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Stereocontrolled synthesis of a potent agonist of group II metabotropic glutamate receptors, (+)-LY354740, and its related derivatives

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Abstract—Efficient synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740: **1**) and its structurally related analogs (−)-**2** and (−)-**3** has been accomplished starting with (1*S*,2*R*)-1-amino-2-hydroxycyclopentane- or cyclohexanecarboxylic acid (**4** or **17**) via an intramolecular cyclopropanation of α-diazo acetamide.

Metabotropic glutamate receptors (mGluRs) are implicated in the regulation of many physiological and pathological processes in the mammalian central nervous system (CNS), including synaptic plasticity, learning and memory, motor coordination, pain transmission, and neurodegeneration.[1] These receptors form a family of three groups (groups I–III) in which presynaptic group II receptors (mGluR2 and 3) negatively regulate glutamate release. An agonist of these receptors markedly suppresses postsynaptic excitation.[2] DCG-IV[3] is a potent and selective agonist of mGluR2 and exhibits anesthetic action in rat, inhibition of AOB memory of rat, and protection of kainate-induced neuronal death both in vivo and in vitro.[2] The structure of DCG-IV fixes its glutamate sub-structure to an extended conformation (*anti–anti* form), which has been proposed as a crucial factor for the conformational requirement of mGluRs.[4,5] These results prompted the design and synthesis of an effective neuroprotecting agent based on the structure of DCG-IV. Thus, (+)-LY354740 (**1**) having a fused bicyclo[3.1.0]hexane skeleton has been developed by Schoepp et al., which is a potent and selective mGluR2 agonist and exhibits anticonvulsant and anxiolytic properties in mice.[6] Therefore, both DCG-IV and **1** have been used as important tools to investigate neurobiological functions of mGluRs.[7,8] Since the synthesis of **1** was performed in racemic form,[6] the absolute configuration of the active enantiomer was confirmed by the synthesis of (+)-**1** started with D-ribonic γ-lactone by Dominguez et al.[9] Relevant to the development of neuroactive glutamate analogs, our current interest was to exploit an alternative route to (+)-**1**, and its γ-epimer **2** whose structure closely mimics that of a potent glutamate transport inhibitor, L-CCG-III.[4,10] In this report, we wish to describe an efficient route to the synthesis of (+)-**1** and the novel γ-epimers **2** and **3**.

Our synthetic plan toward **1** and **2** was the use of (1*S*,2*R*)-1-amino-2-hydroxycyclopentanecarboxylic acid **4** as the starting material, readily available in multigram quantities from racemic 2-hydoxycyclopentanone using an asymmetric version of the Strecker synthesis.[11] Intramolecular cyclopropanation of an α-diazo acetamide would produce a cycloadduct which possesses the requisite consecutive chiral centers corresponding to the γ-epimer **2**. Opening of the γ-lactam followed by epimerization of the resulting γ-ester group would give rise to (+)-**1** (Scheme 1).

The synthesis began with protection of the amino and carboxyl groups of **4** followed by dehydration of the resulting alcohol **5**. Initial attempts for the dehydration using standard conditions (MsCl or TsCl using DBU or 2,6-lutidine in toluene at reflux, or Burgess reagent) did not give any dehydrated product due probably to steric

Keywords: glutamate analog; mGluRs agonist; DCG-IV; LY354740; L-CCG-III; transport inhibitor; dehydration; α-diazo acetamide; [2+3] dipolar cycloaddition:cyclopropanation:epimerization.

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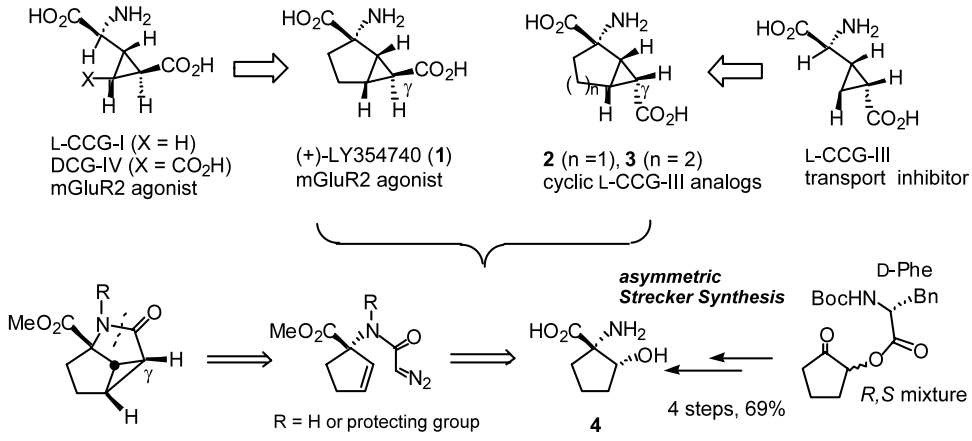
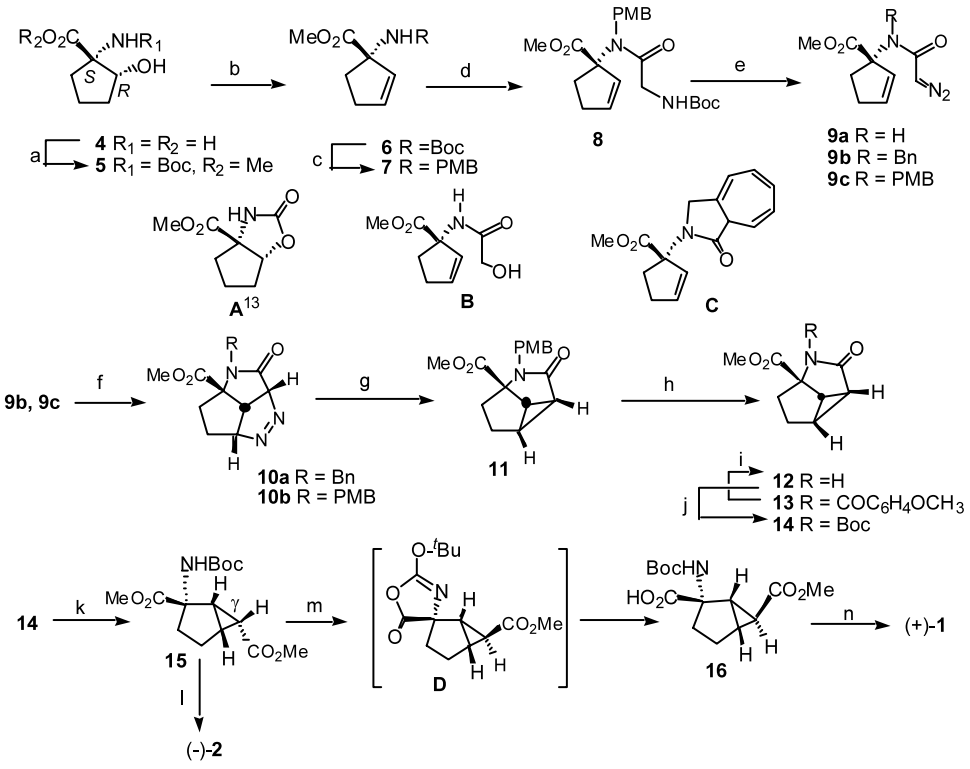


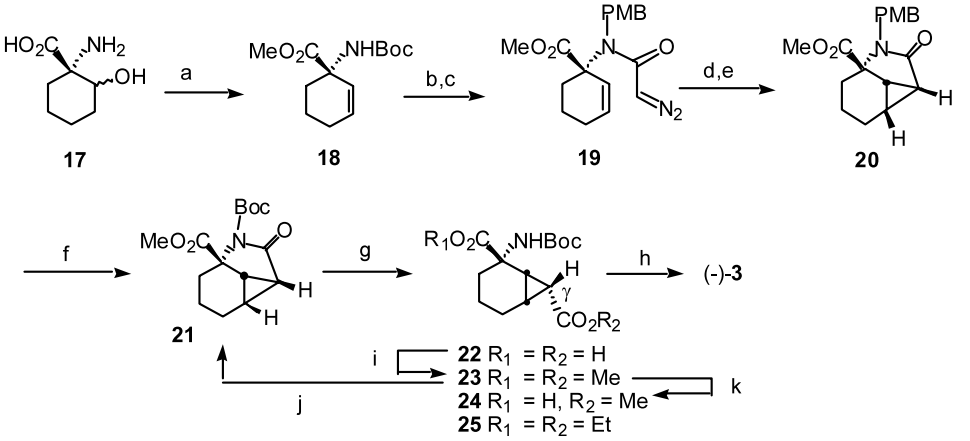
Scheme 1.

reasons. The use of iodine (imidazole, Ph_3P in $CHCl_3$ in a sealed tube at 90–110°C) gave **6** in poor yield (24%). Finally, we found that the use of the Honda method (Tf_2O in pyridine)[12] was quite effective for this transformation to give the desired olefin **6** in 40% yield.[13] This method is advantageous in terms of reproducibility, multi-gram preparation, and purification avoiding hazardous isolation processes, albeit the yield was moderate. With the desired olefin in hand, we next attempted the key cyclopropanation reaction. The use of a protection-free α-diazo acetamide **9a**, prepared in two steps from **6**, was found to be unstable to moisture resulting in the formation of unwanted α-hydroxy amide **B** as the major product (24%). *N*-Benzyl protected **9b**, prepared in three steps from **6**, was stable under the preparation and work-up conditions. Although the cyclopropyl group of the expected cycloadduct would be intolerable under the reductive removal of the *N*-benzyl group,[14] we employed **9b** as a model compound for the key cyclopropanation reaction. Palladium- or rhodium-catalyzed reaction of **9b** did not give any cycloadduct, but afforded insertion product **C** ($Pd(OAc)_2$, 42% and $Rh_2(OAc)_4$, 57%).[15] On the other hand, 1,3-dipolar cycloaddition occurred to give **10a** when **9b** in $CHCl_3$ was stood at room temperature for overnight.[16] Based on these results, we turned our attention to use of a *p*-methoxybenzyl (PMB) group for the amide protecting group because this group can be removed under oxidative conditions at the final stage of the synthesis.[17] After removal of the Boc group of the olefin **5**, the PMB group was introduced using reductive amination[18] to give **7**. Condensation of the resulting *N*-PMB derivative with Boc-Gly (HOAt, HATU, Et_3N) gave glycyl amide **8** (60% yield in three steps).[19] This was converted to α-diazo acetamide **9c** using standard diazotization conditions.[20] The α-diazo acetamide **9c** underwent [3+2] cycloaddition to give desired cycloadduct **10b**. Photo-irradiation (450W high-pressure mercury lamp, Pyrex tube) of **10b** afforded cyclopropyl lactam **11**.[16,21] The PMB group was removed at this stage by oxidation with CAN[17] to give a mixture of deprotected γ-lactam **12** (54%) and benzoyl derivative **13** (26%). The by-produced **13** was converted into **12** by means of LiOOH (59%).[22] Introduction of a Boc group followed by methanolysis gave protected γ-epimer **15**. Removal of the protecting groups furnished (−)-**2**, a cyclic analog of L-CCG-III.[23] The conversion leading to **1** is an inversion of the configuration at the γ-ester group of **15**.[3,4] This was successfully effected by $KN(TMS)_2$ to give a mono ester **16** with unexpected concomitant hydrolysis of the α-ester group.[24] Since the reaction was performed under aprotic reaction conditions, this would be attributed to an internal attack of the carbamate oxygen to the neighboring ester group to form an oxazolone intermediate **D**. Finally, removal of the Boc group followed by hydrolysis gave (+)-**1**: $[\alpha]_D^{17}$ +19.5 (*c* 1.05, 1N HCl). The sign of the optical rotation and ^1H and ^{13}C NMR data of synthetic **1** were identical with those of the reported data [lit. $[\alpha]_D$ +23 (*c* 1.0, 1 *N* HCl)] (Scheme 2).[6,9]

We considered that the present process is applicable to the synthesis of six-membered ring analogs corresponding to **1** and **2**. A mixture of (1*S*,2*R*)- and (1*S*,2*S*)-1-amino-2-hydroxycyclohexanecarboxylic acid (**17**) was used as the starting material.[11c] Contrary to the dehydration of **5**, the treatment of a protected form of **17** with iodine gave the desired olefin **18** in excellent yield. Its conversion to Boc-lactam **21** was performed in the same manner as for the synthesis of **1**. However, subsequent lactam-opening under methanolysis (LiOH, MeOH) afforded an inseparable mixture of the desired diester **23** and starting **21** (**21**/**23** = 1:1). Therefore, this conversion was carried out using a hydrolytic condition (1N NaOH) to give dicarboxylate **22**. Removal of the Boc group using TFA gave (−)-**3**, a six-membered ring analog of L-CCG-III.[25] Our next effort was epimerization of the γ-ester group of the diester **23** leading to a 6-membered ring analog of **1**. The diester **23** was obtained in pure form by treatment of **22** with diazomethane. In spite of our numerous attempts, the desired epimerization did not occur, e.g. the treatment of **23** with $KN(TMS)_2$ gave re-cyclized γ-lactam **21** (−78°C for 1 h, then −15°C for 3 h) or a mono ester **24** (0°C for 5 h), exclusively. The use of $LiN(TMS)_2$ (0°C, 5 h) gave a complex mixture of products. The diethyl ester **25** gave a monoester. These results suggested that the desired epimerization requires further modification of the amino or carboxyl group such as introduction of an additional amino protecting group or reduction of the γ-ester group to an aldehyde (Scheme 3).[26]



Scheme 2. *Reagents and conditions*: (a) i. $(Boc)_2O$, $[(CH_3)_4NOH]5H_2O$, CH_3CN, rt, 6 days, ii. CH_2N_2, 73%; (b) triflic anhydride (Tf_2O), pyridine, −30°C, then rt, 21 h, 40%; (c) i. TFA, CH_2Cl_2; (ii) *p*-anisaldehyde, $NaBH_3CN$, MeOH, rt, 22 h; (d) Boc-Gly, HATU, HOAt, Et_3N, DMF, rt, 7 h, 60% from **6**; (e) i. TFA, CH_2Cl_2, ii. $NaNO_2$, 5% citric acid, Et_2O–H_2O, pH 3, rt, 30 min; (f) $CHCl_3$, rt, 46 h; (g) 450 W high-pressure mercury lamp, benzene/CH_2Cl_2 (10:1), rt, 3 h, 100% from **8**; (h) ceric ammonium nitrate (CAN), CH_3CN/H_2O (2:1), 0°C, then rt, 50 min, 54% for **12** and 26% for **13**; (i) LiOOH, THF/H_2O (3:1), 15 h, then $Na_2S_2O_3$, 59%; (j) $(Boc)_2O$, Et_3N, cat. DMAP, THF, rt, 26 h; (k) cat. LiOH, MeOH, rt, 45 h, 82% from **12**; (l) i. 1N NaOH, THF, ii. TFA, CH_2Cl_2, 84% from **15**; (m) $KN(SiMe_3)_2$, THF, −78°C, 1 h, then −15°C, 2 h, then AcOH, THF, −78°C; (n) i. TFA, CH_2Cl_2, ii. 1N NaOH, THF, 63% from **15**.



Scheme 3. *Reagents and conditions*: (a) i. $(Boc)_2O$, $[(CH_3)_4NOH]_5H_2O$, CH_3CN, rt, 6 days, ii. CH_2N_2, 73%, iii. I_2, imidazole, Ph_3P, $CHCl_3$, sealed tube, 80°C, 3 h, 83%; (b) i. TFA, CH_2Cl_2, ii. *p*-anisaldehyde, $NaBH_3CN$, MeOH, rt, 22 h, iii. Boc-Gly, HATU, HOAt, Et_3N, DMF, rt, 7 h, 64% from **18**; (c) i. TFA, CH_2Cl_2, ii. $NaNO_2$, 5% citric acid, Et_2O–H_2O, pH 3, rt, 2 h; (d) $CHCl_3$, rt, 46 h, 85% for three steps; (e) 450 W high-pressure mercury lamp, benzene–CH_2Cl_2 (10:1), rt, 3 h, 92%; (f) i. CAN, CH_3CN/H_2O (2:1), 0°C, 30 min, 71%, ii. $(Boc)_2O$, Et_3N, cat. DMAP, THF, 100%; (g) 1N NaOH, THF, 35°C, 2 days; (h) TFA, CH_2Cl_2, 100%; (i) CH_2N_2; (j) 2.2 equiv. $KN(SiMe_3)_2$, THF, −78°C, 1 h, then −15°C, 3 h, then AcOH, THF, −78°C, 100%; (k) 2.2 equiv. $KN(SiMe_3)_2$, THF, 0°C, 3 h, then AcOH, THF, −78°C, 100% (crude yield).

In summary, optically active LY354740 (**1**) and its γ-epimers **2** and **3** have been synthesized in a highly diastereoselective manner via 1,3-dipolar cycloaddition of the α-diazo acetamide **9c** or **19**. During the epimerization of the γ-ester group of the diester **15** or **23**, unusual hydrolysis of the α-ester group was observed. Neurobiological studies on glutamate transport systems using the synthetic **2** and **3** are in progress in our laboratories.

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13. Contrary to the dehydration of **5**, its 2*S*-diastereomer did not give the olefin **6** but afforded cyclic carbamate **A** (Scheme 2) as the major product (25%) where an S'_{CN} reaction of the initially formed β-TfO group with the internal carbamate group occurred.
14. In fact, hydrogenation of *N*-benzyl lactam corresponding to **11** gave an *N*-benzyl bicyclic lactam where the cyclopropyl group was cleaved.
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21. Treatment of **10a** or **10b** in benzene at reflux for 4 h resulted in complete recovery of the starting material, respectively.
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23. **2**: Amorphous solid; $[\alpha]_D^{14}$ −14.6 (*c* 0.91, 1N HCl); ^{1}H NMR (400 MHz, D_2O) δ 2.13 (dtd, J=15.1, 10.0. 5.2 Hz, 1H), 2.01 (dd, J=14.0, 10.0 Hz, 1H), 1.84–1.89 (m, 2H), 1.77 (dt, J=9.3, 5.9 Hz, 1H), 1.77 (dt, J=9.3 Hz, 5.9 Hz, 1H), 1.69 (t, J=7.0 Hz, 1H), 1.39–1.47 (m, 1H); ^{13}C NMR (100 MHz, D_2O, MeOH as the internal standard: δ 49.0) δ 176.5, 174.0, 66.1, 32.4, 29.1, 27.2, 25.4, 25.1; HRMS (FAB) m/z $(M-H)^+$ calcd for $[C_8H_{11}O_4N\text{-}H]^+$ 184.0610, found, 184.0591.
24. The same treatment using an *N*-Boc α-amino acid ester (Boc-L-Phe methyl ester) did not give any ester-hydrolyzed product at all.
25. **3**: Amorphous solid; $[\alpha]_D^{18}$ −89.9 (*c* 0.94, 1N HCl); ^{1}H NMR (300 MHz, D_2O) δ 1.90 (ddd, J=14.3, 9.0, 4.6 Hz, 1H), 1.78 (dd, J=10.4, 9.0 Hz, 1H), 1.72–1.78 (m, 1H), 1.47 (dq, J=9.0, 4.0 Hz, 1H), 1.15–1.40 (m, 4H), 0.95 (m, 1H); ^{13}C NMR (100 MHz, D_2O, MeOH as the internal standard: δ 49.0) δ 178.9, 178.2, 59.0, 30.5, 27.5, 18.9, 18.8, 18.2, 15.9; HRMS (FAB) m/z $(M+H)^+$ calcd for $[C_9H_{13}O_4N]^+$ 200.0923, found 200.0899.
26. Calculations (MOPAC: AM1) suggested that the γ-ester group of the bicyclo[4.1.0] system **22** locates at a more proximal position to the amino group (distance between the carboxyl carbon and the nitrogen is 2.64 Å[O1]) than that of the bicyclo[3.1.0] system **15** (2.88 Å).