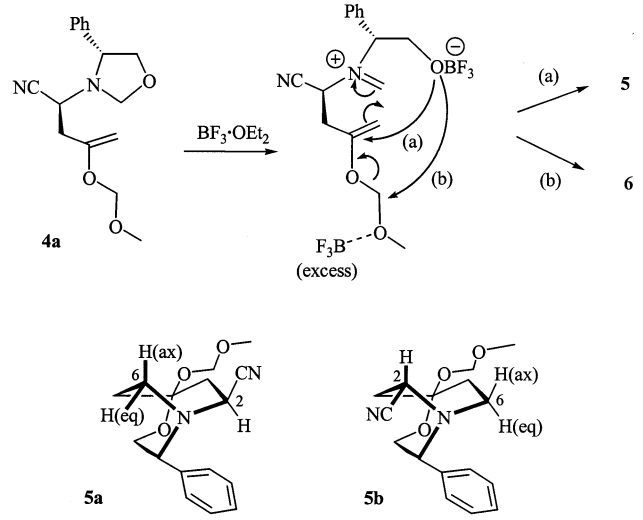
Equivs. $BF_3{\cdot}Et_2O$	Solvent	Yield of **5** [%]	Yield of **6** [%]
0.5	THF	36	12
1.5	THF	72	26
2.5	THF	38	62
1.5	Et_2O	84	10

We interpret the competition between formation of **5** and **6** in terms of the interactions shown in Scheme 3. BF_3-induced oxazolidine ring opening to give an iminium compound is followed smoothly by piperidine ring closure,



Scheme 2

which creates an electrophilic centre at C-4; this is conveniently trapped by the Lewis acid complexed oxygen atom (path a) to give the acetal system **5**. Alternatively, the Lewis acid complexed oxygen atom may attack the electrophilic acetal carbon atom of the MOM group, leading to a transfer of this acetal function to the phenylethoxy side chain (path b). This latter route becomes more favourable in the presence of excess Lewis acid which has an activating effect at the MOM centre. Two diastereomers of **5** were formed in a 1:1 ratio, as a result of nonselective ring closure to form the cyclic acetal, giving a mixture of epimers at the bridgehead carbon atom (C-4 of the piperidine system). The isomers could be separated by chromatography, and their ^{1}H NMR spectroscopic data are consistent with the structures **5a** and **5b** (Scheme 3). Structural analysis of these compounds was aided by examination of Dreiding models. In particular, the 2-H signal is shifted upfield in **5a** compared with that of **5b** (δ = 3.96 and 4.21 ppm, respectively) due to its proximity to the anisotropic cone of the phenyl group in the former isomer, while the inverse applies to the signal of 6-H(eq) (δ = 3.19 and 2.90 ppm, for **5a** and **5b**, respectively). Long-range W coupling (J = 2.0 Hz) was observed between 2-H and 6-H(eq) for **5a** only. These observations are consistent with complete retention of the (*S*) configuration at the piperidine C-2 chiral centre.



Scheme 3

Both **5** and **6** were final products under the reaction condition, i.e. no Lewis acid catalysed equilibration between the two structures was observed in control reactions. Since it seemed possible to influence the formation of one or the other structures from the above observations, and since both were potential candidates for continuation through to the target molecule **1**, we pondered for a while on which intermediate to favour. The decision came down principally to arguments of stability, for compound **6** was difficult to obtain pure and underwent degradation easily. We therefore focused our efforts on the bicyclic derivative **5**, despite the fact that an extra chiral centre had been temporarily created in this intermediate.

Mineral acid mediated hydrolysis of the acetal function of unseparated **5a/5b** mixtures was unfortunately accompanied by facile elimination of HCN, to give a good yield of the unstable (and unuseful) cyclic enaminone **7** (Scheme 2). To avoid this, it was decided to convert the nitrile into a carboxyl function prior to acetal hydrolysis. Basic hydrogen peroxide solution effected the smooth transformation of **5a/5b** into a mixture of amide epimers **8**. The product obtained in this way was sufficiently clean to be used directly in the next step, which was fortunate, since, remarkably, one of the two stereoisomers could not be eluted from a silica gel column. Successive base and then acid treatment of amide epimer mixture **8** completed the transformation of the carboxylate and liberated the 4-oxo function; the alcohol group freed in this process underwent spontaneous lactonisation with the carboxylic acid, finally giving a single bicyclic product **9** in 72% yield. The presence of the chiral benzylic amine type centre was the guarantee that **9** was enantiomerically pure and retained the (*S*) configuration at the C-2 centre. On one occasion, we detected a very small amount (about 3%) of the epimerised compound, *epi*-**9**, which was easily removed by chromatography.

The final step required removal of the chiral auxiliary to free the amino acid system, an operation which was achieved conveniently by hydrogenolysis of **9** in aqueous acid solution in the presence of palladium on charcoal. Target molecule (*S*)-**1** was thus obtained in 70% yield after passage through an ion-exchange resin, and has spectral and physicochemical properties identical with those indicated in the literature, notably $[\alpha]_D^{24} = -17$ (c = 1.0, H_2O) {ref.[8] $[\alpha]_D^{25} = -17$ (c = 1.0, H_2O)}. In both the solid state and in aqueous solution, (*S*)-**1** exists essentially as its hydrate **10**, as evidenced by NMR, IR spectroscopic and mass spectrometric data. This propensity for addition reactions at the C-4 ketone explains the need to carry out the final hydrogenolysis step in non-alcoholic aqueous solution; in the presence of methanol or ethanol as co-solvent, hemiacetal and acetal adducts are obtained.

In summary, this original 3+3 route compares well with previous asymmetric syntheses and gives the title compound reproducibly as a single enantiomer in just over 20% overall yield from the two readily available starting materials **2** and **3**. This figure does not take into account potential recycling of materials, notably the minor diastereomer **4b**. Since C-2- and C-α-substituted derivatives of compound **2** are accessible,[26] this strategy may turn out to be useful for the preparation of C-2- and/or C-6-substituted derivatives of the title product.

Experimental Section

General Remarks: Melting points were recorded with a Kofler hotplate and are uncorrected. Optical rotations were obtained using a Perkin−Elmer 141 MC polarimeter. NMR spectra were recorded with a Bruker AC-300 spectrometer operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C; chemical shifts (δ) are given in ppm and were measured with reference to residual solvent peaks, except for spectra recorded in D_2O, in which case dioxane was added as an

internal standard. IR spectra were obtained with a Perkin−Elmer 1600 Fourier transform instrument. Chemical ionisation mass spectra were recorded with a Nermag 10-10 instrument with ammonia as the vector gas. TLC was carried out using Merck silica gel 60 F_{254} aluminium foil plates (0.2 mm thickness); components were detected first under UV light then by staining with ethanolic phosphomolybdic acid solution. Preparative flash chromatography was carried out with 200−400 mesh silica gel (Merck Kieselgel 60 or SDS silica 60 ACC). Diethyl ether and THF were distilled under argon from sodium benzophenone ketyl. Diisopropylamine and HMPA were distilled under argon from CaH_2. Compounds **2**[23] and **3**[22] were prepared in high yields and purity according to literature procedures without any significant modifications. All other reagents and solvents were used as obtained from commercial sources without further purification.

Enol Ether 4: Under argon, a 2.2 M solution of *n*-butyllithium in hexane (13.4 mL, 29.5 mmol) was added to a solution of diisopropylamine (3.90 mL, 29.5 mmol) in THF (20 mL) at −40 °C. After stirring at this temperature for 15 min, the solution was cooled to −70 °C and HMPA (15.1 mL, 98.4 mmol) was added, followed by the dropwise addition of a solution of compound **2** (4.62 g, 24.6 mmol) in THF (10 mL). After 30 min, neat MOM-allyl chloride (**3**; 5.04 g, 36.9 mmol) was added dropwise. The mixture was stirred at −70 °C for a further 3 h, then a saturated aqueous solution of NH_4Cl (100 mL) was added and the mixture allowed to warm to room temp. The organic phase was collected and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. Flash chromatography of the residual oil with EtOAc/cyclohexane (1:9) gave complete separation of the two diastereomers **4a** (4.00 g, 56%) and **4b** (1.62 g, 23%).

Major Isomer (α*S*)-4a: Colourless oil. R_f = 0.61 (EtOAc/cyclohexane, 3:7). $[\alpha]_D^{24}$ = −214 (*c* = 1.0, CH_2Cl_2). MS: *m*/*z* = 289 $[MH]^+$. IR (film): $\tilde{\nu}$ = 2255 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.51 (d, *J* = 8.0 Hz, 2 H), 3.30 (s, 3 H), 3.67 (t, *J* = 8.2 Hz, 1 H), 3.96 (t, *J* = 8.0 Hz, 1 H), 4.02 (dd, *J* = 7.1, 8.3 Hz, 1 H), 4.14 (d, *J* = 2.3 Hz, 1 H), 4.28 (dd, *J* = 7.1, 7.9 Hz, 1 H), 4.31 (d, *J* = 2.4 Hz, 1 H), 4.50 (d, *J* = 2.5 Hz, 1 H), 4.79 (d, *J* = 6.2 Hz, 1 H), 4.84 (d, *J* = 2.5 Hz, 1 H), 4.91 (d, *J* = 6.2 Hz, 1 H), 7.27−7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 38.7 (CH_2), 49.4 (CH), 56.3 (CH_3), 65.4 (CH), 74.3 (CH_2), 82.3 (CH_2), 88.4 (CH_2), 93.9 (CH_2), 116.6 (Cq), 127.7 (CH), 128.4 (CH), 128.8 (CH), 137.2 (Cq), 154.5 (Cq) ppm. $C_{16}H_{20}N_2O_3$ (288.3): calcd. C 66.65, H 6.99, N 9.72; found C 66.71, H 6.81, N 9.71.

Minor Isomer (α*R*)-4a: Colourless oil. R_f = 0.54 (EtOAc/cyclohexane, 3:7). ^1H NMR ($CDCl_3$): δ = 2.20 (dd, *J* = 9.7, 14.0 Hz, 1 H), 2.35 (dd, *J* = 6.0, 14.0 Hz, 1 H), 3.49 (s, 3 H), 3.67 (dd, *J* = 6.5, 8.3 Hz, 1 H), 3.89 (d, *J* = 2.2 Hz, 1 H), 4.16 (dd, *J* = 6.0, 9.7 Hz, 1 H), 4.19 (d, *J* = 2.3 Hz, 1 H), 4.24 (dd, *J* = 6.8, 7.0 Hz, 1 H), 4.40 (m, 1 H), 4.56 (d, *J* = 4.4 Hz, 1 H), 4.74 (d, *J* = 4.4 Hz, 1 H), 4.90 (s, 1 H), 4.92 (s, 1 H), 7.11−7.49 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.1 (CH_2), 52.7 (CH), 56.2 (CH_3), 63.1 (CH), 75.0 (CH_2), 86.9 (CH_2), 88.4 (CH_2), 93.7 (CH_2), 117.8 (Cq), 126.8 (CH), 127.7 (CH), 128.6 (CH), 141.2 (Cq), 154.1 (Cq) ppm.

Cyclisation Products 5 and 6: Under argon, $BF_3{\cdot}Et_2O$ (2.90 mL, 23.0 mmol) was added dropwise to a stirred solution of (α*S*)-**4a** (4.42 g, 15.3 mmol) in diethyl ether (20 mL) at −70 °C. After stirring at this temperature for 1 h, a saturated aqueous solution of $NaHCO_3$ (40 mL) was added and the mixture allowed to warm to room temp. The organic phase was collected and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. Flash chromatography of the residual oil with EtOAc/cyclohexane (9:1) gave facile separation of a diastereomeric mixture **5a/5b** (ratio 1:1; 3.70 g, 84%) and **6** (0.44 g, 10%). In general, characterisation/identification of **5** was done on the diastereomeric mixture, which was used as such in the next step; on one occasion, the stereoisomers were separated by repeated flash chromatography for more detailed NMR analysis.

Mixture 5a/5b: Colourless oil. MS: *m*/*z* = 289 $[MH]^+$. IR (film): $\tilde{\nu}$ = 2242 cm^{-1}. $C_{16}H_{20}N_2O_3$ (288.3): calcd. C 66.65, H 6.99, N 9.72; found C 66.93, H 7.11, N 9.52. **Fast Isomer 5a:** R_f = 0.40 (EtOAc/cyclohexane, 3:7). ^1H NMR ($CDCl_3$): δ = 2.04 (ddd, *J* = 14.3, 10.1, 4.5 Hz, 1 H), 2.11 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.40 (dddd, *J* = 14.1, 10.5, 5.3, 3.7 Hz, 1 H), 2.64 (ddd, *J* = 14.4, 10.7, 3.6 Hz, 1 H), 3.19 (dddd, *J* = 15.1, 10.6, 4.4, 2.1 Hz, 1 H), 3.37 (s, 3 H), 3.70 (ddd, *J* = 15.3, 10.1, 5.4 Hz, 1 H), 3.86 (dd, *J* = 13.3, 7.9 Hz, 1 H), 3.96 (ddd, *J* = 10.7, 5.5, 2.0 Hz, 1 H), 4.18 (dd, *J* = 7.8, 5.1 Hz, 1 H), 4.36 (dd, *J* = 13.3, 5.1 Hz, 1 H), 4.75 (d, *J* = 7.3 Hz, 1 H), 4.93 (d, *J* = 7.3 Hz, 1 H), 7.21−7.48 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.4 (CH_2), 37.2 (CH_2), 42.4 (CH), 45.1 (CH_2), 55.7 (CH_3), 65.3 (CH_2), 67.4 (CH), 89.9 (CH_2), 100.2 (Cq), 120.2 (Cq), 126.8 (CH), 127.7 (CH), 128.8 (CH), 138.0 (Cq) ppm. **Slow Isomer 5b:** R_f = 0.35 (EtOAc/cyclohexane, 3:7). ^1H NMR ($CDCl_3$): δ = 1.81 (ddd, *J* = 15.6, 10.9, 5.1 Hz, 1 H), 2.31 (dddd, *J* = 15.4, 10.5, 4.5, 3.3 Hz, 1 H), 2.42 (dd, *J* = 14.0, 9.8 Hz, 1 H), 2.59 (ddd, *J* = 14.0, 10.9, 3.2 Hz, 1 H), 2.90 (ddd, *J* = 15.2, 10.9, and 4.5 Hz, 1 H), 3.11 (ddd, *J* = 15.3, 10.6, 5.2 Hz, 1 H), 3.38 (s, 3 H), 3.96 (dd, *J* = 13.0, 10.3 Hz, 1 H), 4.21 (dd, *J* = 9.8, 7.3 Hz, 1 H), 4.31 (dd, *J* = 13.0, 4.7 Hz, 1 H), 4.58 (dd, *J* = 10.2, 4.6 Hz, 1 H), 4.75 (d, *J* = 7.2 Hz, 1 H), 4.96 (d, *J* = 7.2 Hz, 1 H), 7.21−7.48 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.6 (CH_2), 41.2 (CH_2), 41.4 (CH), 48.4 (CH_2), 55.8 (CH_3), 62.5 (CH), 64.9 (CH_2), 90.0 (CH_2), 99.5 (Cq), 119.4 (Cq), 126.8 (CH), 127.5 (CH), 128.6 (CH), 138.4 (Cq) ppm.

Oxopiperidine Derivative 6: Pale yellow oil. R_f = 0.24 (EtOAc/cyclohexane, 3:7). MS: *m*/*z* = 289 $[MH]^+$. IR (film): $\tilde{\nu}$ = 2348, 1723 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.49 (m, 2 H), 2.67 (m, 2 H), 2.99 (dt, *J* = 11.8, 2.9 Hz, 1 H), 3.25 (s, 3 H), 3.69 (m, 1 H), 3.78−3.84 (m, 2 H), 3.89−3.98 (m, 2 H), 4.58 (s, 2 H), 7.30−7.48 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.6 (CH_2), 43.3 (CH_2), 45.6 (CH_2), 51.7 (CH), 55.4 (CH_3), 67.0 (CH), 70.1 (CH_2), 96.5 (CH_2), 115.6 (Cq), 127.8 (CH), 128.4 (CH), 129.0 (CH), 138.9 (Cq), 204.0 (Cq) ppm. $C_{16}H_{20}N_2O_3$ (288.3): calcd. C 66.65, H 6.99, N 9.72; found C 66.43, H 6.81, N 9.74.

Cyclic Enaminone 7: A 0.1 M aqueous hydrochloric acid solution (5 mL) was added to a solution of **5a/5b** mixture (240 mg, 0.83 mmol) in dioxane (2 mL). After stirring at room temp. for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. Flash chromatography of the residual oil with EtOAc/MeOH (9:1) gave the single product **7** (150 mg, 83%) as a yellow oil which degraded rapidly with time. R_f = 0.34 (EtOAc/MeOH, 9:1). MS: *m*/*z* = 218 $[MH]^+$. IR (film): $\tilde{\nu}$ = 3366, 1575 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.37 (m, 2 H), 3.21 (dt, *J* = 13.2, 6.7 Hz, 1 H), 3.28 (m, 1 H), 3.86 (m, 2 H), 4.41 (dd, *J* = 7.3, 5.6 Hz, 1 H), 4.85 (d, *J* = 7.4 Hz, 1 H), 7.18 (d, *J* = 7.4 Hz, 1 H), 7.21−7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.4 (CH_2), 44.9 (CH_2), 69.6 (CH), 61.8 (CH_2), 97.9 (CH), 127.2 (CH), 128.6 (CH), 129.1 (CH), 136.4 (Cq), 154.3 (CH), 192.2 (Cq) ppm.

Amide Diastereoisomers 8: A solution of a **5a/5b** mixture (1.46 g, 4.76 mmol) in methanol was treated with solid K_2CO_3 (0.37 g,

2.67 mmol) followed by 30% hydrogen peroxide solution (2.4 mL, 19.0 mmol). After stirring at room temp. for 10 min, the mixture was heated at 40 °C for 24 h. The mixture was then concentrated by evaporation of methanol under reduced pressure, then diluted with brine (10 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure to give a mixture of epimers of **8** as a viscous oil (1.25 g, 86%), sufficiently pure for use directly in the next step. Attempted flash chromatography with EtOAc/cyclohexane (7:3) was inefficient and wasteful, since one epimer could not be eluted from the column. MS: *m*/*z* = 307 $[MH]^+$. IR (CH_2Cl_2): $\tilde{\nu}$ = 3497, 1682 cm^{-1}. **Mobile Isomer:** R_f = 0.35 (EtOAc/cyclohexane, 7:3). ^1H NMR ($CDCl_3$): δ = 1.89 (ddd, *J* = 13.7, 10.0, 4.0 Hz, 1 H), 2.31 (m, 1 H), 2.45 (d, *J* = 8.3 Hz, 2 H), 3.12 (m, 1 H), 3.30 (ddd, *J* = 15.4, 10.1, 5.8 Hz, 1 H), 3.40 (s, 3 H), 3.58 (t, *J* = 8.4 Hz, 1 H), 3.97−4.13 (m, 2 H), 4.28 (dd, *J* = 12.0, 3.9 Hz, 1 H), 4.80 (d, *J* = 7.1 Hz, 1 H), 4.91 (d, *J* = 7.1 Hz, 1 H), 6.96 (d, *J* = 4.1 Hz, 1 H), 7.08 (d, *J* = 4.3 Hz, 1 H), 7.18−7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 32.8 (CH_2), 34.3 (CH_2), 45.1 (CH_2), 52.9 (CH), 55.3 (CH_3), 65.7 (CH_2), 67.4 (CH), 89.6 (CH_2), 100.8 (Cq), 126.7 (CH), 127.2 (CH), 128.4 (CH), 139.2 (Cq), 175.8 (Cq) ppm. **Non-eluting Isomer:** ^1H NMR ($CDCl_3$): δ = 1.26 (m, 2 H), 2.32 (d, *J* = 9.3 Hz, 2 H), 2.80 (m, 1 H), 3.11 (m, 1 H), 3.37 (s, 3 H), 3.70 (m, 2 H), 4.09 (m, 2 H), 4.55 (d, *J* = 6.9 Hz, 1 H), 4.98 (d, *J* = 6.9 Hz, 1 H), 6.48 (br. s, 1 H), 6.57 (br. s, 1 H), 7.20−7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.8 (CH_2), 38.0 (CH_2), 43.5 (CH_2), 55.7 (CH_3), 59.7 (CH), 62.6 (CH_2), 65.7 (CH), 90.0 (CH_2), 100.7 (Cq), 126.2 (CH), 127.3 (CH), 128.7 (CH), 138.7 (Cq), 172.8 (Cq) ppm.

Lactone 9: A 1 M NaOH solution (10 mL) was added to a solution of amide **8** as a mixture of epimers (1.11 g, 3.61 mmol) in MeOH (20 mL) and the mixture was stirred at room temp. for 18 h. The mixture was then concentrated by evaporation of methanol under reduced pressure, and 6 M HCl was added dropwise until pH = 1 was reached. MeOH (2 mL) was then added and the mixture was stirred at room temp. for 18 h. After this time, the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. Flash chromatography of the residual oil with EtOAc/cyclohexane (3:7) gave the lactone **9** which was recrystallised from diisopropyl ether (0.64 g, 72%). M.p. 141 °C (diisopropyl ether). R_f = 0.25 (EtOAc/cyclohexane, 3:7). $[\alpha]_D^{24}$ = −148 (*c* = 1.0, CH_2Cl_2). MS: *m*/*z* = 246 $[MH]^+$. IR (film): $\tilde{\nu}$ = 1725, 1713 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.12 (dd, *J* = 12.3, 2.6 Hz, 1 H), 2.30 (d, *J* = 15.2 Hz, 1 H), 2.51 (m, 1 H), 2.74 (dd, *J* = 15.3, 12.4 Hz, 1 H), 3.08 (m, 2 H), 3.37 (dd, *J* = 12.2, 3.0 Hz, 1 H), 3.76 (dd, *J* = 10.7, 3.5 Hz, 1 H), 4.30 (dd, *J* = 11.2, 3.5 Hz, 1 H), 4.43 (dd, *J* = 10.7, 11.2 Hz, 1 H), 7.30−7.41 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.7 (CH_2), 43.0 (CH_2), 50.5 (CH_2), 62.3 (CH), 63.8 (CH_2), 72.8 (CH), 128.1 (CH), 129.2 (CH), 129.3 (CH), 135.4 (Cq), 167.6 (Cq), 205.7 (Cq) ppm. $C_{14}H_{15}N_2O_3$ (245.3): calcd. C 68.56, H 6.16, N 5.71; found C 68.44, H 6.16, N 5.97. In one run, traces of a second component were isolated during the chromatography, for which the structure *epi*-**9** was proposed on the basis of ^1H NMR spectroscopic data. ^1H NMR ($CDCl_3$): δ = 2.31 (dt, *J* = 15.1, 4.1 Hz, 1 H), 2.49 (ddd, *J* = 15.1, 10.2, 5.5 Hz, 1 H), 2.68 (ddd, *J* = 12.7, 10.2, 4.0 Hz, 1 H), 2.83 (d, *J* = 7.9 Hz, 2 H), 3.18 (ddd, *J* = 12.7, 5.5, 4.5 Hz, 1 H), 3.86 (t, *J* = 7.9 Hz, 1 H), 4.19 (dd, *J* = 7.0, 4.3 Hz, 1 H), 4.50 (dd, *J* = 11.3, 7.0 Hz, 1 H), 4.64 (dd, *J* = 11.3, 4.3 Hz, 1 H), 7.38 (m, 5 H) ppm.

(*S*)-4-Oxopipecolic Acid Hydrate (10): Lactone **9** (230 mg, 0.93 mmol) was dissolved in 1 M HCl (2 mL) and 10% Pd/C (90 mg) was added. The mixture was stirred vigorously under hydrogen (1 atm) for 4 h. The catalyst was removed by filtration through a plug of Celite, which was washed copiously with water. The filtrate was concentrated to dryness under reduced pressure and the pale yellow solid residue was dissolved in a minimum of water and the solution applied to a column of Dowex 50X8−100 ion exchange resin (H^+ form). The column was eluted with water until the eluent was neutral; subsequent elution with 1 M NH_4OH solution and concentration of the eluent gave the title compound as a white amorphous solid, isolated as its hydrate form **10** (105 mg, 70%). $[\alpha]_D^{24}$ = −17 (*c* = 1.0, H_2O). MS: *m*/*z* = 162 $[MH]^+$. IR (nujol): $\tilde{\nu}$ = 3415, 1625 cm^{-1}. ^1H NMR (D_2O): δ = 1.59−1.78 (m, 3 H), 2.10 (m, 1 H), 2.89 (dd, *J* = 12.9, 4.0 Hz, 1 H), 3.17 (dd, *J* = 12.9, 4.0 Hz, 1 H), 3.49 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.0 (CH_2), 39.3 (CH_2), 43.6 (CH_2), 57.3 (CH), 93.3 (Cq), 173.3 (Cq) ppm.

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