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Concise Synthesis of 4-Acylamino Analogues of 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic Acids (LY354740) from an Acylnitroso Diels−Alder Cycloadduct

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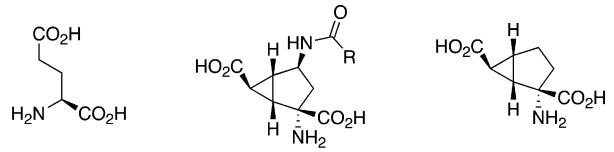
Concise total syntheses of 4-acylamino analogues of LY354740 were accomplished employing an *N*-Boc acylnitroso Diels−Alder cycloadduct as the starting material. The syntheses involved *N*−*O* bond cleavage, oxidation, intermolecular cyclopropanation, Bucherer−Bergs reaction, hydrolysis, and regioselective acylation with a temporary copper chelate. The synthesis of an optically active compound was also achieved.

Introduction

L-Glutamic acid (L-Glu) is the primary excitatory neurotransmitter in the mammalian central nervous system. It participates in a variety of brain functions such as learning and memory, control of movements, and pain sensitivity. Therefore, dysfunctional glutamate neurotransmission has been implicated in brain disorders such as Alzheimer's disease,[1] anxiety,[2] and schizophrenia.[3] The neuronal effects of L-Glu are mediated by two heterogeneous families of cell membrane-associated receptors, the ionotropic (ion-channel-linked) glutamate receptors and the metabotropic (G-protein-coupled) glutamate receptors.[4,5] There are currently eight known subtypes of metabotropic glutamate receptors (mGluR1−8) which can be classified into three subgroups (groups I−III) on the basis of their sequence similarities.[4,6−9] A number of conformationally constrained analogues of L-Glu have been designed and synthesized to elucidate the conformational requirement for the activation of different receptor types.[10] These efforts have resulted in the discovery of several potent and selective agonists for group II metabotropic glutamate receptors,[8,11] including acylamino derivatives (**1**) of LY354740.[11a,b,12,13]



L-Glutamic acid **1** LY354740

The previously reported synthesis of compound **1** involved a 14-step sequence starting with cyclopropanation of cyclopentenone, installation of a β-hydroxyl group through a Saegusa oxidation, followed by epoxidation and epoxide opening. The resultant intermediate was then subjected to Bucherer−Bergs reaction followed[14] by hydrolysis and reprotection to construct the amino acid moiety, conversion of the hydroxyl group to an azide, and finally reduction of the azide and derivatization of the resulting amine (Scheme 1).[13]

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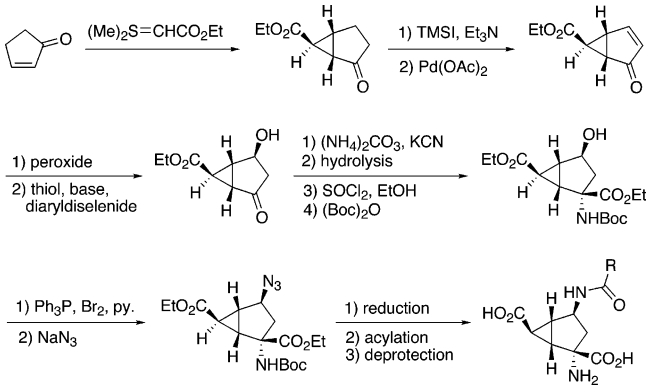
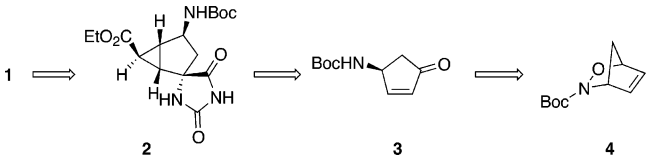
SCHEME 1



SCHEME 2



N-Acylnitroso Diels−Alder cycloadducts are a group of compounds that can generate remarkable molecular diversity despite their deceivingly simple structure. They have been the starting materials for the syntheses of numerous biologically significant compounds in our laboratories and others,[15] including benzodiazepines,[16] human 5-lypoxygenase inhibitors,[17] and carbocyclic nucleosides.[18,19] As part of our efforts to extend the synthetic utility of *N*-acylnitroso Diels−Alder cycloadducts, we envisioned a concise synthesis of compound **1** through intermediates such as the spiro-hydantoin **2** and *β*-aminocyclopentenone **3** using *N*-Boc cycloadduct **4** as the starting material (Scheme 2). Some of the chemistry, including the cyclopropanation and Bucherer−Bergs reaction, delineated in Scheme 1 would be applied to our synthesis; however, in contrast to the reported synthesis, the 4-amino group would be installed at the beginning. This synthetic scheme is even more attractive from the standpoint that the optically active version of compound **1** could be obtained by using an enzymatic resolution developed in our laboratories (*vide infra*).[20]

Results and Discussion

The exploratory synthesis was carried out on racemic materials. The first key intermediate, the α,*β*-unsaturated ketone **3**, was accessed through an *N*−*O* bond cleavage of *N*-Boc cycloadduct **4**, using the procedure developed in our laboratories,[21,22] followed by a Swern oxidation of the resultant alcohol **5** (Scheme 3). Subsequent intermolecular cyclopropanation of **3** was effected by employing sulfonium ylide ethyl (dimethylsulfuranylidene)acetate **6**, generated *in situ* from the corresponding sulfonium bromide and DBU in CH_2Cl_2 at room temperature,[11b] to provide the bicyclic ketone **7** in 60−70% yield. Compound **7** was then subjected to a Bucherer−Bergs reaction by using ammonium carbonate and potassium cyanide in EtOH/H_2O at 45 °C to generate the spiro-hydantoin **2** in 59% isolated yield. The relative stereochemistry of **2** was confirmed by its X-ray crystal structure (see the Supporting Information). Basic hydrolysis of **2** at 100 °C removed all the protecting groups and exposed two amines in the intermediate **8**. At this time, a method to selectively acylate the C4 amine was required and the well-known procedure to differentiate the two amino groups in lysine by using a temporary cupric complex with the α-amino acid moiety appeared to be an attractive option.[23] The constrained conformation of **8** guaranteed the α-amino acid group being the only copper chelation site, and therefore elaboration at the nonchelated C4 amine could be achieved. Indeed, when the crude **8** was treated sequentially with copper(II) carbonate, benzoyl chloride, or benzyloxy chloroformate under Schotten−Baumann type conditions, and finally Chelex resin, compound **1** was obtained with a total yield of ∼30% from spiro-hydantoin **2**. No purification of any of the intermediates was required during this process.

The synthetic sequence delineated in Scheme 3 was subsequently applied to the synthesis of optically active compound **1** by using the highly enantioenriched starting material (−)-**5**, obtained from the lipase-catalyzed enzymatic resolution of (±)-**5** developed in these laboratories (Scheme 4).[19,24]

In conclusion, a highly concise total synthesis of 4-acylamino analogues of LY354740 has been accomplished by using *N*-Boc acylnitroso Diels−Alder cycloadduct as the starting material. The synthesis provides a fast access to a variety of analogues for SAR studies in order to search for new potent and selective agonists for group II metabotropic glutamate receptors. The cupric chelate methodology, well cited in the literature for regioselective derivatization of lysine, proved to be feasible in our molecule and enabled us to selectively acylate the C4 amino group. The synthesis has been applied to the assembly of optically active compound **1** by using one of the enantiomers obtained from the enzymatic resolution of **(**±)-**5**.

Experimental Section

(±)-4-(*N-tert*-Butoxycarbonyl)aminocyclopentenone (3) and (−)-3. To the stirred solution of oxalyl chloride (262 *μ*L, 3.00 mmol) in dry CH_2Cl_2 (7 mL) at −78 °C was added dry

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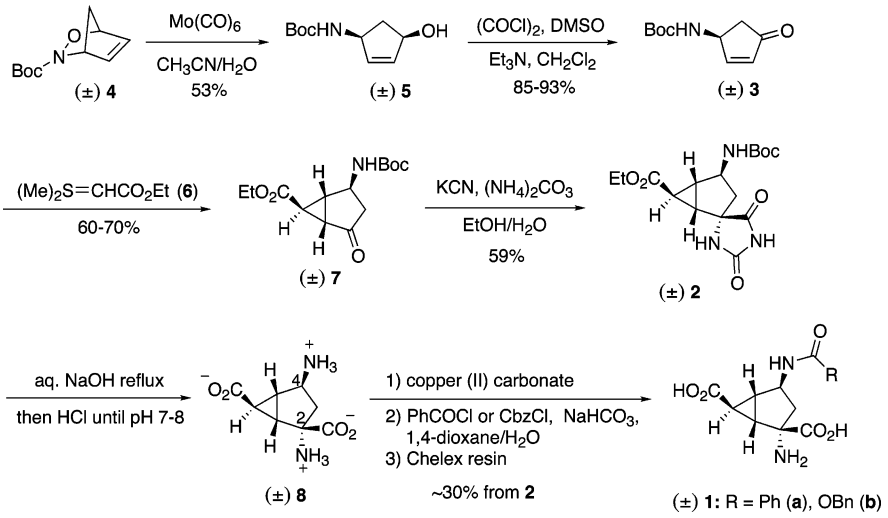
SCHEME 3



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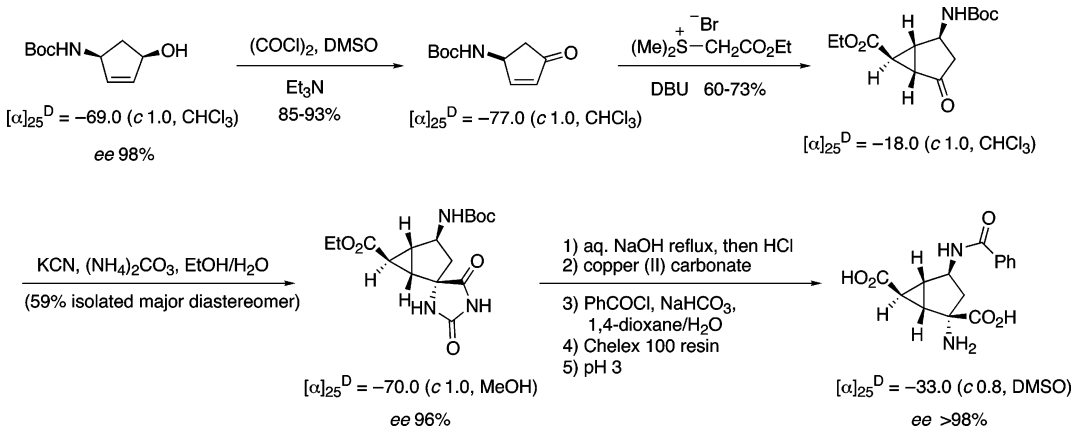

DMSO (426 μL, 6.00 mmol) dropwise via syringe. The resultant solution was stirred at −78 °C for 15 min, after which time the solution of (±)-**5**[21,22] (399 mg, 2.00 mmol) in dry CH_2Cl_2 (6 mL + 2 mL wash) was added *via* cannula. The mixture was stirred at −78 °C for 30 min. To this mixture was then added triethylamine (1.4 mL, 10.00 mmol) and the resultant mixture was stirred at −78 °C for 10 min and at −78 °C to room temperature for 20 min. CH_2Cl_2 was added to dilute the solution and the organic solution was washed with water and brine and was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the product was purified by column chromatography (silica gel, 3:1 hexanes/ethyl acetate) to give a white solid (348 mg, 88%). Mp 124−125 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.15 (d_{app}, 1H, J = 19.0 Hz), 2.81 (dd, 1H, J = 6.3 and 19.0 Hz), 4.96 (m, 2H), 6.20 (dd, 1H, J = 1.5 and 5.7 Hz), 7.51 (dd, 1H, J = 1.8 and 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 28.5, 42.5, 51.2, 80.3, 135.3, 155.2, 162.6, 206.8; FAB HRMS 198.1108 (MH^+, calcd for $C_{10}H_{16}NO_3$ 198.1130). The enantioenriched (−)-**3** was obtained from (−)-**5** ($[\alpha]^D_{25}$ −73 (*c* 1.0, $CHCl_3$), 98% ee) with $[\alpha]^D_{25}$ −73 (*c* 1.0, $CHCl_3$) and spectral data were in accordance with the racemic compound.

(±)-Ethyl 2-(*N*-*tert*-Butoxycarbonyl)amino-4-oxobicyclo-[3.1.0]hexane-6-carboxylate (7) and (−)-7. To the solution of (ethoxycarbonylmethyl)dimethylsulfonium bromide (1.15 g, 5.00 mmol) in anhydrous CH_2Cl_2 (20 mL) at room temperature was added DBU (900 μL, 6.00 mmol) via syringe. The resultant solution was stirred at room temperature for 1 h, after which time the solid (±)-**3** (493 mg, 2.00 mmol) was added in one portion. The stirring was continued overnight. The solvent was removed on a rotary evaporator and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous solution was extracted with another portion of ethyl acetate. The combined ethyl acetate portions were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel, 6:1 to 4:1 hexanes/ethyl acetate) to give a white solid (404 mg, 71%), which contained a minor amount of inseparable diastereomer. Recrystallization from ether gave the major product as white crystals. Mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz), 1.44 (s, 9H), 2.01 (m, 2H), 2.37 (dd, 1H, J = 2.5 and 5.0 Hz), 2.42 (dd, 1H, J = 7.0 and 19.0 Hz), 2.62 (m, 1H), 4.16 (q, 2H, J = 7.0 Hz), 4.36 (m, 1H), 4.91 (bd, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 26.0, 28.5, 34.7, 34.8, 40.8, 48.1, 61.8, 80.4, 155.1, 169.5, 209.0; FAB HRMS 284.1505 (MH^+, calcd for $C_{14}H_{22}NO_5$ 284.1498). The enantioenriched (−)-**7** was obtained from (−)-**3** with $[\alpha]^D_{25}$ −16.6 (*c* 0.85, $CHCl_3$) and spectral data were in accordance with the racemic compound.

(±)-Ethyl 4-(*N*-*tert*-Butoxycarbonyl)aminobicyclo[3.1.0]-hexane-6-carboxylate-2-spiro-5′-hydantoin (2) and (−)-2. To the solution of **7** (99 mg, 0.35 mmol) in 3:2 EtOH/H_2O (2 mL) was added ammonium carbonate (196 mg, 2.04 mmol) followed by KCN (46 mg, 0.70 mmol). The resultant mixture was stirred at 45 °C for 24 h, after which time a white precipitate was observed in the mixture. Water (1 mL) was added and the mixture was cooled to 0 °C and stirred for 2 h. The white precipitate was collected by filtration, washed with cold water, and dried under reduced pressure to give 73 mg (59%) of the major diastereomer as a white solid. Mp 239−242 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.19 (t, 3H, J = 7.2 Hz),

1.39 (s, 9H), 1.78 (m, 2H), 1.83 (dd, 1H, J = 3.0 and 6.0 Hz), 1.85 (overlapping dd, J = 3.0 and 3.0 Hz), 2.12 (dd, 1H, J = 3.0 and 6.0 Hz), 4.06 (dq, 2H, J = 7.2 and 10.8 Hz), 4.15 (m, 1H), 6.42 (d, 1H, J = 9.6 Hz), 8.09 (s, 1H), 10.94 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.1, 19.8, 28.1, 32.4, 32.9, 36.5, 51.1, 60.5, 68.7, 78.4, 154.4, 155.8, 170.9, 178.6; FAB HRMS 354.1688 (MH^+, calcd for $C_{16}H_{24}N_3O_6$ 354.1665). The enantioenriched (−)-**2** was obtained from (−)-**7** with $[\alpha]^{D}_{25}$ −70.0 (*c* 1.0, MeOH) and spectral data were in accordance with the racemic compound. The ee of (−)-**2** was determined to be 96% judging from the NMR of the Mosher amide prepared from Boc removal of (−)-**2** followed by *N*-acylation with a Mosher acid chloride.

(±)-2-Amino-4-benzoylaminobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (1a) and (−)-1a. The mixture of hydantoin (±)-**2** (100 mg, 0.28 mmol) and 2 N NaOH (1 mL) was stirred at reflux for 27 h. The resultant light brown solution was cooled to room temperature and 1 N HCl was added until pH 7 was reached. The precipitate was filtered out and the filtrate was concentrated *in vacuo* to give the crude product **8**. This crude compound was redissolved in water (2 mL) and warmed to 85−90 °C. To this stirred solution was added basic copper(II) carbonate (46 mg, 0.21 mmol). The resultant mixture was brought to reflux and stirred at that temperature for 20 min. The blue solution was hot filtered through a Pasteur pipet equipped with a cotton plug (washed with 0.5−1.0 mL of water). To the filtrate was added $NaHCO_3$ (70 mg, 0.84 mmol), 1,4-dioxane (2 mL), and benzoyl chloride (42 μL, 0.36 mmol). The mixture was stirred at room temperature overnight. The blue precipitate was collected by filtration (washed with small portions of 50% MeOH/H_2O). The filtrate was concentrated under reduced pressure and a small amount of water was added. The undissolved blue solid was collected by filtration (washed with small portions of 50% MeOH/H_2O). The two crops of blue solid were pooled together and suspended in 50% MeOH/H_2O (∼20 mL). Chelex 100 resin (Na^+ form, 1.4 g) was added to the suspension and the blue solid dissolved at this time to give a blue solution. HCl (3 N) was added dropwise until apparent pH ∼5 was reached. Within a short time, the blue solution became colorless and the resin turned blue. The mixture was stirred at room temperature for 1.5 h, after which time it was filtered and the filtrate was concentrated under reduced pressure to give the crude product as a brownish solid. The crude solid was dissolved in 2 mL of water and 1 N HCl was added dropwise until the solution was at pH 3. The mixture was stirred at room temperature for 1 h and at 0 °C for another hour. The precipitate was collected by filtration to give the desired product as an off-white powder (26 mg, 31% from **2**). Mp 260 °C dec; ^{1}H NMR (KOD in D_2O) δ 1.63 (overlapping dd, 1H, J = 3.0, 3.0 Hz), 1.68 (dd, 1H, J = 7.2, 15.0 Hz), 1.90 (dd, 1H, J = 3.0, 6.0 Hz), 2.04 (d, 1H, J = 15.0 Hz), 2.08 (dd, 1H, J = 3.0, 6.0 Hz), 4.53 (d, 1H, J = 7.2 Hz), 7.58−7.80 (m, 5H); ^{13}C NMR (KOD in D_2O) δ 26.1, 34.6, 39.4, 42.7, 54.5, 68.3, 129.2, 131.3, 134.6, 135.7, 170.1, 182.9, 185.4; FAB HRMS 305.1137 (MH^+, calcd for $C_{15}H_{17}N_2O_5$ 305.1117). The (−)-**1a** was obtained from (−)-**2** with $[\alpha]^{D}_{25}$ −33.0 (*c* 0.8, DMSO) and spectral data were in accordance with the racemic compound. The ee of (−)-**1a** was determined to be >98% by converting it to its *o*-phthaldialdehyde-*N*-acetyl-L-cysteine (OPA/NAC) derivative and determined the ratio of two diastereomers on HPLC.[25]

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Supporting Information Available: General methods, the X-ray crystal structure of (±)-**2**, and ^{1}H and ^{13}C NMR of compounds **3**, **7**, **2**, and **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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