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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 873–877

A simple synthesis of the metabotropic receptor ligand (2*S*)-α-(hydroxymethyl)-glutamic acid and its Fmoc protected derivatives

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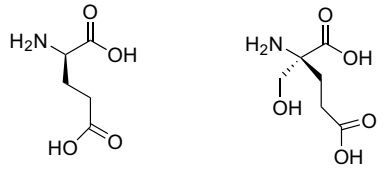
Received 26 February 2007; accepted 27 March 2007
Available online 25 April 2007

Abstract—The highly enantioselective synthesis of (2*S*)-α-(hydroxymethyl)-glutamic acid **2**, a potent metabotropic receptor ligand, was accomplished using the improved Schöllkopf methodology for the construction of quaternary α-amino acids and β-lactams. This was converted to a derivative suitably protected for direct use in Fmoc solid phase peptide synthesis.

1. Introduction

(*S*)-Glutamic acid **1** (Fig. 1), which is the main excitatory neurotransmitter in the central nervous system, plays a central role in memory and learning as well as in the pathogenesis of neuron damage to cause various neuronal diseases.[1] Its association with many acute and chronic neurodegenerative disorders such as cerebral ischemia, epilepsy, Parkinson's, and Alzheimer's diseases is well established.[2] In fact, **1** represents an endogenous ligand for more than 40 glutamate receptors, which are subdivided into ionotropic (iGluRs) and metabotropic glutamate receptors (mGluRs).[3]

To study the functions of these receptors and their modulation mechanism in the nervous system, considerable efforts have been devoted to the discovery of selective agonists and antagonists of the glutamate receptors. To date, numerous (*S*)-glutamic acid analogues have been synthesized some of which displayed great subtype-selectivity. The commonly used concept for designing these molecules is the synthesis of conformationally constrained analogues of (*S*)-glutamic acid.[1,4]



1 **2**

Figure 1.

Among the synthetic ligands disclosed so far, (2*S*)-α-(hydroxymethyl)glutamic acid **2** (Fig. 1) has been recognized as one of the most useful ligands;[5] compound **2** is able to act as a relatively potent agonist of the group 2 receptor mGluR3, while functioning as a weak antagonist of mGluR2. This compound has, in contrast, little or no effect on the group 1 and group 3 mGluRs. Since this initial report, Langlois,[6] Park and Jew,[7] and Casiraghi[8] have also disclosed syntheses of enantiopure **2**.

We have recently reported an efficient enantioselective synthesis of orthogonally protected (*R*)-α-alkylserines.[9] In continuation of our studies on the syntheses of α,α-disubstituted (quaternary) α-amino acids, our attention was focused on the α-hydroxymethyl derivative **2**, which is not only a useful ligand for glutamate receptors, but can also be viewed as a synthetic precursor to various types of natural products,[10] such as (−)-deoxydysibetaine[11] and (−)-kaitocepahalin.[12] Herein we report a simple synthesis of enantiomerically pure **2** and its conversion to an appropriately protected derivative for use in Fmoc-based solid-phase peptide synthesis.

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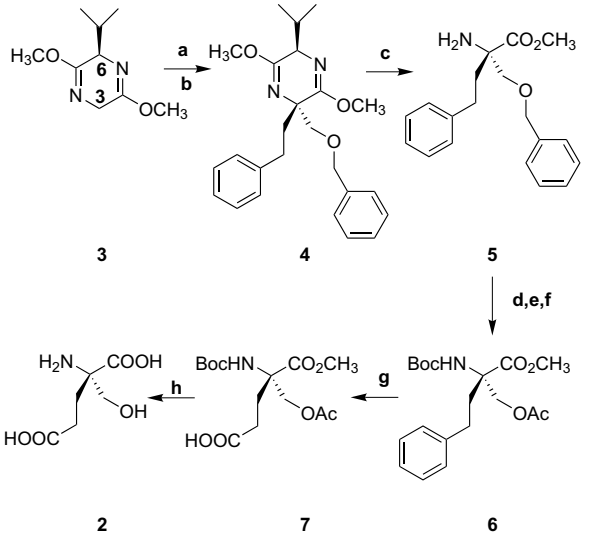
doi:10.1016/j.tetasy.2007.03.028

2. Results and discussion

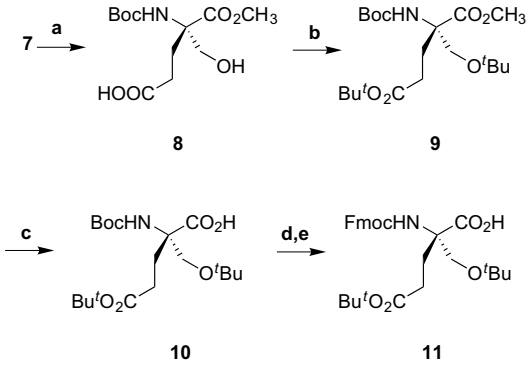
The key features of our proposed syntheses involve (i) enantioselective construction of the quaternary carbon center of **2** employing a highly improved Schöllkopf protocol we have developed,[9,13] (ii) utilization of the phenyl group as a masked carboxylic acid group. As shown in Scheme 1, the lithiated (*R*)-bislactim ether **3** was treated with 2-iodoethylbenezene to generate the monoalkylated Schöllkopf adduct in 89% yield. The diastereomeric ratio (>10:1) of this step is irrelevant, since the stereochemical outcome of the overall sequence is determined by the second alkylation. Therefore, while the minor isomer, *cis* with reference to the isopropyl group, can be removed by column chromatography, separation is not necessary. Next, lithiation of the monoalkylated product was carried out using *tert*-BuLi instead of *n*-BuLi to exploit its more basic action toward the less hindered C-3 hydrogen, as well as its negligible nucleophilicity toward the imino esters.[9,13] Alkylation with chloromethyl benzyl ether,[14] afforded **4** in good yield and high stereoselectivity (>95%), which is generally the rule as we and previous workers have found on a number of occasions.[13,15] The benzyl ether and the isopropyl group have a *trans* relationship in this product and hence the (*S*)-configuration was generated at the C-3 position. It should be stressed that changing the order of the stepwise alkylation, in order to obtain the (3*R*)-stereoisomer is not feasible since tiny amounts of the desired dialkylated product *ent*-**4** were obtained when we attempted this procedure.



Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; then 2-iodoethyl-benzene, −78 °C, 3 h, 81%; (b) *tert*-BuLi, THF, −78 °C; then chloromethyl benzyl ether, −78 °C, 8 h, 87%; (c) TFA, CH_3CN–H_2O, rt, 10 h; (d) $(Boc)_2O$, dioxane, rt, 91%; (e) H_2, Pd/C, MeOH, rt, quant.; (f) $(Ac)_2O$, DIEA, DMAP, CH_2Cl_2, rt, 14 h, 96%; (g) $NaIO_4$, $RuCl_3$, AcOEt, CH_3CN, H_2O, rt, 3 h, 72%; (h) 6 M HCl, reflux 14 h, 86%.

Mild acid hydrolysis using TFA in aqueous acetonitrile was used to effect the hydrolytic cleavage of the pyrazine ring providing the aminoacid ester **5**. Upon treatment with Boc_2O followed by catalytic hydrogenolysis using H_2/10% Pd–C to remove the benzyl group and final reprotection of the free hydroxyl function with Ac_2O, the fully protected amino acid **6** was readily obtained. The Sharpless $RuCl_3$/$NaIO_4$ mediated degradative oxidation of the phenyl group proceeded smoothly affording acid **7** in very good yield (72%).[16] Treatment of acid **7** with 6 M HCl followed by ion exchange chromatography (Dowex 50Wx8-200, 5% aq NH_3) finally afforded (2*S*)-α-(hydroxymethyl)glutamic acid **2** as a white solid.

With monoacid **7** in hand, we next attempted to transform it to a corresponding derivative, which was suitably protected for direct use in Fmoc solid-phase peptide synthesis by careful manipulation of the protecting groups of the four functionalities present in the molecule. After some experimentation, we found that the following reaction sequence is the most efficient for this conversion (Scheme 2): (1) careful treatment of **7** with K_2CO_3 in MeOH to remove the acetyl group while the methyl ester remains intact; (2) introduction of the *tert*-butyl group to both the carboxyl and the hydroxyl side chains by treating **8** with *tert*-butyl tricloroacetimidate. Initial attempts to react **8** with isobutylene and catalytic sulfuric acid or boron trifluoride etherate proved unsuccessful; (3) hydrolysis of **9** with aqueous NaOH to generate the free acid **10**; (4) removal of N-Boc protecting group while retaining both the *tert*-butyl ester and ether was achieved by treating **10** with a 1 M solution of HCl in diethyl ether.[17] Reaction of the precipitated internal salt with Fmoc-Cl/Na_2CO_3 gave rise to the desired compound **11** in excellent ee (≫95%), confirmed by chiral HPLC.



Scheme 2. Reagents and conditions: (a) K_2CO_3, MeOH, rt, 40 min, 92%; (b) *tert*-butyl trichloroacetimidate, cat. $BF_3{\cdot}Et_2O$, cyclohexane, rt, 24 h, 61%; (c) NaOH, MeOH, rt, 16 h, 89%; (d) 1 M HCl Et_2O, rt, 3 h; (e) Fmoc-Cl, Na_2CO_3, dioxane, rt, 10 h, 67%.

3. Conclusions

In conclusion, we have developed an efficient enantioselective synthesis of the potent mGluR3 agonist (2*S*)-α-(hydroxymethyl)-glutamic acid **2**. The synthesis was accomplished in 38% overall yield from commercially available (*R*)-Schöllkopf chiral auxiliary **3**. The other enantiomer can be accessed by using *ent*-**3**. To the best of our knowledge, this report has described the first synthetic protocol to obtain orthogonally protected (2*S*)-α-(hydroxy-

methyl)-glutamic acid, suitable for Fmoc-solid phase peptide syntheses.

4. Experimental

4.1. General

All of the compounds for which analytical and spectroscopic data are quoted were homogeneous by TLC. TLC analyses were performed using silica gel plates (E. Merck silica gel 60 F-254) and components were visualized by the following methods: ultraviolet light absorbance, phosphomolybdic acid and ninhydrin spray. Column chromatography was carried out on silica gel (E. Merck, 70-230 mesh). All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz Mercury Varian spectrometer. Electron spray mass spectroscopy (ESMS) was performed on a Surveyor MSQ instrument. Optical rotations were recorded on a Perkin Elmer 349 Polarimeter ($\lambda = 589$ nm, 1 dm cell). Dry THF was distilled from sodium and benzophenone. HPLC analysis was carried out on an analytical column Chiradex LichroCART-250-4 at a flow rate of 0.5 ml/min using 30% CH_3CN and 70% CH_3COOH/CH_3COONa buffer pH 4.4.

4.2. (3*S*,6*R*)-3-[(Benzyloxy)methyl]-6-isopropyl-1,4-dimethoxy-3-phenethyl-3,6-dihydropyrazine 4

To a solution of (3*R*)-3-isopropyl-5-methoxy-6-methyl-3,6-dihydro-2-pyrazinyl methyl ether (0.60 g, 3.04 mmol) in dry THF (6 ml) under argon at −78 °C was added *n*-BuLi (1.6 M, 1.90 ml, 3.04 mmol) dropwise. The resulting solution was stirred at −78 °C for 15 min and treated slowly with a solution of 2-iodoethylbenzene (0.72 g, 3.10 mmol) in THF (8 ml). The mixture was stirred at −78 °C for 3 h, allowed to slowly warm to ambient temperature, and quenched with saturated NH_4Cl. The aqueous layer was extracted with Et_2O twice and the combined organic layers washed with brine and dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography (silica gel, CH_2Cl_2) to afford the monoalkylated pyrazine as oil in 89% yield.

This pyrazine (0.72 g, 2.50 mmol) was dissolved in dry THF (5.5 ml) under argon, cooled to −78 °C followed by the slow addition of *tert*-BuLi (1.6 M, 1.56 ml, 2.50 mmol). Stirring was continued for 1 h and then a solution of chloromethyl benzyl ether (0.41 g, 2.70 mmol) in THF (6 ml) was added slowly. The reaction mixture was stirred for 8 h at −78 °C, and then allowed to warm to ambient temperature overnight, and quenched with saturated NH_4Cl. The aqueous layer was extracted with Et_2O twice and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, light petroleum–ethyl acetate: 9/1) to afford **4** as an oil (0.89 g, 87%); $[\alpha]_D^{25} = -31.0$ (*c* 1, CH_2Cl_2); ($C_{25}H_{32}N_2O_3$ requires C, 73.50; H, 7.90. Found: C, 73.39; H, 7.84); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.71 (d, 3H, $J = 6.60$ Hz), 1.14 (d, 3H, $J = 6.60$ Hz), 1.75–2.10 (m, 2H), 2.20–2.60 (m, 3H), 3.38 (d, 1H, $J = 8.8$ Hz), 3.68, 4.03 (AB, 2H, $J_{AB} = 9.1$ Hz), 3.73, 3.75 (s, 6H), 4.47 (s, 2H), 7.13–7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.1, 19.8, 30.6, 30.9, 37.7, 52.5, 61.0, 63.2, 97.0, 125.9, 127.5, 127.6, 128.5, 128.6, 138.9, 142.7, 162.5, 164.5; MS (EI): 409.3 (M^+).

4.3. Methyl (2*S*)-2-amino-2-[(benzyloxy)methyl]-4-phenylbutanoate 5

To a solution of compound **4** (0.72 g, 1.76 mmol) in acetonitrile–water 3:1 (8 ml), trifluoroacetic acid (0.9 ml) was added and the resulting solution stirred at ambient temperature for 10 h. After this time the solvents were evaporated and the residue was diluted with ethyl acetate and water. The aqueous layer was neutralized with $NaHCO_3$ 5% solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 9.7/0.3) to afford **5** as semisolid (0.47 g, 85%); $[\alpha]_D^{25} = -17.1$ (*c* 1, CH_2Cl_2); ($C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40. Found: C, 72.48; H, 7.31); ^{1}H (200 MHz, $CDCl_3$): δ 1.70–2.18 (m, 4H), 2.45–2.67 (m, 2H), 3.45, 3.78 (AB, 2H, $J_{AB} = 8.7$ Hz), 3.68 (s, 3H), 4.51 (s, 2H), 7.15–7.32 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.1, 38.4, 52.5, 62.2, 73.5, 97.0, 126.2, 127.1, 127.7, 128.5, 128.6, 138.1, 141.4, 176.2; MS (EI): 314.0 (M^+).

4.4. Methyl (2*S*)-2-[(acetyloxy)methyl]-2-[(*tert*-butoxycarbonyl)amino]-4-phenylbutanoate 6

Compound **5** (0.45 g, 1.44 mmol) was dissolved in dioxane (5 ml) and the mixture cooled in an ice bath for 20 min. Boc anhydride (0.38 g, 1.73 mmol) was added, and the mixture stirred for 10 h (1 h in an ice bath and overnight at abient temperature). The reaction was partitioned between aqueous $NaHCO_3$ 5% and Et_2O. The organic phase was washed with citric acid 10%, water, dried over Na_2SO_4, concentrated under reduced pressure, and purified by chromatography (silica gel, CH_2Cl_2/MeOH = 9.8/0.2) to afford the fully protected amino acid as a highly viscous oil (0.54 g, 91%); $[\alpha]_D^{25} = -8.8$ (*c* 1, CH_2Cl_2); ^{1}H (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.95–2.75 (m, 4H), 3.65, 3.80 (AB, 2H, $J_{AB} = 8.9$ Hz), 3.68 (s, 3H), 4.51 (s, 2H), 5.75 (br s, 1H), 7.12–7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.6, 30.3, 33.8, 52.9, 64.3, 67.3, 71.5, 73.5, 79.6, 126.3, 127.1, 127.7, 128.5, 128.7, 138.2, 141.3, 154.4, 173.0.

To the previous compound (0.50 g, 1.20 mmol) CH_3OH (10 ml) was added followed by 10% Pd/C (50 mg) and the mixture was stirred under hydrogen (1 atm) for 10 h at room temperature. The catalyst was filtered over a Celite pad and washed with CH_3OH. After evaporation to dryness, CH_2Cl_2 (10 ml) was added. The resulting solution was cooled to 0 °C via an ice bath. Next, acetic anhydride (340 μl, 3.6 mmol), DIEA (630 μl, 3.6 mmol), and DMAP (36 mg, 0.3 mmol) were added to the reaction flask. The reaction solution was stirred for 30 min at 0 °C and at ambient temperature overnight, quenched with 10% citric acid and transferred to a separatory funnel with CH_2Cl_2.

The resulting organic layer was washed with water, dried over Na_2SO_4, concentrated on a rotary evaporator, and purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 9.7/0.3) to provide **6** as an oil (0.42 g, 96%). $[\alpha]_D^{25} = -9.8$ (*c* 1, CH_2Cl_2); ($C_{19}H_{27}NO_6$ requires C, 62.45; H, 7.45. Found: C, 62.61; H, 7.57); ^{1}H (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.00 (s, 3H), 1.95–2.78 (m, 4H), 3.69 (s, 3H), 4.27, 4.65 (AB, 2H, $J_{AB} = 10.7$ Hz), 5.65 (br s, 1H), 7.10–7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.9, 28.5, 30.1, 33.6, 53.1, 63.0, 65.3, 79.9, 126.3, 128.6, 140.8, 154.0, 170.5, 172.3; MS (EI): 366.2 (M^+).

4.5. (4*S*)-4-[(Acetyloxy)methyl]-4-[(*tert*-butoxycarbonyl)amino]-5-methoxy-5-oxopentanoic acid 7

To a solution of **6** (1.55 g, 4.24 mmol) in AcOEt (7 ml), CH_3CN (7 ml) and H_2O (14 ml), sodium metaperiodate (2.13 g, 100 mmol) was added. The resulting mixture was stirred vigorously and ruthenium trichloride (85 mg, 0.42 mmol) was added. The solution was stirred for 3 h and after the addition of water, it was extracted with AcOEt (3×30 ml). The combined organic layer was washed with H_2O (30 ml), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using CH_2Cl_2/MeOH = 9.5/0.5 as eluent to give **7** as a semisolid (1.02 g, 72%). $[\alpha]_D^{25} = +2.5$ (*c* 1, CH_2Cl_2); ($C_{14}H_{23}NO_8$ requires C, 50.44; H, 6.95. Found: C, 50.65; H, 7.02); ^{1}H (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.03 (s, 3H), 2.05–2.61 (m, 4H), 3.74 (s, 3H), 4.29, 4.70 (AB, 2H, $J_{AB} = 9.5$ Hz), 5.60 (br s, 1H), 9.5 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.9, 28.5, 28.6, 30.1, 53.4, 62.2, 65.0, 79.8, 154.0, 170.5, 171.9, 177.8; MS (EI): 355.9 (M+Na^+).

4.6. (2*S*)-2-Hydroxymethylglutamic acid 2

A solution of compound **7** (0.10 g, 0.30 mmol) in 6 M HCl (4 ml) was stirred at reflux overnight. After cooling to rt, AcOEt was added and the aqueous phase was selected, concentrated in vacuo, and purified by ion exchange column chromatography (Dowex 50Wx8-200; 5% aq NH_3) giving **2** as a white solid (46 mg, 86%). $[\alpha]_D^{25} = +4.5$ (*c* 1, H_2O); (200 MHz, D_2O): 2.05–2.25 (m, 2H), 2.30–2.45 (m, 2H), 3.73 (d, 1H, $J = 11.8$ Hz), 3.92 (d, 1H, $J = 11.8$ Hz); ^{13}C NMR (50 MHz, D_2O): 175.2, 171.0, 63.9, 63.0, 27.82, 26.12; MS (EI): 176.0 (M^-).

4.7. (4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-4-(hydroxymethyl)-5-methoxy-5-oxopentanoic acid 8

A solution of acetate **7** (0.80 g, 2.40 mmol) in MeOH (62 ml) was treated with K_2CO_3 (0.49 g, 3.59 mmol) at 25 °C. After stirring for 40 min, the mixture was concentrated under reduced pressure in a water bath not exceeding 25 °C to half of the original volume. The mixture was poured into AcOEt and washed with 5% citric acid then the aqueous layer was extracted twice with AcOEt. The combined organic layer was washed with H_2O (20 ml), brine (30 ml), dried over Na_2SO_4, and evaporated to a residue. Purification by column chromatography using CH_2Cl_2/MeOH = 9.3/0.7 as eluent furnished **8** (0.67 g, 92%) $[\alpha]_D^{25} = -22.5$ (*c* 1, CH_2Cl_2) ($C_{12}H_{21}NO_7$ requires C, 49.48; H, 7.27. Found: C, 49.31; H, 7.18); ^{1}H (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.07–2.45 (m, 4H), 3.77 (s, 3H), 3.80, 4.10 (AB, 2H, $J_{AB} = 10.9$ Hz), 5.67 (br s, 1H), 9.5 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.4, 28.5, 28.7, 53.2, 64.3, 65.5, 79.9, 155.3, 172.9, 177.8; MS (EI): 290.5 (M^-).

4.8. 5-(*tert*-Butyl)-1-methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-(*tert*-butoxymethyl)pentanedioate 9

To a solution of **8** (0.61 g, 2.00 mmol) in cyclohexane (4 ml) *t*-butyl trichloroacetimidate (1.75 g, 8 mmol) was added followed by a catalytic amount of boron trifluoride etherate (40 μl). The reaction mixture was stirred at ambient temperature for 24 h and then solid $NaHCO_3$ (0.84 g, 10 mmol) was added. The precipitate was filtered and the filtrate was concentrated and purified by column chromatography using light petroleum ether/diethyl ether = 9/1 to deliver **9** as a viscous oil (0.49 g, 61%). $[\alpha]_D^{25} = -6.9$ (*c* 1, CH_2Cl_2) ($C_{20}H_{37}NO_7$ requires C, 59.53; H, 9.24. Found: C, 59.64; H, 9.32); ^{1}H (200 MHz, $CDCl_3$): δ 1.16 (s, 9H), 1.42 (s, 9H), 1.55 (s, 9H), 2.12–2.50 (m, 4H), 3.79 (s, 3H), 3.67, 4.08 (AB, 2H, $J_{AB} = 10.9$ Hz), 5.60 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.2, 28.4, 28.5, 28.9, 53.5, 64.3, 65.5, 74.7, 79.5, 80.3, 157.0, 172.9, 173.6; MS (EI): 404.1 (M^+).

4.9. (2*S*)-5-(*tert*-Butoxy)-2-[(*tert*-butoxycarbonyl)amino]-2-(*tert*-butoxymethyl)-5-oxopentanoic acid 10

To a solution of **9** (0.42 g, 1.04 mmol) in MeOH (3 ml), 4 N NaOH (0.37 ml, 1.50 mmol) was added and the mixture was stirred at ambient temperature for 10 h. After concentration under reduced pressure, the residue was partitioned between 5% citric acid and Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography using diethyl ether to give **10** as a highly viscous oil (0.36 g, 89%). $[\alpha]_D^{25} = -3.8$ (*c* 1, CH_2Cl_2) ($C_{19}H_{35}NO_7$ requires C, 58.59; H, 9.06. Found: C, 58.83; H, 9.18); ^{1}H (200 MHz, $CDCl_3$): δ 1.16 (s, 9H), 1.42 (s, 9H), 1.55 (s, 9H), 2.17–2.48 (m, 4H), 3.49, 3.78 (AB, 2H, $J_{AB} = 10.5$ Hz), 5.50 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.4, 28.5, 28.6, 28.9, 64.3, 65.5, 74.4, 79.8, 80.3, 155.7, 172.8, 179.4; MS (EI): 411.5 (M+Na^+).

4.10. (2*S*)-5-(*tert*-Butoxy)-2-(*tert*-butoxymethyl)-2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino-5-oxopentanoic acid 11

The *N*-Boc amino acid **10** (0.32 g, 0.82 mmol) was dissolved in 1 M HCl in Et_2O (5 ml) and the reaction mixture stirred at rt for 3 h. After this time, the precipitate was isolated by filtration, dissolved in dioxane (3 ml) and 10% Na_2CO_3 (2 ml) and cooled in an ice bath. Fmoc-Cl (0.26 g, 1.00 mmol) in dioxane (1 ml) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 10 h. After careful acidification with 3 N HCl to pH 2 at 0 °C, the aqueous phase was extracted with Et_2O, the organic layer was washed with H_2O, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography using diethyl ether to yield **11** as a semisolid (0.28 g, 67%). $[\alpha]_D^{25} = -4.1$

(c 1, CH_2Cl_2) ($C_{29}H_{37}NO_7$ requires C, 68.08; H, 7.29. Found: C, 68.32; H, 7.37); ^1H (200 MHz, $CDCl_3$): δ 1.18 (s, 9H), 1.57 (s, 9H), 2.16–2.50 (m, 4H), 3.46, 3.75 (AB, 2H, $J_{AB} = 11.1$ Hz), 4.17 (t, 1H, $J = 7.1$ Hz), 4.28 (d, 2H, $J = 7.1$ Hz), 5.57 (br s, 1H), 7.23–7.38 (m, 4H), 7.65 (d, 1H, $J = 8.8$ Hz), 7.75 (d, 1H, $J = 8.8$ Hz) ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.4, 28.6, 28.9, 47.3, 64.3, 65.5, 67.1, 74.4, 79.8, 80.3, 120.2, 125.3, 127.3, 127.9, 141.5, 144.1, 155.0, 176.5; MS (EI): 534.6 ($M+Na^+$). HPLC: Chiradex LichroCART-250-4, 30% CH_3CN and 70% CH_3COOH/CH_3COONa buffer pH 4.4. $t_R = 16.4$ min.

References

1. Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.
2. Catarzi, D.; Colotta, V.; Varano, F. *Curr. Top. Med. Chem.* **2006**, *6*, 809–821.
3. Blasi, A. D.; Conn, P. J.; Pin, J. P.; Nocoletti, F. *Trends Pharmacol. Sci.* **2001**, *22*, 114–120.
4. (a) Jane, D. E.; Thomas, N. K.; Tse, H. W.; Watkins, J. C. *Neuropharmacology* **1996**, *35*, 1029–1035; (b) Escribano, A.; Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Baker, S. R.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 765–770; (c) Bertrand, H.-O.; Bessis, A.-S.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **2002**, *45*, 3171–3183.
5. Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555–7559.
6. (a) Choudhury, P. K.; Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 463–464; (b) Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558–7564.
7. Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-S.; Park, H.-G. *Org. Lett.* **2005**, *7*, 3207–3209.
8. Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611–2613.
9. Vassiliou, S.; Yiotakis, A.; Magriotis, P. A. *Tetrahedron Lett.* **2006**, *47*, 7339–7341.
10. Shinada, T.; Ohfune, Y. *Eur. J. Org. Chem.* **2005**, *24*, 5127–5143.
11. Langlois, N.; Nguyen, B. K. L. *J. Org. Chem.* **2004**, *69*, 7558–7564.
12. Kawasaki, M.; Shinada, T.; Hamada, M.; Ohfune, Y. *Org. Lett.* **2005**, *7*, 4165–4167.
13. (a) Vassiliou, S.; Magriotis, P. A. *Tetrahedron: Asymmetry* **2006**, *17*, 1754–1757; (b) Vassiliou, S.; Dimitropoulos, C.; Magriotis, P. A. *Synlett* **2003**, 2398–2400.
14. Shipov, A. G.; Savostyanova, L. A.; Baukov, Y. L. *J. Gen. Chem. U.S.S.R.* **1989**, *59*, 1067–1068.
15. Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2359–2368.
16. Calsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
17. Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216–3218.