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Novel enantioselective synthesis of (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV)

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Abstract

A novel enantioselective synthesis of (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV), a potent group II mGluRs agonist is described.

Keywords: metabotropic glutamate receptors; (carboxycyclopropyl)glycines; asymmetric cyclopropanation.

(Carboxycyclopropyl)glycines are conformationally constrained L-glutamate analogs having as a common feature a cyclopropyl moiety that introduces chirality and partially reduces conformational freedom. Several disubstituted and trisubstituted members of this family have been used widely for the pharmacological and physiological characterization of both ionotropic (iGluRs) and metabotropic (mGluRs) glutamate receptor pathways.[1] Among the disubstituted members (Fig. 1), (2*S*,1′*R*,2′*S*)-2-(2′-carboxycyclopropyl)glycine (L-CGA C, **1**)[2] is a highly potent and selective agonist of the *N*-methyl-D-aspartic acid (NMDA) receptor site of the ionotropic NMDA receptor complex, while (2*S*,1′*S*,2′*S*)-2-(2′-carboxycyclopropyl)glycine (L-CCG I, **2**)[3] is a potent albeit not very selective agonist of the mGluR2 subtype of group II mGluRs. The introduction of an additional substituent in the 3′ position leads to compounds

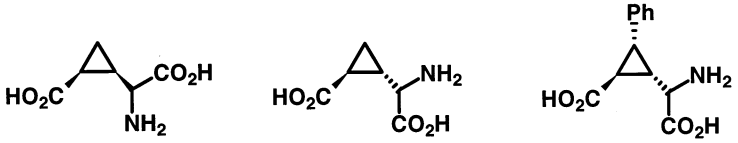

Figure 1.

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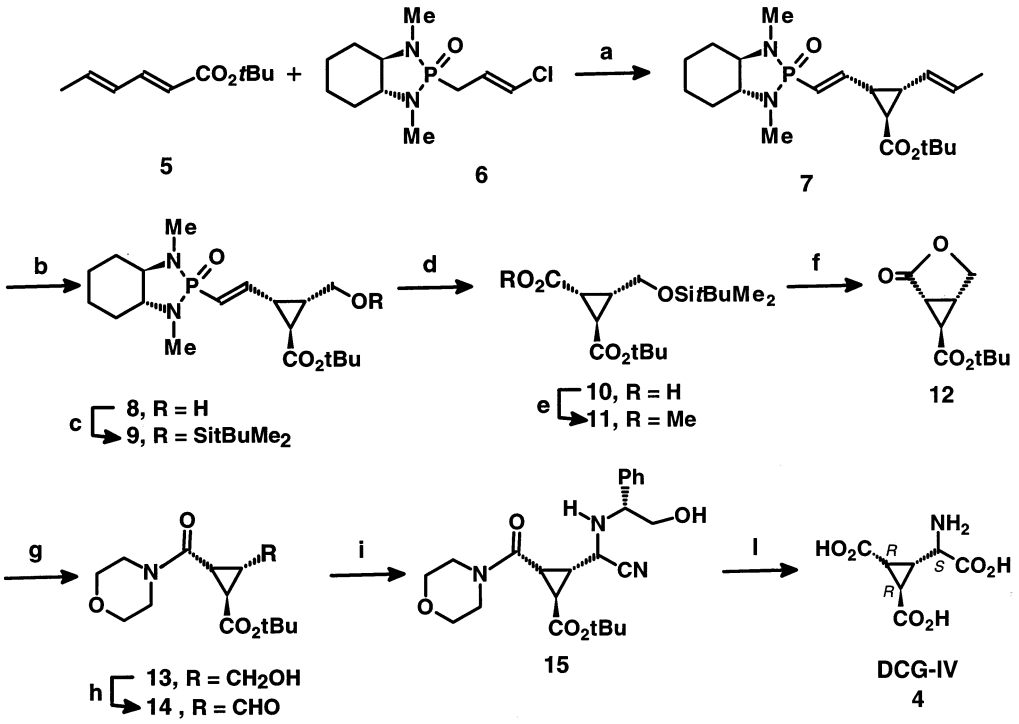
widely differing in their biological properties according to the nature of the substituent and its overall chirality. Thus, (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine (PCCG-4, **3**)[4] characterized by a lipophilic moiety at C-3′ is a mGluR2 antagonist, while (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV, **4**)[5] is a relatively potent and selective agonist of group II mGluR2 and mGluR3 subtypes. Recently, the high potency of DCG-IV (**4**) as an anticonvulsant agent has confirmed the important role of group II mGluRs in the control of seizure activity via modulation of neuronal L-glutamate release.[6]

In connection with our continuing studies in the excitatory amino acids field, we needed large amounts of DCG-IV (**4**) and became engaged in the development of a new route for its preparation. When we started our work, indeed, the only reported synthesis of **4** was suffering from the burden of many steps and a poor overall yield.[7] Although during the course of this work two new improved synthesis[8,9] of DCG-IV (**4**) have appeared, we deem of interest to describe the alternative route that we have followed, which involves as a key step the highly stereocontrolled conjugate 1,4-addition of the anion of a *trans*-chloroallyl phosphonamide reagent to an α,β-unsaturated carbonyl derivative (Scheme 1). Whereas in most auxiliary-controlled formal [2+1] cycloadditions, the auxiliary group is attached to the olefin residue, in this methodology recently developed by Hanessian[10] the chiral information is carried out by the chiral chloroallylphosphonamide, acting as a vinylcarbene equivalent.



Scheme 1. (a) BuLi, THF, −78°C, 54%; (b) i. O_3, CH_2Cl_2–MeOH, solvent red 19, −78°C; ii. $NaBH_4$, 80%; (c) TBDMSiCl, imidazole, CH_2Cl_2–DMF, rt, quantitative; (d) i. O_3, CH_2Cl_2, −78°C; ii. 32% H_2O_2; (e) CH_2N_2, Et_2O, rt, 79%; (f) nBu_4NF, THF, rt, 81%; (g) i. morpholine, $AlMe_3$, CH_2Cl_2, reflux, quantitative; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 86%; (i) i. *R*-α-phenylglycinol, MeOH, rt; ii. TMSCN, 0°C, then rt, iii. mpc, 60%; (l) i. $Pb(OAc)_4$, CH_2Cl_2–MeOH (1:1), rt; ii. 6N HCl, reflux; iii. Dowex 50WX2-200, 1N NH_4OH, 60%

Thus, treatment at −78°C of *trans–trans tert*-butyl sorbate (**5**) with the anion of (*R*,*R*)-*trans*-chloroallyl phosphonamide[10] (**6**) generated at −78°C (BuLi, THF) followed by flash chromatography (EtOAc–methanol 95:5), afforded the corresponding *cis*,*trans*,*trans*-cyclopropane derivative **7** as single diastereoisomer in 54% yield. The key derivative **7** was then transformed into the corresponding alcohol **8** by selective ozonolysis[11] of the propenyl side chain, carried out at −78°C in dichloromethane–methanol (1:1) in the presence of the solvent red 19, followed by reductive quenching with sodium borohydride (80%). Removal of the chiral auxiliary and generation of a second carboxy moiety was then achieved by submitting **8** to protection of the hydroxy group (*tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2–DMF) followed by ozonolysis (CH_2Cl_2, −78°C) of the silyl derivative **9** thus obtained. Esterification of **10** (CH_2N_2, Et_2O, 0°C) followed by removal of the TBDMSi moiety with tetrabutylammonium fluoride in THF afforded the corresponding lactone **12** in 79% yield. Ring opening of the lactone **12** with the Weinreb reagent[12] ($AlMe_3$, morpholine, CH_2Cl_2, rt) provided almost quantitatively the corresponding hydroxymethyl morpholine amide **13** which was readily oxidized to the aldehyde **14** by the Swern protocol[13] in 86% yield. A diastereoselective Strecker synthesis[14] involving the condensation of **14** with optically active *R*-(−)-α-phenylglycinol (MeOH, rt, 3 h) followed by nucleophilic addition of a cyanide ion to the Schiff base (TMSCN, 0°C then rt, 12 h) afforded the (2*S*,2′*R*,3′*R*)-aminonitrile **15** along with minor amounts of the (2*R*,2′*R*,3′*R*)-diastereoisomer (95:5 by ^{1}H NMR). Separation of the two α-aminonitriles by flash chromatography (light petroleum–EtOAc, 8:2) afforded the desired isomer **15** which was then submitted to oxidative cleavage with lead tetraacetate[15] (CH_2Cl_2–MeOH, 0°C, 10 min) acidic (6N HCl) hydrolysis and ion exchange resin chromatography (Dowex 50WX2-200, 1N NH_4OH) to afford (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine DCG-IV (**4**),[16] in 8.5% overall yield with analytical data identical with those of an authentic sample.

In summary, the new synthetic route that we have developed for DCG IV (**4**) can usefully be employed for the preparation of large amounts of the compound, thus satisfying the current large demand for this important pharmacological tool.

Acknowledgements

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16. Analytical data for compounds **12**, **14** and **15**:
12: ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s, *t*Bu), 1.85 (1H, t, $J=3.0$ Hz, C*H*CO_2tBu), 2.45 (1H, m, C*H*CH_2O), 2.60 (1H, m, C*H*CO), 4.21 (1H, d, $J=10.2$ Hz, CH_aO), 4.30 (1H, dd, $J=4.2$ and 10.2 Hz, CH_bO);
14: mp 80–2°C; ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s, *t*Bu), 2.40–2.50 (1H, m, C*H*CHO), 2.80 (1H, dd, $J=6.4$ and 10.7 Hz, C*H*CON), 3.10 (1H, t, $J=6.4$ Hz, C*H*CO_2tBu), 3.45–3.80 (8H, m, morpholine ring), 9.20 (1H, d, $J=7.1$ Hz, C*H*O);
15: mp 49–50°C; $[\alpha]_D^{20}$ −144.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s, *t*Bu), 2.05 (1H, td, $J=$ 6.6, 9.3 and 18.5 Hz, C*H*CHCN), 2.25–2.45 (2H, m, C*H*CON and C*H*CO_2tBu), 2.65 (2H, brs, OH and NH), 3.20–3.80 (11H, m, morpholine ring, CH_2OH and 2-C*H*), 3.90–4.05 (1H, m, C*H*Ph), 7.10–7.30 (5H, m, aromatics); ^{13}C NMR δ 25.30, 27.35, 28.02, 29.63, 42.57, 46.10, 62.98, 66.38, 66.51, 67.25, 81.86, 119.00, 127.34, 128.23, 128.82, 138.09, 165.57, 170.18.