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Stereoselective Synthesis of 2-Amino-3-fluoro Bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid

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Abstract—(+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) is a conformationally restricted glutamate analogue that is a potent, selective and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. Herein, we describe a stereoselective and highly efficient synthesis of its 3-*beta* fluoro derivative using the Corey–Link methodology to create the amino acid stereogenic center.

Introduction

Excitatory aminoacids (EAA), represented by L-glutamate (L-Glu), are major excitatory neurotransmitters in the mammalian central nervous system (CNS).[1] Pharmacological and molecular studies have demonstrated two classes of glutamate receptors. Ionotropic glutamate receptors are ligand-gated ion channels that exist as heteromeric protein complexes composed of heterogeneous subunit proteins.[2] In contrast, metabotropic glutamate receptors (mGluRs) are coupled to cellular effectors via GTP-binding proteins. There currently exist eight distinct mGluR proteins which have been classified into three groups.[3]

(Carboxycyclopropyl)glycines (CCG), conformationally constrained analogues of L-glutamate, have been shown to be a valuable source of potent and selective ligands. (2*S*, 1′*S*, 2′*S*)-2-(2′-Carboxycyclopropyl)glycine **1** (L-CCG-I),[4] (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine **2** (DCG-IV)[5] and (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-methoxymethylcyclopropyl)glycine **3** (*cis*-MCG-I),[6] are among the most widely used agonists for group 2 mGluRs (Scheme 1). Compound **4** (LY354740) was designed as a constrained glutamic acid analogue which closely mimics the proposed bioactive conformation of this neurotransmitter when acting at group 2 mGluRs.[7] Thus, enantiomer (+) **4** turned to be the first orally active group 2 mGluR agonist described thus far.[8] Other heterocyclic amino acid analogues has been published.[9]

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While preparing the present manuscript, some fluorinated (+) **4** (**LY354740**) analogues, (±) **5** and (+) **6** among others were reported.[10] In this paper, we describe the stereoselective synthesis of the racemic 3-*beta* fluoro analogue (±) **5** in a more efficient way.

Results and Discussion

Ketone **7** was obtained from cyclopentenone by cyclopropanation with ethyl-(dimethylsulfuranylidene) acetate (EDSA), generated in situ from the corresponding sulfonium bromide and DBU in $CHCl_3$ at room temperature.[11] Under these reaction conditions, the *exo* adduct was obtained exclusively in good yield (Scheme 2). Fluorination of the silyl enol ether of ketone **7** proceeded with a high degree of stereocontrol yielding exclusively isomer **8** where the fluorine atom is in a *beta* arrangement. The stereochemistry was assigned based on NOE experiments as shown in Scheme 2.

The next step was the installation of the amino acid centre at the carbonylic carbon. This reaction turned out to be quite troublesome, thus, standard Strecker reaction with saturated amonium chloride and potassium cyanide gave rise to a mixture of cianohydrines in very low yield. On the other hand, Bucherer–Berg reaction afforded a complex mixture of products, probably due to instability of the *alpha*-fluoro ketone **8** under the reaction conditions. A modified Strecker reaction using benzyl amine gave only one amino nitrile **9**. We were delighted to check it was the desired stereoisomer. Unfortunately, every attempt to deprotect the amino

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nitrile was unsuccessful. We then turned to the Corey–Link reaction as the last resort.[12] This reaction consists in the addition of trichloromethylcarbanion to a carbonylic compound followed by treatment with sodium azide to give an *alpha* azido ester that is further reduced and hydrolyzed to the corresponding *alpha* amino acid.

The opposite stereochemical outcome was observed when a solution of **7** and **8** and $CHCl_3$ in THF were treated with LiHMDS at −78 °C. Trichlorocarbinols **11** and **10** were respectively obtained. The presence of the fluorine atom has a great steroelectronic effect since the addition of the bulky trichlorocarbonylanion takes place from the most hindered concave face. The sterochemical assignment was based in the NOE's experiment shown in Scheme 2.

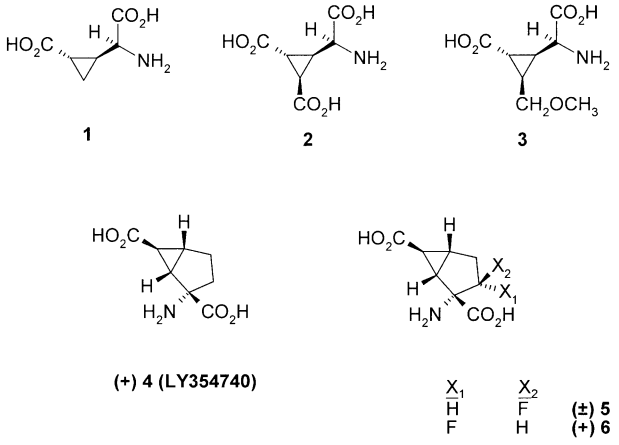
In order to avoid the partial ester hydrolysis when the trichloromethylcarbinol is treated with sodium azide in 1,2-dimethoxy ethane and water at rt, we used DBU as the base in anhydrous ethanol (modified Corey–Link reaction).[13] Under these conditions a *gem*-dichlorooxirane is probably formed and is then attacked in an S_N2 fashion by azide to give an azido acyl chloride intermediate which reacts with ethanol to give the inverted azidoester **12** (Scheme 3).

Hydrogenation of the azide using Pd/C catalyst in ethanol and acetic anhydride gave acetamide **13** which stereochemistry was again established by NOE's observing complete inversion at the amino acid center. Final hydrolysis under acidic conditions afforded the desired bicyclic fluorinated amino acid chlorhydrate salt (±) **5** with the desired stereochemistry *in all five* sterogenic centres.[14]

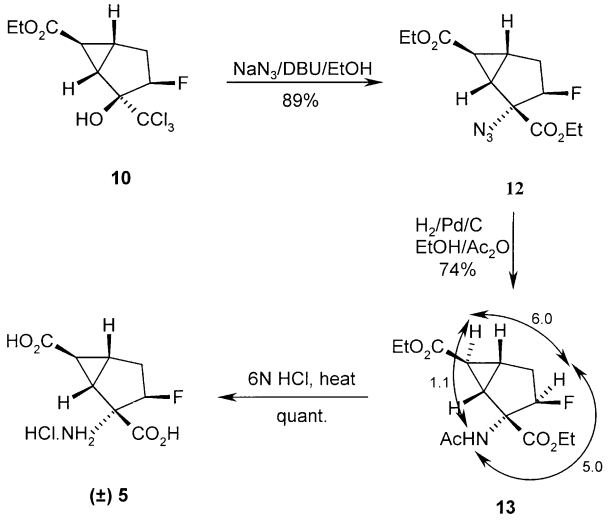
Experimental

Materials and methods

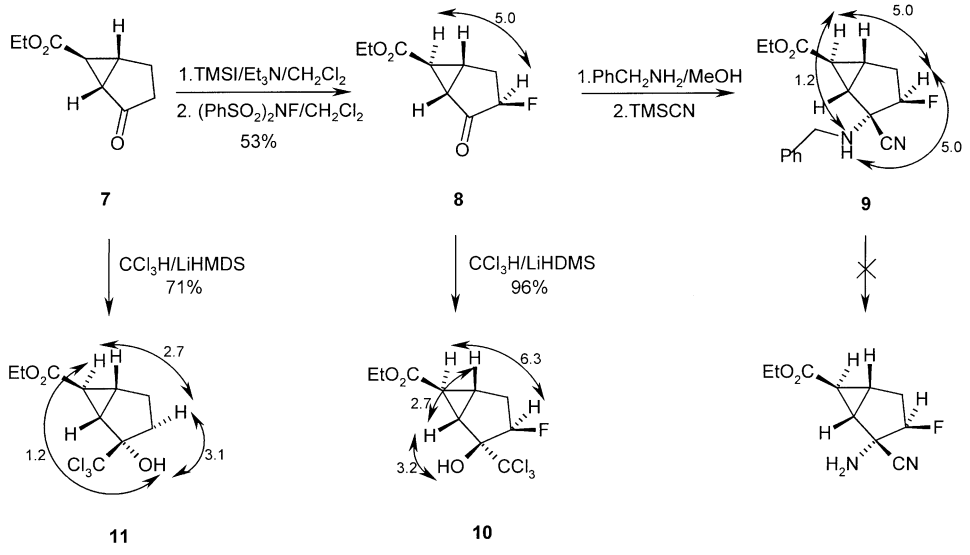
All solvents and reagents were purchased from commercial sources and used as received, unless otherwise



Scheme 1.



Scheme 3.



Scheme 2.

indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under a positive pressure of argon or nitrogen. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker AC-200P or Bruker AC-300. IR spectra were obtained on a Nicolet 510 P-FT (film and KBr). High resolution mass spectra (HRMS) were measured on a VG-Autospec spectrometer. Melting points were determined on a Büchi apparatus and are not corrected. Analytical TLC was performed on Merck TLC glass plates precoated with F_{254} silica gel 60 (UV, 254 nm and Iodine). Chromatographic separations were performed by using 230–400 mesh silica gel (Merck). Elemental analyses were performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia) Madrid.

(1*SR*,3*RS*,5*RS*,6*SR*) Ethyl 3-fluoro-2-oxobicyclo[3.1.0]-hexane-6-carboxylate (8). Iodotrimethylsilane (10.0 g, 49.97 mmol) was added dropwise at 0 °C to a solution of ketone **7**[11] (5.60 g, 33.29 mmol) and triethylamine (13.92 mL, 99.87 mmol) in anhydrous dichloromethane (140 mL). The resulting reaction mixture was allowed to warm to ambient temperature as it is stirred overnight under nitrogen. The reaction mixture was washed with saturated aqueous ammonium chloride solution (3×20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield the crude silylenolether which was used without any further purification (8.0 g). To a solution of this silylenolether (3.0 g, 12.5 mmol) in dichloromethane (20 mL) a solution of *N*-fluorobenzenesulfonimide (NFSI) (6.0 g, 19.03 mmol) in dichloromethane (40 mL) was transferred via cannula and the reaction mixture stirred for 48 h at room temperature. After solvent evaporation the crude mixture was purified by flash chromatography (dichloromethane/acetonitrile; 39:1) affording **8** (1.22 g, 53% yield). ^{1}H NMR ($CDCl_3$) δ 4.80 (dt, 1H, J = 50.7, 8.0 Hz), 4.18 (q, 2H, J = 7.1 Hz), 2.75 (m, 1 H), 2.56 (m, 1H), 2.39–2.20 (m, 3H), 1.28 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 204.4 (d, J = 16 Hz), 169.3, 69.8 (d, J = 180 Hz), 61.6, 32.3, 29.5, 27.6, 26.7, 14.0. Anal. calcd for $C_9H_{11}FO_3$: C, 58.06; H, 5.96. Found: C, 58.00; H, 6.03.

(1*SR*,2*RS*,3*RS*,5*RS*,6*SR*) Ethyl 3-fluoro-2-benzylamine-2-cianobicyclo[3.1.0]-hexane-6-carboxylate (9). To a solution of ketone **8** (100 mg, 0.54 mmol) in methanol (0.54 mL) was added benzyl amine (54 μL, 0.54 mmol) and stirred under nitrogen for 2 h at room temperature. The reaction mixture was then cooled down to 0 °C and trimethylsilylcyanide (143 μL, 1.08 mmol) was added. The resulting solution was stirred overnight. Solvent evaporation yield a crude mixture that was purified by flash chromatography (dichloromethane/acetonitrile; 39:1) affording **9** as the major diastereomer (220 mg, 68% yield). ^{1}H NMR ($CDCl_3$) δ 7.35–7.45 (m, 5H), 4.50 (dt, 1H, J = 51.0, 7.1 Hz), 4.20–4.00 (m, 4H), 2.60–2.20 (m, 3H), 2.10 (m, 2H), 1.70 (t, 1H, J = 3.0 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 170.9, 138.4, 128.5, 128.4, 127.5, 97.0 (d, J = 180 Hz), 66.1, 65.8, 61.1, 50.2, 32.2, 31.5, 24.2, 22.3, 14.1. Anal. calcd for $C_{17}H_{19}FN_2O_2$: C, 67.53; H, 6.33; N, 9.27. Found: C, 67.93; H, 6.63; N, 9.00.

(1*SR*,2*SR*,3*RS*,5*RS*,6*SR*) Ethyl 3-fluoro 2-hydroxy 2-trichloromethylbicyclo[3.1.0]-hexane-6-carboxylate (10). To a solution of ketone **8** (100 mg, 0.54 mmol) in THF (1 mL) chloroform was added (108 μL, 1.35 mmol) at −78 °C and the reaction mixture was treated with 1 M solution of lithium hexamethyldisilazide (1.10 mL, 1.08 mmol). After 0.5 h, the reaction mixture was allowed to reach room temperature and stirred for an additional hour. The crude reaction mixture was quenched with saturated aqueous ammonium chloride solution (1 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield a crude mixture that was purified by flash chromatography (hexane/EtOAc; 4:1) affording **10** as the only diastereomer (157 mg, 96% yield). ^{1}H NMR ($CDCl_3$) δ 5.00 (dt, 1H, J = 52.3, 7.7 Hz), 4.13 (dq, 2H, J = 7.1, 2.4 Hz), 3.55 (d, 1H, J = 5.7 Hz), 2.65–2.20 (m, 3H), 2.10–2.05 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 171.0, 103.2, 89.0 (d, J = 190 Hz), 88.6 (d, J = 15 Hz), 61.1, 32.4 (d, J = 22 Hz), 31.5, 25.7, 21.4 (d, J = 10 Hz), 14.1. IR (KBr) ν (cm^{-1}) 3549, 1721, 1316, 1188, 1047. Anal. calcd for $C_{10}H_{12}Cl_3FO_3$: C, 39.31; H, 3.96; Cl, 34.81. Found: C, 39.71; H, 4.00; Cl, 34.52.

(1*SR*,2*SR*,5*RS*,6*SR*) Ethyl 2-hydroxy-2-trichloromethyl-bicyclo[3.1.0]-hexane-6-carboxylate (11). It was obtained in the same way as described above for trichlorocarbinol **10** and purified by flash chromatography (hexane/EtOAc; 4:1) 71% yield. ^{1}H NMR ($CDCl_3$) δ 4.25 (q, 2H, J = 7.0 Hz), 3.63 (s, 1H, OH), 2.43–1.91 (m, 5H), 1.80 (t, 1H, J = 3.0 Hz), 1.62 (dd, 1H, J = 14.9, 9.1 Hz), 1.18 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 172.7, 106.7, 92.5, 60.9, 35.2, 33.6, 30.4, 28.0, 22.8, 14.1. IR (KBr) ν (cm^{-1}) 3424, 1701, 1213, 814. Anal. calcd for $C_{10}H_{13}Cl_3O_3$: C, 41.77; H, 4.56. Found: C, 41.45; H, 4.84.

(1*SR*,2*RS*,5*RS*,6*SR*) Diethyl 2-azidobicyclo[3.1.0]-hexane-2,6-dicarboxylate (12). To a suspension of **10** (157 mg, 0.51 mmol) and sodium azide (100 mg, 1.54 mmol) in EtOH (1 mL) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.4 mL, 2.63 mmol) was added and the resulting reaction mixture was stirred overnight. Diethyl ether was added (8 mL) followed by saturated aqueous ammonium chloride solution (4 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield a crude mixture that was purified by flash chromatography (hexane/EtOAc; 4:1) affording **12** as the only diastereomer (130 mg, 89% yield). ^{1}H NMR ($CDCl_3$) δ 4.70 (dt, 1H, J = 42.3, 7.7 Hz), 4.35 (q, 2H, J = 7.0 Hz), 4.12 (q, 2H, J = 7.0 Hz), 2.55–2.30 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H), 1.71 (t, 1H, J = 3.2 Hz), 1.36 (t, 3H, J = 7.0 Hz), 1.27 (t, 3H, J = 7.0 Hz).

(1*SR*,2*RS*,5*RS*,6*SR*) Diethyl 2-acetylaminobicyclo[3.1.0]-hexane-2, 6-dicarboxylate (13). To a solution of diester **12** (130 mg, 0.45 mmol) in EtOH (5 mL) and acetic anhydride (0.1 mL) 10% Pd on charcoal was added (31 mg) and the resulting suspension stirred under hydrogen atmosphere overnight. The reaction mixture was filtered off through a short path of Celite and the solvent evaporated to yield an oily residue that was purified by flash chromatography (ethyl acetate) affording pure **13** (103 mg, 75% yield). ^{1}H NMR ($CDCl_3$) δ 7.23 (s, 1H, NH), 4.75 (dt, 1H, J = 44.5, 7.8

Hz), 4.32 (q, 2H, $J=7.0$ Hz), 4.12 (q, 2H, $J=7.0$ Hz), 2.80 (dt, 1H, $J=7.0$, 3.0 Hz), 2.50–2.35 (m, 2H), 2.10–2.00 (m, 1H), 2.04 (s, 3H), 1.70 (t, 1H, $J=3.1$ Hz), 1.30 (t, 3H, $J=7.0$ Hz), 1.23 (t, 3H, $J=7.0$ Hz). ^{13}C NMR ($CDCl_3$) δ 174.7, 171.6 (d, $J=21$ Hz), 168.2, 95.0 (d, $J=194$ Hz), 69.1 (d, $J=31$ Hz), 62.2, 60.3, 32.4, 31.5 (d, $J=22$ Hz), 25.3 (d, $J=9$ Hz), 22.9, 20.6, 14.0 (2C). IR (KBr) ν (cm^{-1}) 2982, 1722, 1668, 1545, 1305, 1240. Anal. calcd for $C_{14}H_{20}FNO_5$: C, 55.81; H, 6.69; N, 4.65. Found: C, 56.15; H, 6.73; N, 4.72.

(1*SR*,2*RS*,5*RS*,6*SR*) 2-Aminobicyclo[3.1.0]-hexane 2,6-dicarboxylic acid hydrochloride salt (±5). A solution of diester **13** (300 mg, 0.99 mmol), in 6 N HCl solution (7 mL) was heated under reflux overnight. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether several times to afford (**5**) (179 mg, 75% yield). ^{1}H NMR (MeOH-d_4) δ 4.90 (dt, 1H, $J=52.0$, 7.8 Hz), 2.60–2.40 (m, 2H), 2.20–2.00 (m, 3H). ^{13}C NMR (MeOH-d_4) δ 174.2, 168.4 (d, $J=6$ Hz), 95.0 (d, $J=195$ Hz), 69.5 (d, $J=24$ Hz), 33.60 (d, $J=22$ Hz), 31.2, 26.4 (d, $J=9$ Hz), 23.6. IR (KBr) ν (cm^{-1}) 3431, 2953, 1721, 1198, 1115. Anal. calcd for $C_8H_{10}FNO_4HCl$: C, 40.10; H, 4.63; Cl, 14.79; N, 5.85. Found: C, 40.22; H, 4.95; Cl, 14.48 ;N, 6.00.

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