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Preparation of Enantiopure 4-Oxygenated Pipecolic Acid Derivatives

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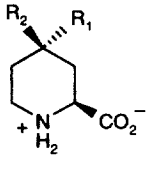
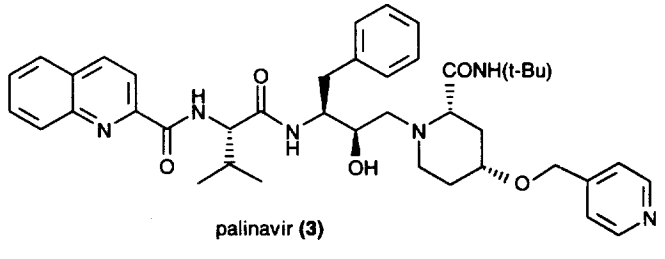
Abstract: Two approaches to enantiopure 4-oxo- and 4-(*R*)-hydroxypipecolic acid derivatives from protected L-aspartic acid were developed. The first route exploits an intramolecular Michael addition on the stable enaminone **8**. Hydrogenation and concomitant decarboxylation gave the 4-oxo derivative **11** which was reduced selectively to the 4-(*R*)-hydroxy derivative **12**. The second route starts with a Michael addition followed by an intramolecular Dieckmann condensation to build the piperidine ring. The 4-oxo derivatives **11** and **19** are thus obtained in an expeditious manner on large scale without any chromatographic purification. Both sequences proved to be highly stereoselective.

Introduction

Pipecolic acid derivatives oxygenated at the 4-position are naturally occurring, nonproteogenic α-amino acids. The 4-oxo derivative **1** is a constituent of peptidolactone antibiotics isolated from *streptomyces* strains (1). Studies have shown that its biosynthetic pathway originates from lysine in *streptomyces virginae* (2). The 4-*R*-hydroxy derivative **2** can be found in the leaves of *Calliandra pittieri* and *Strophantus scandeus* (3) and is also found incorporated in the cyclodepsipeptide virginiamycin S_2 (4). Syntheses of protected **1**, **2** and derivatives in both racemic (5) and optically pure (6) form have been previously reported. These amino acids have also been used as synthetic intermediates in the preparation of potential therapeutic agents such as NMDA agonists (5cd) and an antagonist (6b).



1: R_1=R_2=O
2: R_1=H, R_2=OH



palinavir **(3)**

Our interest in these molecules originated from our involvement in a program targeting the inhibition of the human immunodeficiency virus (HIV) protease. Several series of compounds were investigated and in the most promising series, palinavir **(3)** (7) was the lead compound. A *R*-hydroxyethylamine transition state mimic (8) and a novel *cis*-4-hydroxypipecolic acid derived moiety were incorporated in its structure. Although our laboratories have published a practical

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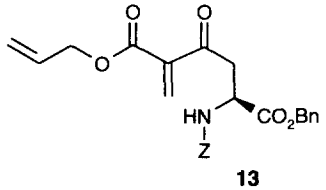
route to **2** which relies on an iminium ion cyclization (9), we wish to communicate two new stereospecific approaches to derivatives of **1** and **2**, one of which is rather expeditious and well-adapted for large scale preparation of compounds with either oxidation state at C-4.

Results and Discussion

Appealing starting materials for the synthesis of these oxygenated pipecolic acids were protected forms of L-aspartic acid since they offer atom economy, have the correct configuration at the α-center, are relatively inexpensive and eventually offer a versatile oxidation state at C-4.

The first route we developed (Scheme 1) exploits the intramolecular Michael addition of an elaborated aspartic acid derivative to construct the piperidine ring. Thus *N*-Boc-L-Asp-γ-OBn **(4)** (Bachem) was coupled with *tert*-butylamine using BOP (Benzotriazol-1-yloxy-tris[dimethylamino]phosphonium hexafluorophosphate) (10) to give amide **5**. We chose to introduce the desired *tert*-butylamide early in the synthesis to avoid a sequence of protection/deprotection at the α-carboxyl. The benzyl ester was next hydrogenolyzed to give free γ-acid **6**. Extension of the side chain was accomplished under mild conditions following Masamune's procedure (11) which required activation of the carboxylate with carbonyldiimidazole followed by addition of the magnesium salt of monobenzyl malonate (12) to generate β-ketoester **7**. Upon treatment with dimethylformamide dimethyl acetal, enaminone **8** was obtained (13). The use of this stable function as a Michael acceptor proved to be critical since attempts to prepare doubly activated olefins, such as in structure **13**, failed. This failure most likely originates from the high reactivity of the olefin which polymerizes rapidly even at 0 °C (14). Removal of the Boc protecting group with anh. HCl, followed by cyclization (presumably via a 1, 4 addition and subsequent retro-Michael elimination of dimethylamine hydrochloride) yielded salt **9**. In contrast with Jackson's observation (6d) where in the case of a simple enone, the cyclization took up to 48 hours, this process proved to be rapid, going to completion after a few hours. The resulting salt was moisture sensitive (partial decomposition was observed) so the nitrogen was reprotected before further manipulations. Thus treatment with di-*tert*-butyldicarbonate in the presence of DIPEA generated Boc derivative **19** which could be easily purified. Following catalytic hydrogenation, spontaneous decarboxylation occurred to give *tert*-Bu-*N*-Boc-4-oxo-L-pipecolamide **(11)**. Stereoselective reduction of the carbonyl with K-Selectride® (6e) gave the desired 4-*R*-hydroxy derivative **12.** The physical properties and spectral data of this product were in accord with literature values (9a, 15).



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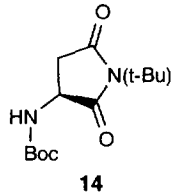
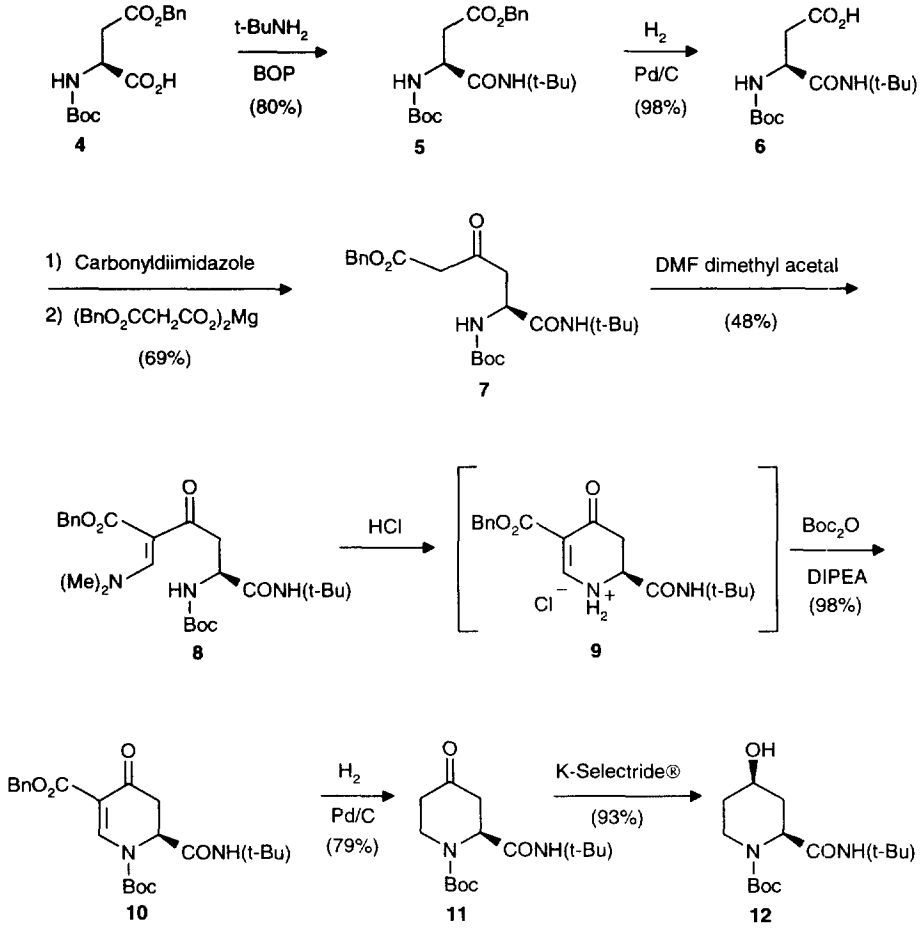


14

This eight step synthesis gave us optically pure material in 19% overall yield which was sufficient to fulfill the needs for SAR studies. However, when this sequence was attempted on a 250 g scale, considerably lower yields were obtained. When the carboxyl group of **6** was activated a sideproduct which was difficult to remove was obtained. It' s structure was consistent with imide **14**, which would result from an intramolecular cyclisation. As a consequence, when palinavir was selected for preclinical studies and greater amounts of material were needed, this route was judged unsuitable for scale-up.

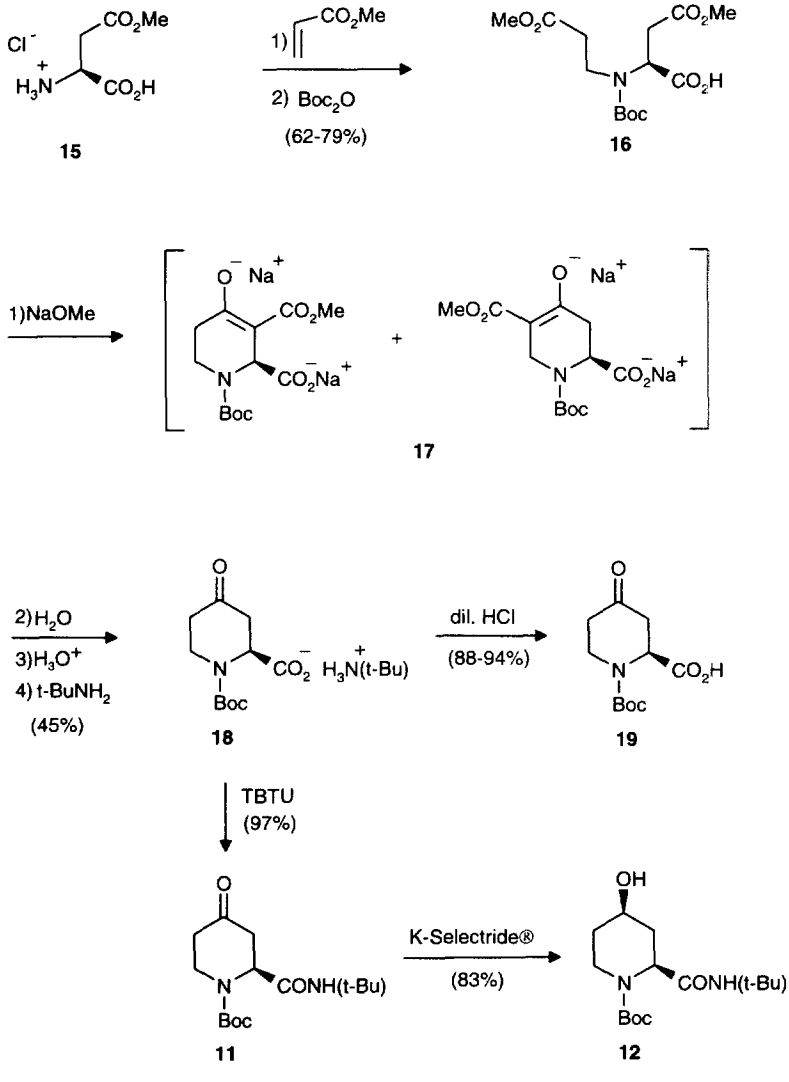
Scheme 1



The second approach we developed (Scheme 2) to circumvent this problem combines both the Michael addition of an aspartic acid derivative and an intramolecular Dieckmann condensation to build the piperidine ring (16). This sequence was carried out on the free α-carboxylic acid to avoid racemization. Thus, β-methyl-L-aspartate hydrochloride **(15)** (17) was treated with excess triethylamine and methyl acrylate followed by *in situ* *N*-protection with di-*tert*-butyldicarbonate, diester **16** was obtained in a one pot operation (79% yield on a 2 kg scale). Formation of the piperidine ring was next accomplished by treating diester **16** with sodium methoxide (18). The mixture of enolized β-ketoesters **(17)** obtained was decarboxylated *in-situ* by the addition of water and heating. Subsequent acidification permitted extraction of the crude product which was isolated as salt **18** by addition of *tert*-butylamine to the organic solution. The desired building block **12** was obtained after treatment of salt **18** with TBTU (2-[1H-Benzotriazol-1-yl]-1,1,3,3-tetramethyluronium tetrafluoroborate) (19) followed by reduction of ketone **11** as previously described (83% yield on a

500 g scale). The optical rotation, melting point and spectroscopic data for (2*S*,4*R*)-**12** prepared by this route matched the values obtained from the previous route and the literature values (9a). Alternatively, 4-oxo amino acid **19** could be obtained from salt **18** following a simple wash with dilute acid. The optical purity of this compound was determined by preparing esters with each enantiomer of 1-indanol (20) under Stieglich conditions (21) and analyzing the crude reaction mixtures by HPLC. The diastereomeric excess of the crude esters were found to be >99.5% (22).

Scheme 2



Conclusion

We have developed two new routes to 4-oxo- and 4-(*R*)-hydroxypipecolic acid derivatives. Although the first route was only carried out on a small scale, it has the advantage of providing synthetically versatile intermediate **10** which we are currently investigating as an entry into polyfunctionalised pipecolic acid derivatives. The second route which is more expeditious, does not require any chromatographic purifications and is amenable to large scale. It also provides easy access to enantiopure ketone **19** , a potentially useful building block in peptidomimetics.

Acknowledgments

We wish to thank Colette Boucher and Julia Hambrock of our analytical department for developing the HPLC method employed in the diastereomeric excess determination. We would also like to acknowledge Dr. Pierre Beaulieu's guidance in the preparation of this manuscript.

Experimental Section

General. All reagents, solvents and starting materials were obtained from commercial sources and used as received. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 or 50 MHz as indicated (solvent resonance was used as the internal standard). Compounds **11**, **12** and **19** have been confirmed as mixtures of rotamers by variable temperature ^{1}H NMR (coalescense of signals observed in toluene d_8 at 336 °K). Similar products have been previously reported as mixtures of rotamers (5ce, 6f). Mass spectra were recorded under FAB ionization mode. Melting points are uncorrected. All reactions requiring anhydrous conditions were conducted under a positive nitrogen atmosphere in oven or flame dried glassware using standard syringe techniques. Flash chromatography was performed using 10-40 μ type H silica gel from Sigma.

***N*-*tert*-Butoxycarbonyl-*L*-Asp-(OBn)-*tert*-butylamide (5)**
Boc-L-Asp-γ-OBn **(4)** (50.0 g, 155 mmol) was dissolved in a mixture of acetonitrile (500 mL) and DMF (50 mL), stirred under an atmosphere of nitrogen and cooled to 0 °C. *tert*-Butylamine (17.9 mL, 170 mmol) was added (a suspension was obtained) followed by BOP (75.3 g, 170 mmol) and diisopropylethylamine (81.0 mL, 465 mmol). The solution was allowed to warm to room temperature and was stirred for 2 hours. After evaporation to 25% of its original volume and dilution with ethyl acetate (400 mL) the solution was washed successively with ice cold 0.5N HCl (2 x 250 mL), 5% aq $NaHCO_3$ (3 x 250 mL) and saturated NaCl (5 x 200 mL). The solution was dried (Na_2SO_4) and evaporated. The residual solid was crystallized from ethyl acetate / hexane to yield 46.8 g (80%) of amide **5** as a white flaky solid. Mp 113.5-114.0 °C. $[\alpha]_D^{25}$-3.5° (*c* 1.0, $CHCl_3$). IR (KBr) ν 3380, 3325, 1730, 1685, 1675 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.31-7.37 (m, 5H), 6.29 (s, 1H), 5.61 (s, 1H), 5.16 (d, J = 12.0 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 4.39 (s, 1H), 2.98 (dd, J_1 = 4.5 Hz, J_2 = 16.8 Hz, 1H), 2.68 (dd, J_1 = 6.7Hz, J_2 = 16.8 Hz, 1H), 1.45 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.6, 155.5, 135.4, 128.5, 128.2, 128.1, 80.2, 66.6, 51.1, 51.0, 36.2, 28.5, 28.2. MS *m* / *z* 379 (MH^+), 323 (100%), 279. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.40; N, 7.99. Found: C, 63.25; H, 7.29; N, 8.05.

***N*-*tert*-Butoxycarbonyl-*L*-Asp-*tert*-butylamide (6)**
To a solution of benzyl ester **5** (1.00 g, 2.64 mmol) in ethanol (20 mL) under an atmosphere of nitrogen, was added 5% Pd/C (0.10 g, 10% w/w). The system was purged 3 times with hydrogen gas and the mixture was stirred for 3 hours under a hydrogen atmosphere (balloon). The catalyst was filtered over Celite and the filtrate was evaporated to dryness. The residual solid was crystallized from acetonitrile to yield 723 mg (95%) of acid **6** as a white solid. Mp 165-166 °C (dec). $[\alpha]_D^{25}$-27.0° (*c* 1.0, CH_3OH). IR (KBr) ν 3350, 2966 (broad), 1720, 1691, 1649 cm^{-1}. ^{1}H NMR (DMSO d_6)

δ 12.19 (s, 1H), 7.23 and 7.16 (2s, 1H), 6.95 (d, J = 7.9 Hz, 1H), 4.15 and 4.05 (2m, 1H), 2.55 (dd, J_1 = 5.1 Hz, J_2 = 16.2 Hz, 1H), 2.39 (dd, J_1 = 8.3 Hz, J_2 = 16.2Hz, 1H), 1.38 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (50 MHz, DMSO d_6) δ 171.8, 170.2, 155.2, 78.3, 51.4, 50.1, 36.3, 28.4, 28.1. MS *m / z* 289 (MH^+), 233 (100%), 189. Anal. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72. Found: C, 54.31; H, 8.58; N, 9.88.
When carried out on a 10.0 g scale, acid **6** was obtained in 98% yield. Mp 163-165 °C. $[\alpha]_D^{25}$-26.5° (*c* 1.0, CH_3OH).

(5*S*)-*tert*-Butoxycarbonylamino-5-*tert*-butylcarbamoyl-3-oxopentanoic acid benzyl ester (7)
To a stirred suspension of acid **6** (7.60 g, 26.4 mmol) in dry THF (100 mL) under an atmosphere of nitrogen at 0 °C, was added carbonyldiimidazole (4.27 g, 26.4 mmol) in 4 portions over 15 min. After 1 hour at 0 °C the solution was stirred 3 hours at room temperature. The magnesium salt of monobenzyl malonate (10.82 g, 26.4 mmol) was added and the resulting suspension stirred for 16 hours after which a further 0.2 eq (2.16 g, 5.3 mmol) of the magnesium salt was added. After 4 hours of stirring, the solvent was evaporated to 25% of its original volume, the mixture diluted with ethyl acetate (150 mL) and washed successively with ice cold 0.5N HCl (2 x 50 mL), 5% aq $NaHCO_3$ (50 mL) and saturated NaCl (50 mL). The resulting solution was dried (Na_2SO_4) and evaporated to give 12.80 g of an orange oil. This product was purified by flash chromatography (gradient : 4 to 6% *i*-PrOH/hexane) to yield 7.69 g (69%) of ketoester **7** as an amber oil which crystallized on standing. Mp 78 °C. $[\alpha]_D^{25}$-2.6° (*c* 0.85, $CHCl_3$). IR (KBr) ν 3340, 2980, 1750, 1720, 1695, 1675 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.30-7.39 (m, 5H), 6.32 (s, 1H), 5.60 (s, 1H), 5.17 (s, 2H), 4.39 (s, 1H), 3.60 (d, J = 16.2 Hz, 1H), 3.55 (d, J = 15.9 Hz, 1H), 3.16 (dd, J_1 = 4.1 Hz, J_2 = 17.8 Hz, 1H), 2.80 (dd, J_1 = 6.0 Hz, J_2 = 17.5 Hz, 1H), 1.45 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.1, 169.6, 166.6, 155.5, 135.1, 128.5, 128.3, 128.2, 128.0, 80.2, 67.02, 51.1, 49.3, 43.9, 28.4, 28.1. MS *m / z* 421 (MH^+), 365 (100%), 321. Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H,7.67; N, 6.66. Found: C, 62.45; H,7.74; N, 6.57.
Analytical data for isolated impurity **14** : Mp 138-140 °C. $[\alpha]_D^{25}$+3.13° (*c* 0.48, $CHCl_3$). IR (KBr) ν 3321, 2981, 1701. ^{1}H NMR ($CDCl_3$) δ 5.30 (d, J = 5.4 Hz, 1H), 4.20 (m, 1H), 3.00 (dd, J_1 = 9.4 Hz, J_2 = 17.6 Hz, 1H), 2.64 (dd, J_1 = 6.6 Hz, J_2 = 17.6 Hz, 1H), 1.58 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.0, 175.2, 155.3, 80.6, 58.8, 50.0, 36.9, 28.3, 28.2. MS m / z 271 (MH^+), 215 (100%), 115. Anal. Calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H,8.20; N, 10.36. Found: C, 58.12; H,8.62; N, 10.28.

2-[3-(*S*)-*tert*-Butoxycarbonylamino-3-*tert*-butylcarbamoylpropionyl]-3-dimethylamino acrylic acid benzyl ester (8)
To a solution of ketoester **7** (7.46 g, 17.7 mmol) in DMF (70 mL) was added dimethylformamide dimethyl acetal (3.53 mL, 26.6 mmol). After stirring 4 hours under an atmosphere of nitrogen at room temperature, the resulting heavy precipitate was filtered, washed with ice cold DMF (10 mL) and ether (20 mL) to give 2.20 g of a white solid. To the filtrate was added DMF dimethyl acetal (1 mL) and the solution was stirred for 16 hours. The solid was filtered and washed as above to give an additional 1.00 g of a white solid. The filtrate was diluted with water (300 mL) and extracted with ethyl acetate (2 x 50 mL) to give 1.00 g of a yellow solid after evaporation of the solvent. The three crops were combined and triturated with ether to yield 4.02 g (48%) of enaminone **8** as a white flaky solid. Mp 170-171 °C. $[\alpha]_D^{25}$+45.6° (*c* 1.04, $CHCl_3$). IR (KBr) ν 3320, 2960, 2920, 1670, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.75 (s, 1H), 7.26-7.39 (m, 5H), 6.60 (s, 1H), 5.76 (d, J = 6.0 Hz, 1H), 5.19 (s, 2H), 4.40 (s, 1H), 3.29 (dd, J_1 = 5.1Hz, J_2 = 17.2 Hz, 1H), 3.21 (s, 3H), 3.08 (d, J = 16.5 Hz, 1H), 2.79 (s, 3H), 1.42 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 195.8, 170.8, 167.4, 158.3, 155.6, 136.4, 128.5, 128.3, 128.0, 101.3, 79.5, 65.8, 51.8, 50.7, 47.6, 44.0, 42.3, 28.5, 28.2. MS *m / z* 476 (MH^+), 215 (100%). Anal. Calcd for $C_{25}H_{37}N_3O_6$: C, 63.14; H, 7.84; N, 8.84. Found: C, 63.42; H, 7.97; N, 8.70.

(6*S*)-*tert*-Butylcarbamoyl-4-oxo-5,6-dihydro-4*H*-pyridine-1,3-dicarboxylic acid 3-benzyl ester 1-*tert*-butyl ester (10)

Enaminone **8** (3.90 g, 8.20 mmol) was dissolved in a 4N solution of HCl/dioxane (25 mL) and stirred under an atmosphere of nitrogen at room temperature for 3.5 hours. The solvent was evaporated to a volume of *ca* 10 mL and the resulting paste was stirred with ether (100 mL) for 15 min. The pink suspension was filtered and the solid was dried under high vacuum to yield 3.00 g (100%) of salt **9**. This salt was suspended in acetonitrile (30 mL), stirred under an atmosphere of nitrogen and cooled to 0 °C. Diisopropylethylamine (2.14 mL, 12.3 mmol) was added, followed by DMAP (107 mg, 0.80 mmol) and di-*tert*-butyldicarbonate (1.98 g, 9.00 mmol). The resulting suspension was allowed to warm to room temperature and was stirred for 4 hours. It was then diluted with ethyl acetate (175 mL), washed successively with ice cold 0.5 N HCl (50 mL), saturated NaCl (50 mL) and filtered. A beige solid (1.35 g) was isolated. The filtrate was dried (Na_2SO_4) and evaporated. The residual solid was purified by flash chromatography (5% $CH_3OH/CHCl_3$) to give a white solid which was crystallized from ethyl acetate/hexane to yield 1.90 g of Boc derivative **9**. The beige solid isolated earlier (1.35 g) was suspended in DMF (10 mL) and treated with DMAP (0.05g, 0.40 mmol) and di-*tert*-butyldicarbonate (1.30 g, 3.94 mmol) under an atmosphere of nitrogen at room temperature for 3 hours. The solution was poured into water (80 mL) and extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, worked-up and purified as above to give 1.56 g of Boc derivative **10** in a combined yield of 3.46 g (98%). Mp 250-251°C (dec). $[\alpha]_D^{25}$+52.1° (*c* 1.05, $CHCl_3$). IR (KBr) ν 3340, 2980, 1740, 1720, 1690, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.82 (s, 1H), 7.26-7.44 (m, 5H), 5.64 (s, 1H), 5.27 (d, J = 12.7 Hz, 1H), 5.22 (d, J = 12.7 Hz, 1H), 4.84 (d, J = 7.2 Hz, 1H), 2.87 (dd, J_1 = 7.2 Hz, J_2 = 16.4 Hz, 1 H), 2.79 (dd, J_1 = 2.3Hz, J_2 = 16.4 Hz, 1H), 1.56 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 166.7, 162.9, 150.7, 150.5, 106.9, 85.6, 77.2, 65.8, 56.5, 51.6, 38.7, 28.4, 27.6. MS *m* / *z* 431 (MH^+), 331, 223 (100%). Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51. Found: C, 64.45; H, 7.26; N, 6.57.

(2*S*)-*N*-*tert*-Butoxycarbonyl-4-oxopipecolic acid, *tert*-butylamide (11)

To a stirred solution of benzyl ester **10** (250 mg, 0.60 mmol) in ethanol (10 mL) under an atmosphere of nitrogen, was added 10% Pd/C (50 mg). The system was purged 3 times with hydrogen gas and the mixture was stirred for 3 hours under a hydrogen atmosphere (balloon). The catalyst was filtered over Celite and the filtrate was evaporated to dryness. The residual solid was purified by flash chromatography (gradient 5 to 10% *i*-PrOH/hexane) to yield 142 mg (79%) of ketone **11** as a white solid. Mp 98-99 °C. $[\alpha]_D^{25}$-117.0°(*c* 1.0, $CHCl_3$). IR (KBr) ν 3329, 2976, 1729, 1688, 1664 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.52 and 5.80 (2 broad s, 1H), 4.84 and 4.66 (2 broad m, 1H), 3.90 and 4.05 (2 broad m, 1H), 3.54 (ddd, J_1 = 8.3 Hz, J_2 = 8.6 Hz, J_3 = 13.3 Hz, 1H), 2.82 (dd, J_1 = 3.2Hz, J_2 = 16.2Hz, 1H) 2.57 (ddd, J_1 = 5.4Hz, J_2 = 5.7Hz, J_3 = 16.8Hz, 1H), 2.35-2.52 (m, 2H), 1.52 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.7, 169.6, 156.1, 81.6, 54.8, 51.2, 40.2, 39.7, 38.9, 28.6, 28.3. MS *m* / *z* 299 (MH^+), 243 (100%), 199. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39. Found: C, 60.51; H, 8.69; N, 9.12.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxypipecolic acid, *tert*-butylamide (12)

To a stirred solution of ketone **11** (85 mg, 0.3 mmol) in dry THF (3 mL) under an atmosphere of nitrogen and cooled to -5 °C (brine/ice bath) was added K-Selectride® (370 µL, 0.37 mmol). After 1.5 hour at -5 °C a solution of 2N NaOH (185 µL, 0.37 mmol) was added. After a further 15 min of stirring a solution of 30% w/w H_2O_2 (163 µL, 1.44 mmol) was added and stirring was continued for 3 hours. The solution was diluted with ethyl acetate (50 mL), washed with saturated $Na_2S_2O_3$ (20 mL) and saturated NaCl (20 mL), dried ($MgSO_4$), filtered and evaporated. The residual solid was purified by flash chromatography (4% *i*-PrOH/hexane) to yield 78 mg (93%) of the (2*S*,4*R*)-alcohol **12**. Mp 129-130°C. $[\alpha]_D^{25}$-63.0° (*c* 1.0, CH_3OH), $[\alpha]_D^{25}$-212.9° (*c* 1.00, $CHCl_3$) [lit. (9a) Mp 131-133 °C, $[\alpha]_D^{25}$-64.9° (*c* 1.0, CH_3OH)]. IR (KBr) ν 3341, 2974, 1671, 1647 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.75 (broad s, 1H), 5.88 (broad s, 1H), 4.70 (broad s, 1H), 3.99 (s, 1H), 3.80 (m, 1H), 3.11 (dt, J_1 = 2.5Hz, J_2 = 13.3 Hz,

1H), 2.21 (broad d, J = 14.3Hz, 1H), 1.79 (ddd, J_1 = 3.6Hz, J_2 = 6.8 Hz, J_3 = 14.3 Hz, 1H), 1.50-1.60 (m, 1H), 1.47 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 156.3, 80.9, 61.3, 53.4, 51.3, 35.8, 32.4, 30.4, 28.5, 28.3. MS *m / z* 301 (MH^+), 245, 201. Anal. Calcd for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.39; N, 9.33. Found: C, 59.92; H, 9.75; N, 9.25.
When carried out on a 542 g scale, **12** was obtained in 83% yield. Mp 130-131 °C. $[\alpha]_D^{25}$-210.0° (*c* 1.0, $CHCl_3$). In this case, the crude product was purified by trituration with hexane. For safety reasons the quench with NaOH was done at - 30 °C and the addition of hydrogen peroxide was done slowly at -50 °C (CAUTION HIGHLY EXOTHERMIC !).

(2*S*)-[*tert*-Butoxycarbonyl-(2-methoxycarbonyl-ethyl)-amino]-succinic acid 4-methyl ester (16)
To a solution of γ-methyl -L- aspartate hydrochloride **(15)** (25.0 g, 136 mmol) in water (60 mL) cooled to 0 °C was added triethylamine (47.4 mL, 340 mmol) and methyl acrylate (36.8 mL, 409 mmol). The mixture was stirred vigorously and allowed to warm back to room temperature (*c.a.* 4 hours). After washing with hexane (2 x 200 mL), *tert*-butanol (20 mL) and di-*tert*-butyldicarbonate (37.0 g, 170 mmol) were added and vigorous stirring continued for 16 hours. The mixture was washed with hexane (2 x 200 mL), the aqueous solution was cooled to 0 °C and the pH was adjusted to 3.0 with conc. HCl. The product was extracted with ethyl acetate (3 x 100 mL) and the organic extracts were combined, washed with saturated NaCl (100 mL), the solution was dried ($MgSO_4$) and evaporated to yield 28.1 g (62%) of diester **16**. $[\alpha]_D^{25}$-95.4° (*c* 1.05, $CHCl_3$). IR (neat) ν 3482, 2978, 1737, 1702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.45 (broad s, 1H), 4.44 (m, 1H), 3.80-3.87 (m,1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.43-3.53 (m, 1H), 3.20 (dd, J_1 = 4.77 Hz, J_2 = 16.85 Hz, 1H), 2.57-2.90 (m, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 175.2, 173.3, 172.5, 172.1, 171.7, 155.0, 154.1, 81.8, 81.2, 58.9, 58.7, 52.0, 51.9, 51.7, 45.6, 36.0, 35.0, 33.8, 33.2, 28.3, 28.2. MS *m / z* 334 (MH^+), 234 (100%). Anal. Calcd for $C_{14}H_{23}NO_8$: C, 50.45; H, 6.95; N, 4.20. Found: C, 50.07; H6.89; N, 4.31.
When carried out on a 2.0 kg scale, diester **16** of comparable purity was obtained in 79% yield. $[\alpha]_D^{25}$ -98.1° (*c* 1.0, $CHCl_3$).

(2*S*)-*N*-*tert*-Butoxycarbonyl-4-oxopipecolic acid, *tert*-butyl-ammonium salt (18)
To a solution of diester **16** (1.01 kg, 3.03 mol) in dry THF (4.0 L), mechanically stirred under an atmosphere of nitrogen, and cooled to 10 °C was added a 25% w/w solution of sodium methoxide in methanol (1.94 L, 9.09 mol) in *ca* 15 min. The resulting yellow solution was refluxed for 3 hours (after 1 hour a suspension was obtained). THF (3.0 L) was distilled off under reduced pressure and water (3.0 L) was added. Following 20 hours of reflux the remaining THF was distilled off and the aqueous solution was washed with ethyl acetate (2 x 2.0 L), cooled to 5 °C (ice bath) and the pH was adjusted to 2.5 with conc. HCl. The crude product was extracted with ethyl acetate (2 x 1.5 L), then the organic solution was washed with saturated NaCl, dried ($MgSO_4$) and filtered. The filtrate was cooled to 5 °C (ice bath) and *tert*-butylamine (0.32 L, 3.03 mol) was added with stirring. The yellow solid was filtered and air dried overnight, then boiled in isopropyl alcohol (2.6 L). The suspension was cooled to 5 °C (ice bath) for 2 hours, then the solid was filtered, washed with ice cold isopropyl alcohol (0.25 L) and dried under high vacuum to yield 328.0 g of a white solid. The mother liquor and the isopropanol filtrate were combined and evaporated to dryness. The residue was treated as previously described (0.70 L of isopropyl alcohol) to give 101.0 g of a white solid for a total yield of 429.0 g (45%) of salt **18**. Mp 190-191 °C (dec). $[\alpha]_D^{25}$-14.4° (*c* 1.0, H_2O). IR (KBr) ν 3440, 2980, 1730, 1705 cm^{-1}. ^{1}H NMR (D_2O) δ 4.50-4.70 (broad, m, 1H), 3.85-4.15 (broad, m, 1H), 3.60-3.80 (broad, m, 1H), 2.72-2.95 (broad, m, 2H), 2.50-2.68 (broad, m, 2H), 1.45 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, D_2O, int. ref. DMSO) δ 214.6, 179.0, 157.3, 82.8, 57.6, 52.7, 42.3, 39.7, 39.6, 28.4, 27.5. MS *m / z* 317 (MH^+), 227, 188. Anal. Calcd for $C_{15}H_{28}N_2O_5$: C, 56.95; H, 8.92; N, 8.85. Found: C, 57.08; H, 9.05; N, 8.82.

(2*S*)-*N*-*tert*-Butoxycarbonyl-4-oxopipecolic acid, *tert*-butylamide (11)

To a suspension of salt **18** (681.5 g, 2.15 mol) in acetonitrile (6.0 L) mechanically stirred under an atmosphere of nitrogen at 10 °C, was added triethylamine (750 mL, 5.38 mol), *tert*-butylamine (22.6 mL, 215 mmol) and TBTU (809.0 g, 2.52 mol). After 4.5 hours at room temperature the solvent was evaporated to dryness, the residue taken up in ethyl acetate (2.5 L) and washed successively with 10% aq HCl (2 L), saturated Na_2CO_3 (1 L) and saturated NaCl (1 L). The solution was dried ($MgSO_4$), filtered and evaporated to yield 628.0 g (97%) of ketone **11** as a yellowish solid. Mp 97-98 °C. $[\alpha]_D^{25}$ -116.9° (*c* 1.0, $CHCl_3$). ^1H, ^{13}C NMR and MS data were identical to that of the material obtained by the previous route. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39. Found: C, 60.29; H, 8.89; N, 9.37.

(2*S*)-*N*-*tert*-Butoxycarbonyl-4-oxopipecolic acid (19)

To a suspension of salt **18** (41.0 g, 130 mmol) in ethyl acetate (300 mL) stirred at 0 °C (brine/ice bath), was slowly added aqueous 0.5N HCl (500 mL) saturated with NaCl. After complete dissolution was observed, the organic layer was decanted, washed with saturated NaCl, dried ($MgSO_4$), filtered and the solvent evaporated to yield 29.7 g (94%) of acid **19** as a faint yellow solid. Mp 127 °C (dec). $[\alpha]_D^{25}$-19.0° (*c* 1.0, $CHCl_3$), $[\alpha]_D^{25}$-17.4° (*c* 1.0, H_2O). IR (KBr) ν 2972, 1749, 1723 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.29 (broad s, 1H), 4.89-5.10 (m, 1H), 4.00-4.10 (m, 1H), 3.68 (m, 1H), 2.75-2.95 (m, 2H), 2.45-2.60 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (100MHz, $CDCl_3$) δ 205.9, 175.9, 175.0, 155.4, 154.4, 81.8, 54.5, 53.7, 40.7, 40.5, 39.6, 39.3, 28.2. MS *m / z* 244 (MH^+), 144. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.36; H, 7.06; N, 5.81.

When caried out on a 429 g scale, acid **19** of similar purity was obtained in 88% yield. $[\alpha]_D^{25}$-17.3° (*c* 1.1, H_2O).

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