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A CHIRAL POOL APPROACH TOWARD THE SYNTHESIS OF THALIDOMIDE METABOLITES[1, 2]

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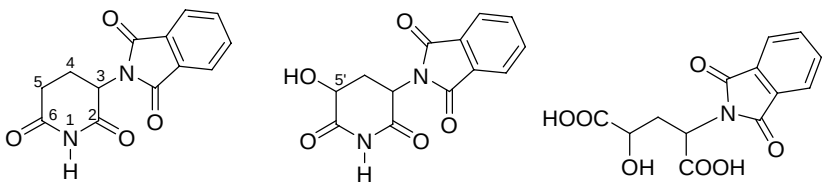
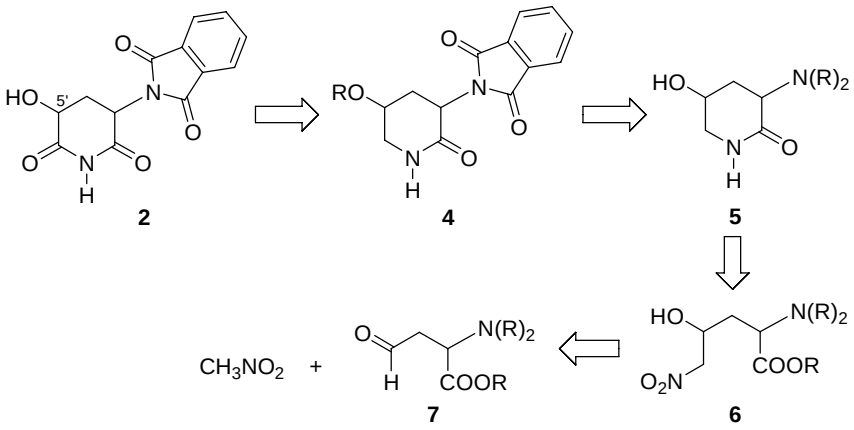
Abstract — A synthetic strategy toward the glutarimide-derived metabolite of thalidomide, 5′-hydroxythalidomide (5′-OH THD, **2**) was developed which utilizes aspartic acid as a "chiral pool"-type starting material. The synthesis incorporates a Henry reaction as the key carbon-carbon bond-forming step followed by a tandem reduction-cyclization of the intermediate nitroalcohol in forming the heterocyclic core of 5′-OH THD.

INTRODUCTION

Angiogenesis is the generation of new blood vessels from preexisting vasculature and is a necessary process for normal tissue growth and nutrition. Similarly, angiogenesis plays an important role in certain types of cancers since growing tumors require new blood vessels for the transport of oxygen and nutrients. Consequently, compounds which are angiogenesis inhibitors may find application as cancer chemotherapeutics due to their ability to arrest tumor growth by cutting off its blood supply.[3] A number of small molecules, both synthetic and naturally-derived, are undergoing structure-activity studies in the inhibition of angiogenesis and are serving as starting points for the development of clinically useful analogues. Although compounds such as artesunate, borrelidin, fumagillin, imiquimod, terbinafine, TNP-470 and withaferin A are angiogenesis inhibitors which are mechanistically diverse,[4a-g] thalidomide (**1**) is the compound which has garnered the most attention.[5] Considered an "orphan drug" the status of thalidomide has been varied and is now an approved drug as well as an experimental chemotherapeutic in several phases of clinical trials.[6] Thalidomide and closely-related analogues exhibit antiangiogenic activity in a number of in vivo and in vitro assays in which a "metabolic activation" step has been implicated.[7] While the evidence clearly points to the generation of some type of active species or



complex, the identification of the intermediate and clarification of its mode of interaction with the angiogenic target remain unsolved. Microsomal metabolism of thalidomide results in hydroxylation of the phthalimide ring ultimately giving phenolic hydroxyl groups, while metabolic conversion of the glutarimide ring methylenes gives diastereotopic hydroxyl groups.[8] For some time we have been exploring the synthesis of the glutarimide-hydroxylated metabolites of thalidomide with the goals of verifying antiangiogenic activity and exploring the stereospecificity of the glutarimide hydroxylation.[9] The successful syntheses of 5′-hydroxythalidomide (**2**) have delivered the racemic compound and a preliminary report of a stereoselective synthetic route only provided the 5′-OH protected ester of the so-called hydroxy PG acid (**3**).[9a,10] Our retrosynthesis of **2** can be traced back to protected *N*-phthaloyl-lactam (**4**, Scheme 1), where in the synthetic direction, the 6-methylene oxidation of **4** will provide

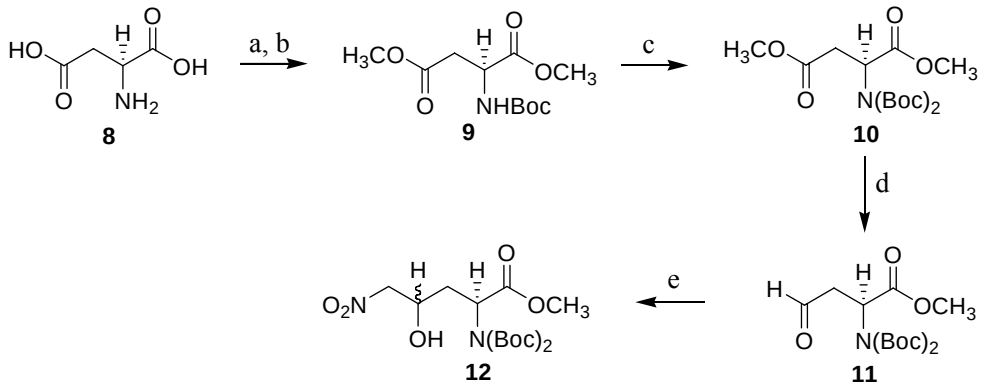


Scheme 1. Retrosynthesis of 5'-Hydroxythalidomide **2**.

protected imide (**2**). The lactam (**4**) can be traced back to a reduction-cyclization of a protected hydroxyornithine analogue (**6**) through suitably *N*-protected (base stable) hydroxylactam (**5**). The nitro amino acid derivative (**6**) would arise from a nitroaldol (Henry) reaction of aspartate aldehyde (**7**) and nitromethane giving the requisite five-carbon hydroxyornithine synthon. In summary, reduction of the nitroalcohol (**6**) followed by cyclization, deprotection and phthaloylation will provide **4** in preparation for the key methylene oxidation. The lactam cyclization strategy is similar to one previously reported by us where 3-hydroxyornithine derivatives were prepared stereoselectively and cyclized to 4′-hydroxythalidomide analogues.[9b, 11]

RESULTS AND DISCUSSION

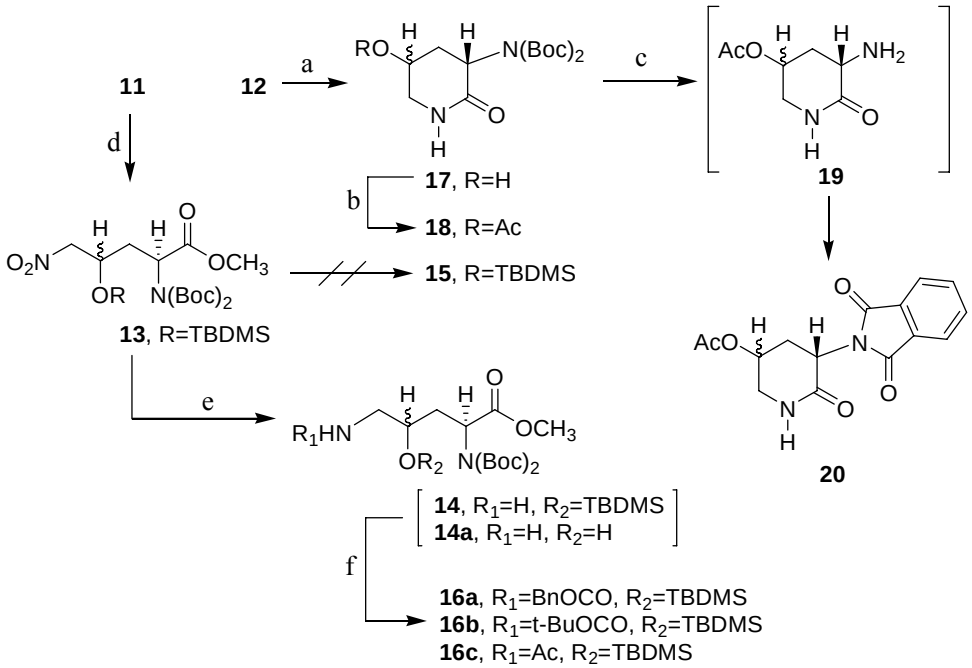
Commercially-available (*S*)-(+)-aspartic acid (**8**) is converted to the *N*-Boc-dimethyl ester (**9**) by treatment with chlorotrimethylsilane in methanol followed by direct exposure of the intermediate dimethyl ester hydrochloride to *tert*-butoxycarbonyl anhydride (Boc_2O) in the presence of triethylamine (**Scheme 2**). A second *N*-Boc group is added to **9** through treatment with Boc_2O and 4-dimethylamino-



Scheme 2. *Reagents and Conditions*:(a) TMSCl/MeOH/0°C to rt; (b) TEA/Boc_2O/MeOH/ 0°C to rt, 80% for a and b; (c) DMAP/Boc_2O/CH_3CN, quant; (d) DIBAL-H/Et_2O/-78°C to rt, 74%; (e)CH_3NO_2/TMG/THF, 79%.

pyridine (DMAP) in acetonitrile thereby furnishing the di-*N*-Boc dimethyl ester (**10**) in quantitative yield. Selective reduction of the γ–carbonyl of diester (**10**) to provide the di-*N*-Boc semialdehyde (**11**) was accomplished by slow addition of diisobutylaluminum hydride in toluene to a solution of **10** in diethyl ether at -78 °C. Several synthetic runs were required to obtain an optimal yield of 74% for the DIBAL-H reduction of **10**. The reaction of semialdehyde (**11**) with excess nitromethane proceeded smoothly in THF at room temperature in the presence of a catalytic amount of 1,1,3,3-tetramethylguandine (TMG) to afford the di-*N*-Boc nitroalcohol (**12**) in 79% yield as a chromatographically inseparable (65/35) mixture of (2*S*,4*S*) and (2*S*,4*R*)-diastereoisomers. The presence of trace amounts of TMG promotes the retro-Henry reaction during the purification process and results in reduced yields of the di-*N*-Boc nitroalcohol (**12**). An immediate solution to the retro-Henry problem was to *O*-silylate **12** (*tert*-butyldimethylsilyl triflate/2,6-lutidine) the nitroalcohol to provide silyl ether (**13**). Reduction of the nitro group of the di-*N*-Boc-*O*-*tert*-butyldimethylsilyloxy ether (**13**) using either hydrogenation over palladium or aluminum amalgam/Raney-nickel gave the corresponding silylated amino alcohol (**14**) without cyclization to the expected silyloxylactam (**15**). The presence of the β–silyloxyamino compound (**14**) was confirmed by *N*-acylation with a number of agents such as benzyloxycarbonyl chloride (Z-chloride), Boc_2O or acetic anhydride giving the carbamates (**16a**), (**16b**) or amide (**16c**). While cyclization of **14** to the silyloxylactam (**15**) was not facilitated, a one-pot reduction-cyclization of **12** to the hydroxypiperidinone (**17**) was possible. Cyclization of **12** to the *N*,*N*-diBoc hydroxypiperidinone (**17**) was effected by

treatment of nitroalcohol (**12**) with aluminum amalgam in a mixture of THF/water. Surprisingly, the

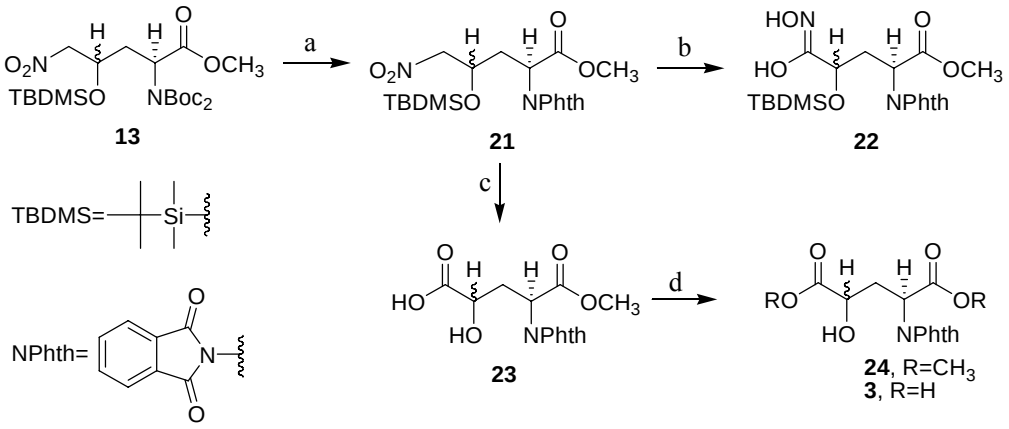


Scheme 3. *Reagents and Conditions:* (a) Al(Hg)/THF/H_2O/rt/24 h, 68%; (b)Ac_2O/pyr/rt/16 h, quant; (c) TFA/CH_2Cl_2/rt/45 min, then TEA/THF/*N*-carbethoxyphthalimide/reflux/5 h, 51%; (d) CH_3NO_2/TMG/THF/17 h/rt, then TBDMS triflate, 2,6-lutidine, 0°C/30 min, 90% (from **11**); (e) Raney-Ni/THF/H_2/rt/18-21 h, then (f) for **16a**, BnOCOCl/$NaHCO_3$/rt/48 h, 62%; (f) for **16b**, Boc_2O/DIPA/rt/22 h, 68%; (f) for **16c**, Ac_2O/pyr/rt/18 h, 60%.

reduction-cyclization of **12**→**17** was reluctant with catalytic hydrogenation or catalytic hydrogenation in the presence of Raney nickel and only provided the *N*,*N*-diBoc-hydroxyornithine methyl ester (**14a**). The hydroxypiperidinone (**17**) was treated with acetic anhydride in pyridine to give the 5-acetoxy-*N*,*N*-di-Boc-piperidinone (**18**) in 95% yield after chromatographic purification. Exposure of the 5-acetoxypiperidinone (**18**) to trifluoroacetic acid in dichloromethane followed by treatment of the unstable intermediate 3-amino-5-acetoxylactam (**19**) with *N*-carbethoxyphthalimide in THF/triethylamine afforded the 3-phthalimido-5-acetoxylactam (**20**) in 51% yield (from **18**).

The biological relevance of acyclic thalidomide derivatives in which the glutarimide ring has been hydrolyzed in vivo has been demonstrated in angiogenesis assays and has implicated the so-called "hydroxy PG acid" or 4-hydroxy-2-*N*-phthaloyl glutamic acid (**3**). The suspected biological activity of **3** has piqued our interest in preparing the esters of the hydroxy PG acid (**24**) as prototypical prodrug-type compounds. Hence, both the Boc groups of the nitro-diBoc silyl ether (**13**) were removed with trifluoroacetic acid in dichloromethane (Scheme 4). The *N*-deprotection of **13** was directly followed by *N*-phthaloylation with *N*-carbethoxyphthalimide to provide the 2-*N*-phthalimido-5-nitro-4-silyloxy methyl ester (**21**) in 68% overall yield. Next, the conditions for a mild Nef-type reaction that would convert the nitromethylene of

21 directly to a carboxyl group were sought. Furthermore, such a Nef-type removal of the nitro group would have to be conducted under acidic conditions, a requisite due to the inherent base-sensitivity of the



Scheme 4. *Reagents and Conditions:* (a) TFA/CH_2Cl_2 then TEA/THF/*N*-carbethoxy-phthalimide/16 h/reflux 2 h, 68%; (b) $NaNO_2$ (3 eq)/AcOH (10 eq)/DMSO/rt/16 h, 16%; (c) $NaNO_2$(3 eq)/AcOH (10 eq)/DMSO/40°C/17 h, 51%; (d) TMSCl/MeOH/rt/20 h, 90%.

N-phthaloyl group. Interestingly, treatment of the 2-*N*-phthalimido-5-nitro-4-silyloxy methyl ester (**21**) with sodium nitrite (3 eq), acetic acid and dimethylsulfoxide (DMSO) at room temperature (16h) gave the nitrolic acid (**22**) (16%), whereas under elevated temperatures (40°C), the desired methyl ester of 4-hydroxy-2-*N*-phthaloylglutamic acid (**23**) was obtained in 51% isolated yield. With the α-monomethyl ester of hydroxyl-PG acid now in hand, the γ-carboxyl group was esterified by treatment of **23** with a catalytic amount of trichlorosilane in methanol thereby affording the desired *N*-phthaloyldiester (**24**) in 90% yield.

In summary, we have detailed a new synthetic approach to 5′-hydroxythalidomide which utilizes an amino acid other than glutamic acid or glutamine as a readily available synthon. A notable feature of the synthesis is the employment of a Henry reaction as the key carbon-carbon bond forming step in homologating the aspartate fragment.[13] The reduction-cyclization with aluminium amalgam further demonstrates the usefulness of the Al(Hg)/THF/H_2O protocol as a mild expedient for nitroalkanol conversion rather than the usual catalytic reduction or Raney nickel. The compatibility the *N*-phthaloyl group with an unusually mild Nef-type conversion of the silylated nitroalcohol function was also demonstrated. Ongoing work involves the use of asymmetric catalysis for stereocontrol in the aspartate-nitromethane Henry reaction and the *N*-methylene oxidation of the appropriately derivatized lactams to the target glutarimide derivatives.[14]

EXPERIMENTAL SECTION

General.

NMR spectra were recorded on a Varian INOVA 500 instrument using $CDC1_3$, or DMSO-d_6, as solvent and internal standard unless otherwise indicated. FTIR spectra were recorded with a Mattson Galaxy Series 5000 FT instrument. Melting points were measured using a Thomas Hoover capillary melting point apparatus and are uncorrected. Dichloromethane and acetonitrile were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium metal, followed by a second distillation from sodium/benzophenone ketyl. All other reagents and solvents were ACS reagent grade and used as commercially available. Flash column chromatography was carried out using silica gel 60 (E. Merck 9385, 235-400 mesh). Gravity column chromatography was carried out using silica gel 60 (E. Merck 7734, 70-230 mesh). Analytical thin-layer chromatographic separations (TLC) utilized 0.25 mm glass-backed silica gel plates (E. Merck 5715, silica gel 60 F254). The TLC chromatograms were developed by immersing the plates in 2.5% phosphomolybdic acid in ethanol or in 1.0% ninhydrin in ethanol, followed by heating (hot plate). Solutions, reactions mixtures, and chromatographic fractions were concentrated using a standard rotary evaporator unless specified otherwise.

Dimethyl (*S*)-2-(*N*-*tert*-butoxycarbonyl)aminobutanodioate (9): To a stirred suspension of (*S*)-(+)-aspartic acid (1.33 g, 10.0 mmol) in methanol (33 mL, 0.3 M) cooled in an ice/ water bath was added slowly trimethylsilyl chloride (TMSCl, 5.6 mL, 44 mmol). After the addition was complete, the reaction mixture was a clear and colorless solution. The ice/water bath was removed and the reaction solution was stirred at rt for 23 h. The reaction solution was cooled with an ice/water bath, and triethylamine (9.0 mL, 64.6 mmol) was added slowly and carefully (HCl fumes released), followed by *tert*-butoxycarbonyl anhydride (2.45 g, 11 mmol). The ice/water bath was removed and the reaction solution was stirred at rt (23 h) after which time TLC analysis showed full conversion. The solvent was evaporated to yield a white solid which was thoroughly washed with ether (8 × 50 mL) followed by filtration through a Hirsh funnel. The collected filtrate was concentrated and purified by flash column chromatography (hexane/ether, 1:1) to afford pure **9**[12] as a white solid (2.09 g, 80.0 %): R_f 0.18 (hexane/Et_2O, 1:1), mp 64 - 65 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.50 (d, J = 5.9 Hz, 1H), 4.58 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.00 (dd, J = 4.5, 17.0 Hz, 1H), 2.82 (dd, J = 4.7, 17.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 171.6, 155.6, 80.4, 52.9, 52.2, 50.1, 36.9, 28.5; IR (KBr, cm^{-1}) 3406, 2981, 1753, 1705, 1504, 1442, 1349, 1165, 1041, 543.

Dimethyl (*S*)-2-(*N*,*N*-di-*tert*-butoxycarbonyl)aminobutanodioate (10): To a stirred solution of mono-Boc-protected diester (**9**) (1.67 g, 6.40 mmol) in acetonitrile (21 mL, 0.3 M) were sequentially added DMAP (0.16 g, 1.28 mmol) and Boc_2O (1.73 g, 7.69 mmol) at rt. The resulting clear solution was stirred at rt (4 h), during which time TLC analysis showed partial conversion. Additional Boc_2O (0.70g, 3.21 mmol) was added and the reaction mixture was stirred for a additional 18 h. The solvent was evaporated and the resulting thick oily residue was purified by flash column chromatography (hexane/Et_2O, 1:1) to

yield pure **10**[12] as a white solid (2.47 g, quant.): R_f 0.23 (hexane/Et_2O, 1:1), mp 56 - 57 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (d, *J* = 6.8 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.25 (dd, *J* = 7.1, 16.4 Hz, 1H), 2.73 (dd, *J* = 6.5, 16.4 Hz, 1H), 1.50 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.2, 151.5, 83.5, 54.9, 52.5, 51.9, 35.7, 27.9; IR (KBr, cm^{-1}) 2985, 1755, 1443, 1389, 1319, 1250, 1169, 1010, 856, 795.

Methyl (*S*)-2-(*N*,*N*-di-*tert*-butoxycarbonyl)amino-5-oxopentanoate (11): To a solution of di-Boc-protected diester (**10**) (1.0g, 2.77 mmol) in dry ether (27.7 mL, 0.1 M) was added DIBAL-H (1.6 M solution in toluene, 2.0 mL, 3.00 mmol) at -78 °C. The reaction mixture was stirred at -78 °C under argon (15 min), during which time TLC analysis showed full consumption of the starting material. The reaction mixture was quenched by addition of distilled water (350 μL at -78 °C, and the reaction mixture was allowed to warm to rt over a 20 – 25 min period. Anhydrous $MgSO_4$ was then added and the resulting white suspension was stirred at rt for 20 min, followed by filtration of the salts through a Celite while washing with ether (5 × 5 mL). The filtrate was concentrated and the resulting crude residue was purified by flash column chromatography (hexane/Et_2O, 3:2) to yield **11**[12] as a colorless oil (0.24g, 74%): R_f 0.18 (hexane/Et_2O, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.79 (s, 1H), 5.54 (d, *J* = 6.3 Hz), 3.74 (s, 3H), 3.42 (dd, *J* = 6.8, 17.9 Hz, 1H), 2.83 (dd, J = 5.9, 17.8 Hz, 1H), 1.58 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7; 170.5, 151.9, 84.0, 53.2, 45.2, 28.2; IR (film, cm^{-1}) 3062, 2981, 2937, 2732, 1792, 1744, 1698, 1369, 1268, 1235, 1145.

(2*S*,4*S*)- and (2*S*,4*R*)- Methyl 5-nitro-4-hydroxy-2-(*N*,*N*-di-*tert*-butoxycarbonyl)aminopentanoate (12): Aspartate semialdehyde (**11**) (484mg, 1.46 mmol) was stirred in THF (7.3 mL, 0.2 M) in the presence of nitromethane (790 μL, 14.6 mmol) and a catalytic amount of *N, N, N',N'*-tetramethylguanidine (TMG, 9 μL, 0.07 mmol) at rt for 17 h. The reaction mixture which was a clear orange solution was then diluted with Et_2O (10 mL). The resulting solution was washed with aqueous HCl (3 × 10 mL, 3 % by volume), brine (10 mL), dried over $MgSO_4$, and was concentrated. Purification of the resulting dark orange oil by flash column chromatography afforded **12** (453mg, 79%) as a clear oil which was a mixture of diastereomers: R_f 0.10 (hexane/Et_2O, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (t, *J* = 6.2 Hz, 0.6 × 1H), 5.02 (dd, *J* = 4.0, 10.5 Hz, 0.4 × 1H), 4.57 (m, 0.6 × 1H), 4.51-4.35 (m, 2H), 4.28 (m, 0.4 × 1H), 3.73 (s, 0.6 × 3H), 3.72 (s, 0.4 × 3H), 3.03 (bs, 1H), 2.50 (ddd, *J* = 4.0, 6.9, 10.9 Hz, 0.6 × 1H), 2.23 (ddd, *J* = 4.0, 11.2, 14.8 Hz, 0.4 × 1H), 2.07 (ddd, *J* = 2.3, 10.5, 14.4 Hz, 0.6 × 1H), 1.86 (ddd, *J* = 5.7, 8.7, 14.5 Hz, 0.4 × 1H), 1.50 (s, 0.4 × 18), 1.49 (s, 0.6 × 18); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 152.9, 152.2, 84.6, 84.1, 80.3, 80.2, 66.9, 65.6, 55.3, 55.1, 35.2, 34.5, 28.2; IR (film, cm^{-1}) 2485, 2981, 1745, 1556, 1369, 1145, 866, 785; HRMS (M+Na) calcd for $C_{16}H_{28}N_2O_9$ 415.1693, found 415.1696.

(2*S*,4*S*) and (2*S*,4*R*) Methyl-5-nitro-4-(*tert*-butyl-dimethylsilyloxy)-(*S*)-2-(-*N*,*N*-di-*tert*-butoxycarbonyl)aminopentanoate (13): Methyl aspartate semialdehyde (**11**) (114 mg, 0.346 mmol) was stirred in

THF (1.4 mL, 0.25 M) in the presence of nitromethane (190 μL, 3.508 mmol) and TMG (2 μL, 0.016 mmol) at rt for 17 h. The solvent and excess nitromethane were evaporated and the resulting oily residue containing the crude nitroalcohol was dissolved in dry dichloromethane (1.4 mL). 2,6-lutidine (100 μL, 0.858 mmol) was added, followed by *tert*-butyl dimethyl silyl triflate (100 μL, 0.435 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then at rt (5 h). The reaction was then quenched by addition 5 % (by volume) of aqueous sodium bicarbonate (5 mL, 5 % by volume). The product was then extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were then combined and washed using 5% aqueous HCl (10 mL), brine (10 mL) followed by drying over $MgSO_4$. Evaporation of the solvent led to a crude oil which was purified by flash column chromatography (hexane/Et_2O, 1:1) to yield **13** (156mg, 88.9 %) as a colorless oil: R_f 0.48 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.93 (dd, J = 4.7, 9.4 Hz, 0.6 × 1H), 4.88 (t, J = 6.0 Hz, 0.4 × 1H), 4.56 – 4.34 (m, 3H), 3.71 (s, 0.4 × 3H), 3.70 (s, 0.6 × 3H), 2.58 (ddd, J = 4.3, 6.5, 14.9 Hz, 0.4 × 1H), 2.47 – 2.41 (m, 0.6 × 1), 2.21 – 2.16 (m, 0.6 × 1H), 1.90 (ddd, J = 5.6, 7.5, 14.9 Hz, 0.4 × 1H), 1.49 (s, 0.6 × 18), 1.48 (s, 0.4 × 18), 0.83 (s, 0.4 × 9), 0.82 (s, 0.6 × 9), 0.10 (s, 0.2 × 6), 0.08 (s, 0.1 × 9), 0.05 (s, 0.3 × 6), (s, 0.2 × 6), 0.00 (s, 0.3 × 6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 170.6, 152.1, 83.9, 83.7, 80.8, 80.6, 68.3, 67.7, 54.2, 52.5, 37.1, 35.6, 28.0, 25.5, 17.8, -4.8, -5.4; IR (NaCl, film) 3054, 2985, 1746, 1557, 1369, 1146; HRMS (M+Na) calcd for $C_{22}H_{42}N_2O_9Si$ 529.2557, found 529.2542.

(2*S*,4*S*) and (2*S*,4*R*) Methyl 5-*N*-(benzyloxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-di-(*tert*-butyloxycarbonyl) pentanoate (16a): Nitrosilyloxy ether (**13**) (71.0 mg, 0.140 mmol) was stirred in THF (1.5 mL) in the presence of Raney nickel under an atmosphere of hydrogen (1 atm) at rt (18 h). The reaction suspension was then filtered through a celite pad and the pad was washed with THF. The combined filtrate was concentrated to afford the crude silyloxyamine which was then dissolved in EtOAc (1.2 mL). The resulting solution was stirred in the presence of benzyl chloroformate (CbzCl, 25 μL, 0.166 mmol) and 5 % aqueous sodium bicarbonate (1.2 mL) at rt (48 h). Extraction of the product using EtOAc (4 × 2 mL), followed by washing of the combined organic layers with brine, drying over Na_2SO_4, and evaporation of the solvent led to a crude oil which was purified by flash column chromatography (hexane/Et_2O, 1:1) to yield the pure Cbz amine (**16a**) (53mg, 62%) as a clear colorless oil: R_f 0.63 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 5H), 5.20 (m, 0.3 × 1H), 5.10 (m, 2H), 4.99 (t, J = 6.2 Hz, 0.7 × 1H), 3.95 (m, 1H), 3.69 (s, 3H), 3.41 (ddd, J = 4.6, 7.1, 13.5 Hz, 0.6 ×1H), 3.27 – 3.17 (m, 1H + 0.4 × 1H), 2.49 (dt, J = 5.8, 14.7 Hz, 0.4 × 1H), 2.43 (m, 0.6 × 1H), 1.91 (ddd, J = 5.5, 7.6, 14.3 Hz, 0.7 × 1H), 1.83 (dt, J = 5.9, 14.7 Hz, 0.6 ×1H), 1.49 (s, 18H), 0.88 (s, 0.3 × 9H), 0.87 (s, 0.7 × 9H), 0.08 (s, 0.3 × 6H), 0.04 (s, 0.7 × 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 171.2, 156.5, 156.4, 152.0, 136.6, 128.4, 128.0, 83.2, 68.5, 66.6, 54.7, 53.3, 52.3, 52.3, 45.9, 45.6, 36.4, 35.2, 17.9, -4.7, -4.9; IR (film, cm^{-1}) 3055, 2985, 1724, 1369, 1265, 1145; HRMS (M+Na) calcd for $C_{30}H_{50}N_2O_9Si$ 633.3183,

found 633.3189.

(2*S*,4*S*) and (2*S*,4*R*) Methyl 5-*N*-(*tert*-butyloxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-di-(*tert*-butyloxycarbonyl)pentanoate (16b): Nitrosilyloxy ether (**13**) (103 mg, 0.203 mmol) was stirred in THF (1.5 mL) in the presence of Raney nickel under an atmosphere of hydrogen (1 atm) at rt (21 h). The reaction suspension was filtered through a celite pad and the filter pad was washed with THF. The combined filtrate was concentrated to afford the crude silyloxyamine which was dissolved in CH_2Cl_2 (1.5 mL). The resulting solution was stirred in the presence of Boc_2O (44.5 mg, 0.20 mmol) and diisopropylethylamine (70 μL, 0.402 mmol) at rt (22 h). Evaporation of the solvent, followed by the purification of the crude residue by flash column chromatography (hexane/Et_2O, 1:1) yielded the pure protected BOC-amine (**16b**) (80mg, 68 %) as a clear colorless oil: R_f 0.85 (CH_2Cl_2/MeOH, 92:8); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.97 (m, 1H), 4.86 (m, x × 1H), 4.74 (m, x × 1H), 3.93 – 3.86 (m, 0.6 × 1H), 3.69 (s, 0.4 × 3H), 3.68 (s, 0.6 × 3H), 3.30 (m, 0.4 × 1H), 3.11 (m, 1H), 2.45 (dt, *J* = 5.9, 14.7 Hz, 0.4 × 1H), 2.40 (ddd, *J* = 5.6, 7.1, 14.5 Hz, 0.6 × 1H), 1.88 (ddd, *J* = 5.4, 7.7, 14.4, 1H), 1.81 (dt, *J* = 6.0, 14.7 Hz, 0.6 × 1H), 1.48 (s, 18H), 1.41 (s, 9H), 0.87 (s, 0.4 × 9H), 0.86 (s, 0.6 × 9), 0.08 (s, 0.4 × 6), 0.04 (s, 0.3 × 6H), 0.03 (s, 0.3 × 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 171.2, 156.0, 155.8, 152.0, 146.7, 85.1, 83.1, 79.0, 78.9, 68.7, 68.6, 54.7, 54.4, 52.3, 52.2, 45.5, 45.1, 36.3, 35.1, 31.5, 28.3, 27.9, 27.3, 25.8, 25.7, 22.6, 17.9, 14.1, -4.9; IR (film, cm^{-1}) 3452, 3054, 2983, 1745, 1710, 1506, 1369, 1265, 1147; HRMS (M+Na) calcd for $C_{27}H_{52}N_2O_9Si$ 599.3340, found 599.3334.

(2*S*,4*S*) and (2*S*,4*R*) Methyl 5-*N*-acetylamino-4-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-di-(*tert*-butyloxy-carbonyl)pentanoate (16c): Nitrosilyloxy ether (**13**) (113 mg, 0.22 mmol) was stirred in THF (1.5 mL) in the presence of Raney nickel under an atmosphere of hydrogen (1 atm) at rt (24 h). The reaction suspension was filtered through a Celite pad and the filter pad was washed with THF. The collected filtrate was concentrated to afford the crude silyloxyamine which was dissolved in pyridine (450 μL, 4.49mmol). The resulting solution was stirred in the presence of acetic anhydride (25 μL, 0.289 mmol) at rt (18 h). Evaporation of the solvent followed by purification of the crude residue by flash column chromatography (hexane/EtOAc, 1:1) yielded pure protected amine (**16c**) (69.2 mg, 59.6 %) as a clear colorless oil: R_f 0.29 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.06 (m, 0.4 × 1H), 5.80 (m, 0.6 × 1H), 4.97 (t, *J* = 5.9 Hz, x × 1H), 4.95 (dd, *J* = 5.7, 7.6 Hz, x × 1H), 3.97 – 3.90 (m, 1H), 3.68 (s, 0.4 × 3H), 3.67 (s, 0.6 × 3H), 3.51 – 3.44 (m, 0.6 × 1H), 3.32 (dt, *J* = 5.7, 13.6 Hz, 0.4 × 1H), 3.21 – 3.15 (m, 1H), 2.44 (dt, *J* = 5.8, 14.8 Hz, 0.4 × 1H), 2.33 (m, 0.6 × 1H), 1.93 (s, 0.6 × 3H), 1.92 (s, 0.4 × 3H), 1.84 (ddd, *J* = 5.5, 7.7, 14.4 Hz, 0.6 × 1H), 1.75 (dt, *J* = 5.8, 14.8 Hz, 0.4 × 1H), 1.47 (s, 18H), 0.87 (s, 0.4 × 9H), 0.86 (s, 0.6 × 9H), 0.08 (s, 0.4 × 6H), 0.04 (s, 0.6 × 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 171.2, 170.2, 170.1, 152.0, 83.3, 68.3, 68.0, 54.7, 54.2, 52.4, 52.2, 44.3, 44.0, 36.6, 35.4, 27.9, 25.8, 25.7, 23.2, 17.9; IR (film, cm^{-1}) 2985, 1745, 1369, 1265, 1147. For (2*S*,4*R*)-**16c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ

6.01 (m, 1H), 5.00 (t, *J* = 5.9 Hz, 1H), 3.95 (quint, *J* = 5.5 Hz, 1H), 3.71 (s, 3H), 3.34 (dt, *J* = 5.9, 13.6 Hz, 1H), 3.20 (dt, *J* = 5.5, 13.6 Hz, 1H), 2.51 (dt, *J* = 5.7, 14.7 Hz, 1H), 1.98 (s, 3H), 1.81 (dt, *J* = 5.7, 14.8 Hz, 1H),1.50 (s, 18H), 0.90 (s, 9H), 0.10 (s, 6H). For (2*S*,4*S*)-**16c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.75 (m, 1H), 4.98 (dd, *J* = 5.7, 7.7 Hz, 1H), 3.98 (m, 1H), 3.70 (s, 3H), 3.51 (ddd, *J* = 4.4, 6.8, 13.7 Hz, 1H), 3.22 (dt, *J* = 4.6, 13.7 Hz, 1H), 2.39 (ddd, *J* = 5.7, 7.2, 14.5 Hz, 1H), 1.99 (s, 3H), 1.90 (ddd, *J* = 5.4, 7.7, 14.4 Hz, 1H),1.50 (s, 18H), 0.89 (s, 9H), 0.06 (s, 6H); HRMS (M+Na) calcd for $C_{24}H_{46}N_2O_8Si$ 541.2921, found 541.2919.

(3*S*,5*S*)- and (3*S*,5*R*)-3-*N*,*N*-di-(*tert*-butyloxycarbonyl)-5-hydroxypiperidinone (17): Aluminum amalgam [Al(Hg)] was prepared upon dipping coiled strips (5mm x 40mm) of aluminum foil (260 mg, 9.637 mmol) sequentially in ether (20 seconds), 2% aqueous mercuric chloride (20 seconds), again in ether (20 seconds), followed by immediate transfer into the reaction flask containing nitroalcohol (**12**) (257 mg, 0.655 mmol) in THF/H_2O (9:1, 13 mL). The resulting grey suspension was stirred at rt (16 h) during which time decomposition of the Al foil was complete. The reaction suspension was filtered through a celite pad and the filter cake was washed thoroughly using MeOH. The combined clear filtrate was concentrated under vacuum to afford a crude oil which was purified by flash column chromatography (CH_2Cl_2/ MeOH, 9:1) to yield pure **17** as a clear colorless oil (147.5 mg, 68.2 %) as a mixture of diastereomers (60/40, *trans*-: *cis*-). R_f 0.23 (CH_2Cl_2/MeOH, 9:1); for (3*S*,5*R*)-**17**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.28 (dd, *J* = 9.0, 10.5 Hz, 1H), 4.66 (m, 1H), 3.04 (dd, *J* = 3.5, 13.7 Hz, 1H), 2.79 (dd, *J* = 5.5, 13.7 Hz, 1H), 2.48 (dt, *J* = 9.3, 12.6 Hz, 1H), 2.37 (ddd, *J* = 3.1, 10.6, 13.1 Hz, 1H), 1.50 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 151.5, 84.1, 78.7, 54.0, 46.0, 29.7, 28.0; for (3*S*,5*S*)-**17**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.19 (dd, *J* = 9.3, 11.1 Hz, 1H), 4.41 (m, 1H), 3.00 (d, *J* = 5.3 Hz, 2H), 2.50 (ddd, *J* = 6.3, 9.3, 11.9 Hz, 1H), 2.27 (m, *J* = 11.0, 22.2 Hz, 1H), 1.50 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 151.6, 84.1, 78.8, 55.2, 46.1, 29.7, 28.0; IR (NaCl, film) 3421, 3054, 2984, 1788, 1732, 1695, 1557, 1369, 1146; HRMS (M+Na) calcd for $C_{15}H_{26}N_2O_6$ 353.1688, found 353.1687.

(3*S*,5*S*)- and (3*S*,5*R*)-3-*N*,*N*-di-(*tert*-butyloxycarbonyl)-5-*O*-acetoxypiperidinone (18): Hydroxypiperidinone (**17**) (46 mg, 0.139 mmol) was stirred in pyridine (0.7 mL) in the presence of acetic anhydride (20 μL, 0.212 mmol) at rt (16 h). The solvent and excess acetic anhydride were removed under high vacuum. The resulting crude residue was purified by flash column chromatography (CH_2Cl_2/ MeOH, 19:1) to yield the pure acetyl ester (**18**) (58.1 mg, >99%) R_f 0.35 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.16 (m, 0.5 × 1H), 5.98 (m, 0.5 × 1H), 5.18 (t, *J* = 10.2 Hz, 0.5 × 1H), 5.11 (dd, *J* = 8.3, 10.8 Hz, 0.5 × 1H), 4.79 (m, 0.5 × 1H), 4.59 (m, 0.5 × 1H), 3.72 – 3.66 (m, 1H), 3.57 (dt, *J* = 5.8, 14.6 Hz, 0.5 × 1H), 3.35 (ddd, *J* = 5.9, 7.1, 14.5 Hz, 0.5 × 1H), 2.55 (ddd, *J* = 7.0, 9.8, 12.4 Hz, 0.5 × 1H), 2.42 (dt, *J* = 8.7, 13.2 Hz, 0.5 × 1H), 2.37 – 2.25 (m, 1H), 2.02 (s, 3H), 1.51 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.9, 151.5, 84.3, 75.8, 55.0, 53.5, 43.5, 42.1, 29.4, 28.7, 28.0, 27.9, 23.1; IR (film, cm^{-1}) 3311, 2981, 2937,

1787, 1697, 1369, 1236, 1147; HRMS (M+Na) calcd for $C_{17}H_{28}N_2O_7$ 395.1794, found 395.1794.

(3*S*,5*S*)- and (3*S*,5*R*)-3-*N*-Phthaloyl-5-*O*-acetoxypiperidinone (20): Acetoxypiperidinone (**18**) (15.0 mg, 0.040 mmol) was stirred in trifluoroacetic acid (TFA)/CH_2Cl_2 (30%, 1 mL) at rt (45 min). The solvent and excess TFA were then removed under high vacuum. The dry residue was then dissolved in CH_2Cl_2 (2 x 1mL) followed by removal of the solvent and finally dissolving in THF (1 mL). The resulting THF solution was stirred with triethylamine (25 μL, 0.180 mmol) and *N*-carbethoxyphthalimide (7.0 mg, 0.047 mmol) under reflux (5 h). Evaporation of the reaction solvent led to an oily residue which was purified by flash column chromatography (CH_2Cl_2/EtOAc, 1:4) to yield **20** (6.2 mg, 51%): R_f 0.23 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (m, 2H), 7.77 (m, 2H), 6.15 (s, 0.5 × 1H), 6.01 (s, 0.5 × 1H), 5.17 (dd, *J* = 10.0, 11.3 Hz, 0.5 × 1H), 5.09 (dd, *J* = 8.4, 10.7 Hz, 0.5 × 1H), 4.98 (m, 0.5 × 1H), 4.74 (m, 0.5 × 1H) , 4.13 (quart, *J* = 7.2 Hz, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.46 (m, 1H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 171.6, 170.9, 166.8, 134.6, 131.5, 123.9, 77.8, 76.6, 48.1, 46.2, 43.0, 41.7, 29.2, 28.5, 23.2; IR (film, cm^{-1}) 3055, 2987, 2929, 1722, 1421, 1265; HRMS (M+Na) calcd for $C_{15}H_{14}N_2O_5$ 325.0800, found 325.0792.

(2*S*,4*S*) and (2*S*,4*R*) Methyl 5-nitro-4-(*tert*-butyldimethylsilyloxy)-2-(-*N*-phthaloyl)aminopentanoate (21): A solution containing the silylnitroalcohol (**13**) (215.5 mg, 0.425 mmol) in CH_2Cl_2 (0.5 mL) was treated with TFA (50 % solution by volume in CH_2Cl_2, 1 mL) at rt (1 h). The solvent and excess TFA were removed under high vacuum and the resulting oily residue was dissolved in THF (1.5 mL), followed by the addition of TEA (150 μL, 1.081 mmol) and *N*-carbethoxyphthalimide (93 mg, 0.425 mmoles). The reaction mixture was stirred at rt (16 h) and under reflux (2 h). The solvent was then evaporated and the resulting solid residue was dissolved in CH_2Cl_2, applied to a flash column and eluted with hexane/Et_2O, 1:1. The *N*-phthaloyl ester (**21**) (126.5 mg, 68%) was obtained as a clear colorless oil: R_f 0.32 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (m, 2H), 7.79 (m, 2H), 5.05 (dd, *J* = 6.3, 8.0 Hz, 0.6 × 1H), 5.02 (dd, *J* = 4.4, 9.0 Hz,; 0.4 × 1H), 4.60 (m, 1H), 4.51 (m, 1H), 4.42 (m, 1H), 3.75 (m, s, 3H), 2.69 (dt, *J* = 6.6, 14.6 Hz, 0.6 × 1H), 2.63 (dt, *J* = 5.1, 15.1 Hz, 0.4 × 1H), 2.54 (dd, *J* = 3.6, 9.2 Hz, 0.6 × 1H), 2.51 (dd, *J* = 3.6, 9.2 Hz, 0.4 × 1H), 2.37 (ddd, *J* = 5.8, 8.1, 14.2 Hz, 1H), 0.89 (s, 0.6 × 9H), 0.80 (s, 0.4 × 9H), 0.10 (s, 0.3 × 6H), 0.03 (s, 0.5 × 6H), 0.00 (s, 0.3 × 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 169.2, 167.5, 167.4, 134.5, 134.4, 131.7, 131.6, 123.8, 123.7, 80.3, 80.2, 67.5, 67.4, 53.1, 53.0, 48.2, 47.5, 34.7, 34.5, 25.5, 17.9, 17.8; IR (film, cm^{-1}) 3059, 2956, 2858, 1720, 1556, 1388, 1265, 1132; HRMS (M+Na) calcd for $C_{20}H_{28}N_2O_7Si$ 459.1563, found 459.1557.

(2*S*,4*S*) and (2*S*,4*R*) Methyl-5-nitro-5-hydroxylimino-4-(*tert*-butyldimethylsilyloxy)-2-*N*-phthaloylpentanoate (nitrolic acid 22): Nitrosilyloxyester (**21**) (30.2 mg, 0.07 mmol) was stirred in a mixture of dimethylsulfoxide (DMSO, 140 μL, 0.5 M), sodium nitrite (9.5 mg, 0.14 mmol) and acetic acid (40 μL, 0.70 mmol) at rt under argon (16 h). The reaction mixture was then quenched by addition 5 % aqueous

HCl (1 mL) at rt, then diluted with EtOAc (3 mL) and H_2O (3 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3 x 3 mL). The organic layers were combined, washed with brine (5 mL), dried over $MgSO_4$ and concentrated to give a light yellow oil. Purification of the residual oil by flash column chromatography (hexane/EtOAc, 2:1) afforded **22** as a colorless oil (5.2 mg, 16%): R_f 0.26 (hexane/EtOAc, 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.91 (s, 0.1 × 1H), 8.83 (s, 0.3 × 1H), 8.45 (s, 0.1 × 1H), 8.26 (s, 0.3 × 1H), 7.87 (m, 2H), 7.76 (m, 2H), 5.59 (dd, *J* = 5.2, 8.8 Hz, 1H), 5.27 (dd, *J* = 4.8, 8.5 Hz, 0.5 × 1H), 5.12 – 5.01 (m, 1H), 4.77 (t, *J* = 7.0 Hz, x × 1H), 4.76 (t, *J* = 6.7 Hz, x × 1H), 3.11 (ddd, *J* = 4.9, 8.5, 14.5 Hz, 0.2 × 1H), 3.03 (ddd, *J* = 5.2, 8.3, 13.8 Hz, 0.4 × 1H), 2.93 – 2.82 (m, 0.7 × 1H), 2.78 – 2.71 (m, 0.5 × 1H), 2.66 (ddd, *J* = 6.6, 8.7, 15.1 Hz, 0.4 × 1H), 3.73 (s, 3H), 0.86 (s, 9H), 0.10 (s, 0.5 × 6H), 0.08 (s, 0.5 × 6H), 0.06 (s, 0.5 × 6H), 0.04 (s, 0.5 × 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 173.0, 139.9, 137.3, 129.4, 67.0, 66.5, 64.9, 58.6, 52.0, 51.6, 42.4, 40.6, 30.9, 23.5.

(2*S*,4*S*) and (2*S*,4*R*) O^{α}-Methyl-N^{α}-phthaloyl-γ-hydroxyglutamate (23): Nitrosilyloxyester (**21**) (38.0 mg, 0.087 mmol) was stirred in a mixture of DMSO (180 μL, 0.5 M), sodium nitrite (18.6 mg, 0.261 mmol) and acetic acid (50 μL, 0.873 mmol) at 35 °C under argon (17 h). The reaction mixture was then quenched by addition of 5 % aqueous HCl (1 mL) at rt, then diluted with EtOAc (3 mL) and H_2O (3 mL). The layers were then separated and the aqueous layer was further extracted with EtOAc (3 x 2 mL). The organic layers were combined, washed with distilled water (5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated to yield a light yellow oil. Purification of the residual oil by flash column chromatography afforded **23** as a white solid (13.7 mg, 51%): R_f 0.51 (DCM: MeOH, 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 – 7.84 (m, 4H), 5.14 (m, 1H), 4.79 (d, *J* = 9.0 Hz, 0.3 × 1H), 3.71 (m, 0.7 × 1H), 3.63 (s, 3H), 2.77 (dd, J = 9.3, 12.1 Hz, 0.3 × 1H), 2.63 (m, 0.7 × 1H), 2.46 (dd, *J* = 9.3, 12.2 Hz, 0.3 × 1H), 2.08 (dt, *J* = 0.7 × 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.8, 167.1, 166.7, 134.9, 134.6, 131.3, 131.0, 123.5, 123.2, 76.5, 69.2, 52.5, 49.6, 46.9, 33.4, 30.8.

(2*S*,4*S*) and (2*S*,4*R*) O^{α},O^{ω}-Dimethyl-N^{α}-phthaloyl-γ-hydroxyglutamate (24): The *N*-phthaloyl carb-oxylic acid (**23**) was stirred in methanol in the presence of chlorotrimethylsilane (TMSCl) for 30 min at 0^{o}C and at rt for 16 h. Concentration of the reaction mixture, followed by purification by flash column chromatography (CH_2Cl_2/EtOAc, 7:1) led to the *N*-phthaloyl dimethyl ester (**24**) as a clear colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (m, 2H), 7.76 9m, 2H), 5.24 (m, 1H), 4.43 (t, *J* = 5.4 Hz, 0.6 × 1H), 4.07 (bd, *J* = 9.0 Hz, 0.4 × 1H), 3.79 (s, 0.4 × 3H), 3.75 (s, 3H), 3.55 (s, 0.6 × 3H), 2.88 (dt, *J* = 4.9, 14.8 Hz, 0.6 × 1H), 2.83 (ddd, *J* = 3.2, 10.4, 11.3 Hz, 0.4 × 1H), 2.57 (ddd, *J* = 6.3, 9.8, 14.8 Hz, 0.6 × 1H), 2.52 (ddd, *J* = 4.0, 10.5, 14.5 Hz, 0.4 × 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 174.4, 169.5, 169.4, 167.6, 167.3, 134.6, 134.3, 131.8, 123.9, 123.7, 123.5, 53.0, 52.7, 48.6, 47.9, 33.2, 32.8; IR (NaCl, film) 3054, 2987, 1739, 1721, 1437, 1422, 1389, 1129; HRMS (M+Na) calcd for $C_{15}H_{15}NO_7$ 344.0746, found 344.0748.

REFERENCES AND NOTES

1. Submitted in recognition of the career contributions of Professor Steven M. Weinreb to the art and science of synthetic chemistry.
2. Presented in part at the 229th National Meeting of the American Chemical Society; San Diego, CA, March 13, 2005. ORGN 158
3. J. Folkman, *Nat. Med.*, 1995, **1**, 27.
4. (a) T. Efferth, *Current Drug Targets*, 2006, **7**, 407. (b) T. Wakabayashi, R. Kageyama, N. Naruse, N. Tsukahara, Y. Funahashi, K. Kitoh, and Y. Watanabe, *J. Antibiot.*, 1997, **50**, 671. (c) M. S. Furness, T. P. Robinson, T. Ehlers, R. B. Hubbard, J. L. Arbiser, D. J. Goldsmith, and J. P. Bowen, *Curr. Pharm. Design*, 2005, **11**, 357. (d) R. Sidbury, N. Neuschler, E. Neuschler, P. Sun, X. Q. Wang, R. Miller, M. Tomai, E. Puscasiu, S. Gugneja, and A. S. Paller, *J. Invest. Dermatol.*, 2003, **121**, 1205. (e) P. Y. Ho, Y. C. Liang, Y. S. Ho, C. T. Chen, and W. S. Lee, *Int. J. Cancer*, 2004, **111**, 51. (f) M. Okroj, W. Kamysz, E. M. Slominska, A. Mysliwski, and J. Bigda, *Anti-Cancer Drugs*, 2005, **16**, 817. (g)
5. M. E. Franks, G. R. Macpherson, and W. D. Figg, *Lancet*, 2004, **363**, 1802. W. D. Figg, *Clin. Pharm. Thera.*, 2006, **79**, 1.
6. G. Gasparini, R. Longo, M. Fanelli, and B. A. Teicher, *J. Clin. Oncol.*, 2005, **23**, 1295. F. A. Luzzio and W. D. Figg, *Exp. Opin. Ther. Patents*, 2004, **14**, 215. P. Richardson, T. Hideshima, and K. Anderson, *Ann. Rev. Med.*, 2002, **53**, 629. J. B. Marriot, G. Muller, D. Stirling, and A. G. Dalgleish, *Exp. Opin. Biol. Ther.*, 2001, **1**, 675. N. Raje and K. Anderson *N. Engl. J. Med.*, 999, **341**, 1606. B. F. Hales, *Nat. Med.*, 1999, **5**, 489.
7. R. J. D'Amato, M. S. Loughnan, E. Flynn, and J. Folkman, *Proc. Nat Acad. Sci., U.S.A.* 1994, **91**, 4082. K. S. Bauer, S. C. Dixon, and W. D. Figg, *Biochem. Pharmacol.*, 1998, **55**, 1827.
8. B. Knoche and G. Blaschke, *Chirality*, 1994, **6**, 221. T. Eriksson, S. Bjorkman, B. Roth, H. Bjork, and P. Hoglund, *J. Pharm. Pharmacol.*, 1998, **50**, 1409. M. Meyring, J. Muhlbacher, K. Messer, N. Kastner-Pustnet, G. Bringmann, A. Mannschreck, and G. Blaschke, *Anal. Chem.*, 2002, **74**, 3726.
9. (a) F. A. Luzzio, A. V. Mayorov, and W. D. Figg, *Tetrahedron Lett.*, 2000, **41**, 2275. (b) F. A. Luzzio, E. M. Thomas, and W. D. Figg, *Tetrahedron Lett.*, 2000, **41**, 7151. (c) F. A. Luzzio, D. Y. Duveau, E. R. Lepper, and W. D. Figg, *J. Org. Chem.*, 2005, **70**, 10117.
10. U. Teubert, K. Zwingenberger, S. Wnendt, and K. Eger, *Arch. Pharm. Pharm. Med. Chem.*, 1998, **331**, 7.
11. The ornithine→aminoglutarimide cyclization route was also used by Takeuchi (See Y. Takeuchi, T. Shiragami, K. Kimura, E. Suzuki, and N. Shibata, *Org. Lett.*, 1999, **1**, 1571.) for the preparation of fluorinated glutarimide analogues of thalidomide.

12. J. M. Padrón, G. Kokotos, T. Martín, T. Markidis, W. A. Gibbons, and V. S. Martín, *Tetrahedron, Asym.*, 1998, **9**, 3381.
13. F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915.
14. F. A. Luzzio 'Science of Synthesis, Houben Weyl's Methods of Molecular Transformations: Compounds with Three and Four Carbon Heteroatom Bonds' Vol 21, ed. by S. M. Weinreb, Georg Thieme Verlag, Stuttgart, 2005, pp. 301-302.