Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4537–4541

TETRAHEDRON: *ASYMMETRY*

An efficient and stereoselective synthesis of (2*S*,1′*S*,2′*S*)-2-(carboxycyclopropyl) glycine (LCCG-I): conformationally constrained L-glutamate analogues

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Received 26 September 2000; accepted 24 October 2000

Abstract

Conformationally restricted metabotropic glutamate receptor agonist (2*S*,1′*S*,2′*S*)-2-(Carboxycyclopropyl) glycine (LCCG-I) **1** have been efficiently synthesized in a stereoselective manner. A convenient five step synthesis of **1** from readily available (−)-dimenthyl (1*S*,2S)-cyclopropane-1,2-dicarboxylate **5** in 49% overall yield is described.

1. Introduction

Rigid or conformationally restricted analogues of L-glutamate of known stereochemistry have been synthesized for the elucidation of the pharmacology of the large family of glutamate receptors.[1,2] (2*S*,1′*S*,2′*S*)-2-(Carboxycyclopropyl) glycine **1** (LCCG-I),[3,4] which is the extended glutamate conformation, has received much attention from neuroscientists recently, because it is a selective agonist for metabotropic glutamate receptors mGLu2 and mGLu3 and it is capable of activating multiple other mGLu subtypes at low micromolar concentrations.[5] The mGLuRs are coupled to G-proteins that mediate a variety of transduction mechanisms. As a part of our ongoing program to develop new and efficient routes for the synthesis of α-amino acids and related compounds, we have developed a methodology utilizing readily available (−)-dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate for the synthesis of LCCG-I **1**.

2. Synthesis

The synthesis of LCCG-I **1** is shown in Scheme 1. In designing a practical asymmetric synthesis we chose (−)-dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate **5** $\{[\alpha]_D^{25} = +17.8$

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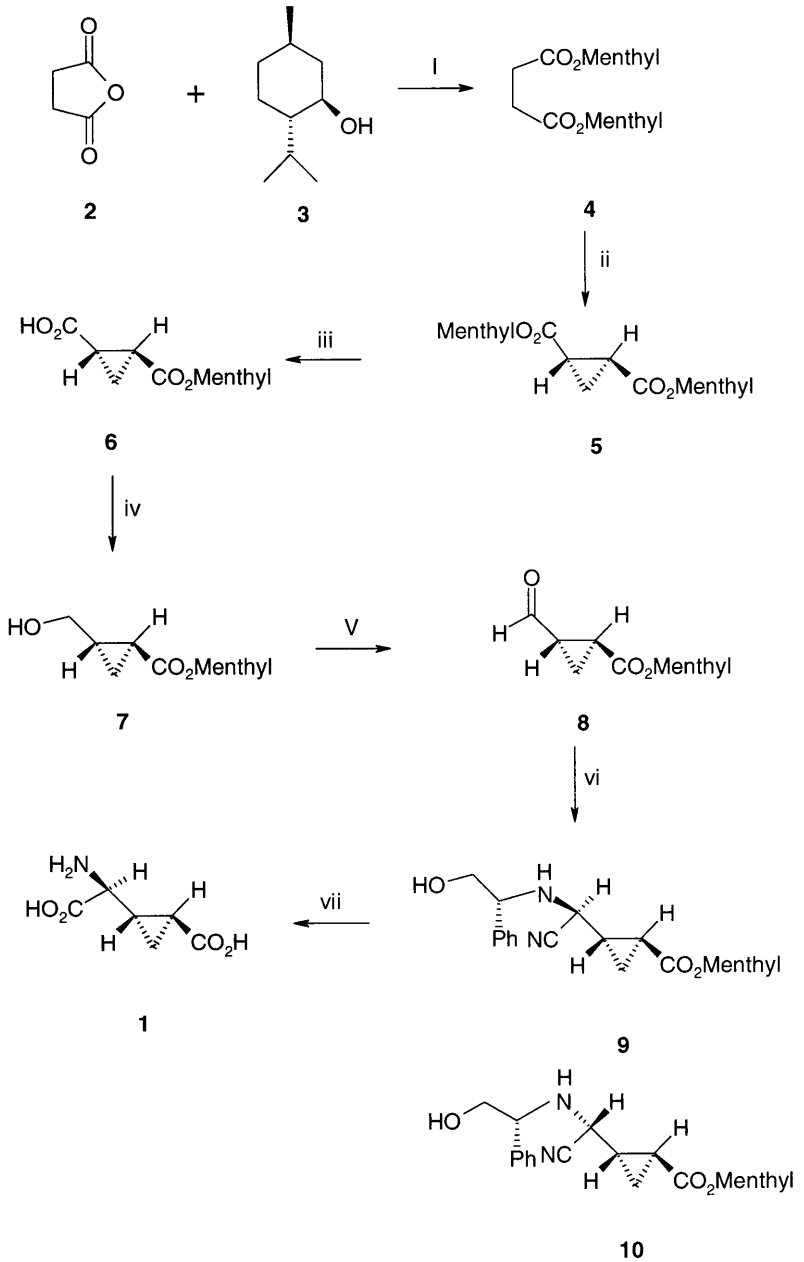
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00434-1



Scheme 1. **Reagent and conditions**: (i) *p*-Toluenesulfonic acid monohydrate, toluene, 140°C, 24 h, Dean–Stark; (ii) LiTMP (1.6 M *n*-butyllithium, 2,2,6,6-tetramethylpiperidine), −78°C, THF, N_2, 1 h, then bromochloromethane, 2 h; (iii) NaOH, *i*-PrOH, 50°C, overnight, then 85°C, 2 h, yield 96%; (iv) 1.0 M BH_3·THF, −78°C, N_2, THF, 4 h, then rt, overnight, yield 81%; (v) DMSO, CH_2Cl_2, oxalylchloride, −78°C, N_2, 20 min, Et_3N, 0°C, yield 96%; (vi) *(R)*-α-phenylglycinol, MeOH, 1 h, rt, TMSCN, 0°C, then rt, overnight, flash chromatography, yield 88%; (vii) lead tetraacetate, CH_2Cl_2:MeOH (1:1, v/v), 0°C, 10 min, work-up, 6N HCl, 6 h, reflux, then anion-exchange chromatography (elution with 0.5 M HOAc), yield 75%

($CHCl_3$, $c = 1.0$}, which can be easily prepared via stereoselective cyclopropanation of (−)-dimenthyl succinate **4** by known procedures.[6] Choosing this key intermediate as a starting material and with two fixed stereogenic centers now gives us the opportunity to synthesize LCCG-I **1**,

simply by a few functional group transformations. The diester **5** was partially hydrolyzed with NaOH to the mono-acid **6** in 96% yield. The reduction of this compound to alcohol **7** was accomplished with BH_3·THF at −78°C and then at room temperature overnight. Swern oxidation[7] of **7** gave aldehyde **8** almost in a quantitative yield. Asymmetric Strecker reaction of aldehyde **8** using the inexpensive chiral auxiliary (*R*)-α-phenylglycinol (MeOH, room temperature, 2 h)[8] followed by treatment of the resulting Schiff base with TMSCN for 12 h to give a 90:10 (^{1}H NMR) mixture of the two expected diastereomeric α-aminonitrile derivatives **9** and **10** in 95% yield which were easily separated by standard silica gel column chromatography. The α-aminonitrile **9** was finally submitted to oxidative cleavage with lead tetraacetate followed by hydrolysis[8] with 6N HCl and ion exchange chromatography using Dowex 1X8-50 (0.5 M HOAc) to afford (2*S*,1′*S*,2′*S*)LCCG-I **1** {$[\alpha]_D^{20} = +103.5$ (c = 0.31, H_2O)} in 49% overall yield from **5**.

Structures of all intermediates were confirmed by ^{1}H NMR and the enantiomeric excess of **1** was established by comparison of its physical properties with those reported in the literature[4] and by chiral HPLC (Chirex D-penicillamin column).

The methodology described here has the generality for the synthesis of other diastereomeric forms such as (2*R*,1′*S*,2′*S*) CCG by simply changing the (*R*)-α-phenylglycinol to (*S*)-α-phenylglycinol. This general synthetic methodology allows for the synthesis of (LCCG-I) on at least 4–6 g scale. The yields and stereochemical purities make this the most convenient and efficient method for the production of this biologically important and active compound.

3. Experimental

3.1. General

Melting points were obtained with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. ^{1}H and ^{13}C spectra were recorded on a Bruker AC-200 spectrometer with $SiMe_4$ as internal standard and using $CDCl_3$ as solvent. Elemental analysis were performed by the Canadian Microanalytical Service Ltd. HPLC was carried out with a Varian 9012 pump and Varian 9050 UV–vis detector. Column chromatography was performed using silica gel 60 of 230–400 mesh.

3.2. Synthesis of 2-carbomenthyloxy (1S,2S)-cyclopropane-1-carboxylic acid **6**

To a suspension of diester **5** (70.2 g, 172.8 mmol) in 450 ml isopropyl alcohol was added a solution of NaOH (7.56 g) in 36 ml of water. The reaction mixture stirred at 50°C overnight and then for an additional 2 h at 85°C. The mixture was then concentrated and 360 ml of water was added. The aqueous layer was extracted with ether three times and it was then acidified with 2N HCl and extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated to give 44.2 g (96%) of pure **6** as oil. δH ($CDCl_3$): 0.7 (d, 3H, $J = 7.0$), 0.9 (d, 6H, $J = 6.8$), 0.95–2.0 (complex 11H), 2.2 (m, 2H), 3.7 (t, 1H), 4.68 (dt, 1H, $J = 5.4$, 10.5), 10.1 (br, 1H).

3.3. Synthesis of 2-carbomenthyloxy (1S,2S)-cyclopropane-1-hydroxymethyl **7**

The mono-acid **6** (38.4 g, 143.4 mmol) was dissolved in THF (120 ml) and cooled to −78°C under nitrogen. BH_3·THF (1.0 M, 157.8 ml) was added dropwise and the resulting solution was stirred at the same temperature for 4 h and gradually warmed to room temperature overnight. Water (180 ml) was added and stirred for 30 min and then followed by addition of K_2CO_3 (51 g). The solution was extracted with ether several times and the combined ether extracts were dried and evaporated. The residue was purified by flash chromatography (hexane:ether, 7:3) to give 29.3 g (81%) of alcohol **7**. δH ($CDCl_3$): 0.7 (d, 3H, $J=7.0$), 0.82 (d, 6H, $J=6.8$), 0.98–2.0 (complex, 14 H), 3.5 (m, $J=6.0$, 8.0, 2 H), 4.6 (dt, 1H, $J=5.4$, 10.5).

3.4. Synthesis of 2-carbomenthyloxy (1S,2S)-cyclopropane-1-carboxaldehyde **8**

A solution of dry DMSO (27 ml, 380 mmol) in CH_2Cl_2 (420 ml) was added dropwise to a solution of oxalyl chloride (16.68 ml, 191 mmol) in CH_2Cl_2 (420 ml) at −78°C under N_2. The resulting solution was stirred at the same temperature for 20 min. Then alcohol **7** (25.5 g, 100 mmol) was added and stirred for an additional 20 min at −78°C. Et_3N (80 ml) was added and gradually warmed to 0°C. To the residue a sat. aqueous solution of NH_4Cl was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried and evaporated. The residue was purified by flash column chromatography (hexane:ether, 7:3) to give 24.2 g (96%) of aldehyde **8**. δH ($CDCl_3$): 0.78 (d, 3H, $J=7.0$), 0.82 (d, 6H, $J=6.8$), 0.98–2.0 (m, 11H), 2.2 (m, 1H), 2.38 (dt, 1H, $J=6.0$, 12), 4.7 (dt, 1H, $J=5.4$, 10.5), 9.22 (s, 1H).

3.5. Synthesis of (2S,1′S,2′S)-N-[(R)-α-phenylglycinol]-[2′-carbomenthyloxycyclopropyl]-glycinonitrile **9**

To a solution of aldehyde **8** (24.16 g, 95.8 mmol) in 720 ml of methanol was added (*R*)-phenyl glycinol (13.4 g, 97.72 mmol) and the resulting solution stirred at rt for 1 h. The solution was then cooled to 0°C and TMSCN (25.6 ml, 191.6 mmol) was added dropwise, and the mixture was stirred at rt overnight. To the solution was added 3N HCl (600 ml) and the mixture was extracted with $CHCl_3$. The combined organic layer was dried and evaporated. The residue was purified by column chromatography (ether:hexane 1:1) to give 33.4 g (88%) of diastereomerically pure **9**. $[\alpha]_D^{20}$ −49.4 ($c=0.80$, CH_2Cl_2). δH ($CDCl_3$): 0.78 (d, 3H, $J=7.0$), 0.95 (d, 6H, $J=6.8$), 0.98–2.0 (m, 6H), 3.3–3.50 (m, 2H), 3.7–3.8 (m, 2H), 4.2 (dd, 1H, $J=9.0$, 4.0) 4.6 (m, 1H) 7.4 (m, 5H).

3.6. Synthesis of (2S,1′S,2′S)-2-(carboxycyclopropyl) glycine **1**

Lead tetraacetate (16.64 g, 37.57 mmol) was added to a cold solution of nitrile **9** (13.65, 34.19 mmol) in CH_2Cl_2:CH_3OH (1:1) (290 ml). The resulting reaction mixture was stirred at 0°C for 10 min. Water (220 ml) was added and the resulting mixture was filtered with the aid of Celite. The aqueous layer was extracted with CH_2Cl_2 and it was then dried and evaporated. The residue was dissolved in 6N HCl (500 ml) and refluxed for 6 h. The reaction mixture was washed with CH_2Cl_2 two times and evaporated to dryness. The residue was submitted to anion-exchange resin chromatography to give 4.0 g (74%) of pure LCCG-I **1**. $[\alpha]_D^{20}=+103.5$ ($c=0.31$, H_2O); δH (D_2O): 1.3 (ddd, 1H, $J=5.0$, 6.1, 8.6), 1.4 (ddd, 1H, $J=5.0$, 5.1, 9.0), 1.8 (dddd, 1H, $J=4.0$, 6.1,

9.0,10.0), 1.85 (ddd, 1H, $J=4.0$, 5.0, 8.6). Anal. calcd for $C_6H_9O_4N$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.31; H, 5.73; N, 8.71.

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