A concise and efficient stereoselective synthesis of protected (2R,1'S,2'S)-2-(carboxycyclopropyl)glycine (D-CCG-I)

Debendra K. Mohapatra

OCT Division, National Chemical Laboratory, Pune-411 008, India.
E-mail: dkm_77@yahoo.com; Fax: 91-020-5893614/5892456

The stereoselective synthesis of protected D-carboxycyclo-propylglycine (D-CCG-I) was achieved, as an extension of Taguchi's protocol for Simmons–Smith cyclopropanation to a chiral, amino-containing allyl alcohol derivative, in 8 steps (40% overall yield).

L-Glutamic acid functions at many synapses in mammalian central nervous systems (CNS) as an excitatory neurotransmitter[1] and is implicated in the development of memory and early learning,[2] as well as in the pathogenesis of neuron damage to cause various neuronal diseases.[3] Recent years have seen, in particular, a growing interest in the field of the metabotropic glutamate receptor (mGluR) family,[4–6] due to the intriguing therapeutic opportunities offered by the modulation of its members. Indeed, mGluRs have been shown to play important roles in spatial learning[7] and the process of postaral-vinetic integration,[8] as well as in the pathogenesis of either acute (ischemia, epilepsy, hypoxia) or chronic (*e.g.*, Alzheimer's disease, Parkinsonism, AIDs-related dementia) diseases.

Among the several classes of glutamate analogs, carboxy-cyclopropylglycines (CCGs) represent a valuable source of potent and selective ligands for the various members of the glutamate receptor family. (2R,1'S,2'S)-2-(Carboxycyclo-propyl)glycine (D-CCG-I), which restricts the conformation of D-glutamate in the extended form, has received much attention from neuroscientists because it is a potent and selective *N*-methyl-D-aspartate (NMDA) agonist.[9,10]

Prompted by the above observations and by our interest in the synthesis of bioactive natural products containing cyclo-propyl rings,[11] we undertook synthetic studies on the above class of compounds. Herein, we would like to report a facile and stereoselective synthesis of protected D-CCG-I, extending Taguchi's asymmetric cyclopropanation protocol[12] to a chiral, amino-containing allylic alcohol derivative. To our knowledge, no analogous studies have been reported so far on such compounds in which the chiral oxygen group has been replaced by a nitrogen functionality.

For the proposed synthesis, we decided to utilize the easily available and widely used L-serine-derived Garner's aldehyde **3** (Scheme 1) as a chiral template in which the stereodefined amine functionality, along with a primary hydroxy group (both of
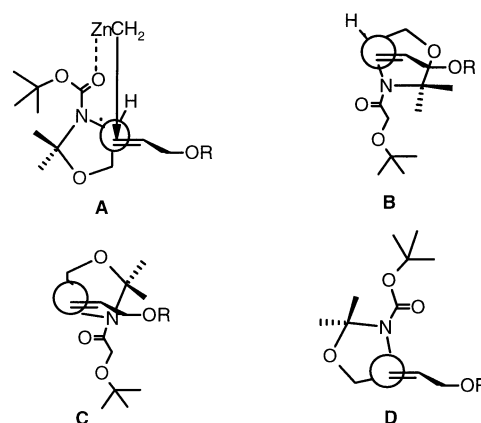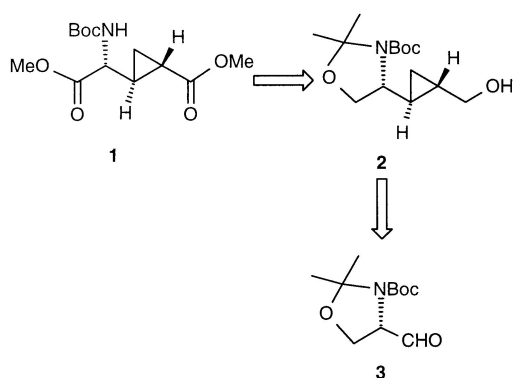

Scheme 1

Fig. 1

which can ultimately be utilized in the α-amino acid precursor), and the aldehyde functionality would assist in building the cyclopropane skeleton.

Following a retrosynthetic strategy, the journey began with a diastereoselective two-carbon Wittig reaction of Garner's alde-hyde with (ethoxycarbonylmethylene)triphenylphosphorane in benzene which provided (*E*)-allyl ester **4** (Scheme 2) in 92% yield. The (*E*)-geometry of the double bond was confirmed by the coupling constant between the olefinic protons ($J = 15.8$ Hz). Compound **6** was obtained by the exposure of compound **4** to 2.5 equivalents of DIBAL-H in CH_2Cl_2 followed by protection with a TBDPS group.

In order to investigate the Simmons–Smith cyclopropanation reaction on chiral, amino-containing allyl alcohol derivatives and to synthesize the intermediate **2** with the required stereo-chemistry, compound **6** was treated with Et_2Zn and CH_2I_2, following Taguchi's protocol, to afford the disubstituted cyclo-propane derivative **7** in 93% yield (Scheme 3). At this stage, we could not determine the diastereomeric excess as the silyl alcohol accompanied the product during purification by silica gel column chromatography.

Compound **7** was then treated with tetrabutylammonium fluoride to afford the free hydroxy compound **2**, which on HPLC analysis was found to be a mixture of diastereomers (90 : 10). Chelation-controlled positioning of the reagent (the complexation-induced proximity effect) has been proposed to account for this diastereoselective addition to the allylic alco-hol. Four models can be considered as possible transition state models (Fig. 1). Among them conformer **A** is most favourable compared to the rest in terms of steric repulsion between the *N,O*-acetonide ring and the TBDPS group. Owing to the bulki-ness of the TBDPS group, the reagent might co-ordinate to the carbonyl oxygen of the Boc group and the methylene transfer may then occur from the less hindered face of the double bond, providing the major cyclopropane in the required (1*S*,2*S*)-stereochemistry.[12,13]
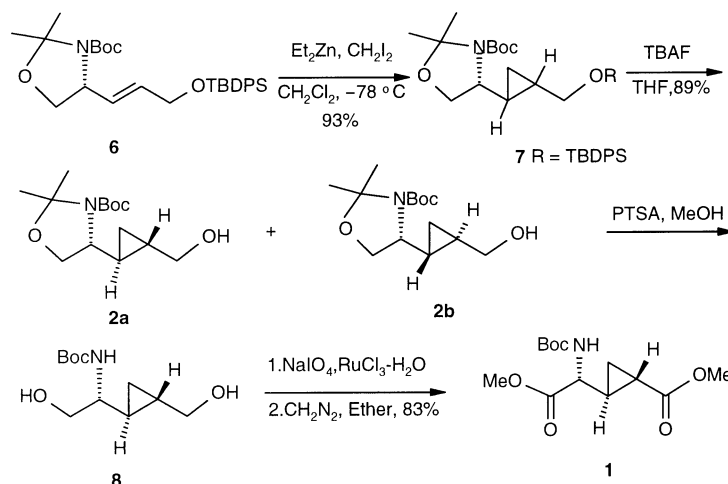
Finally, hydrolysis of the acetonide linkage of **2** with PTSA in methanol yielded the intermediate **8** and oxidation of the hydroxy groups to carboxylic acids, followed by esterification with diazomethane under standard reaction conditions,
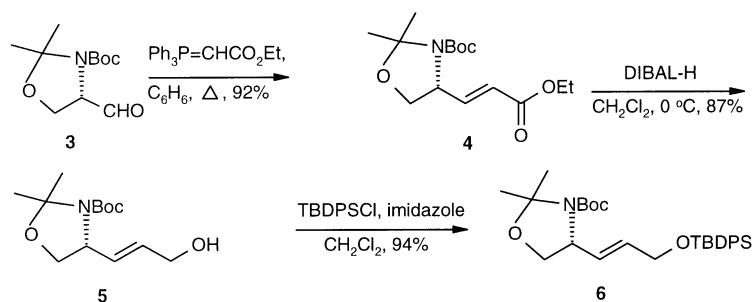
Scheme 2

Scheme 3

afforded the target cyclopropylglutamic acid analogue **1** in good overall yield. The structure of **1** was established on the basis of ¹H NMR, ¹³C NMR and mass spectra.[14]

In conclusion, an efficient stereoselective synthesis of protected D-CCG-I has been developed using as the key step a chelation-controlled Simmons–Smith cyclopropanation, following Taguchi's protocol, on a readily available L-serine-derived chiral template. Utilizing *ent*-**3** and/or changing the starting alkene geometry, it is possible to synthesize all four of the possible isomers of CCG following the approach described above, thereby, showing the versatility of this method. The reported methods either involve multistep reactions or give a poor overall yield. Following our protocol, it is, however, possible to prepare large amounts of the carboxycyclopropyl-glycine, which is important for pharmacological applications. The synthesis of other cyclopropyl-containing bioactive molecules is in progress and will be reported in due course.

Acknowledgements

References

1 (*a*) D. T. Monaghan, R. J. Bridges and C. W. Cotman, *Annu. Rev. Pharmacol. Toxicol.*, 1989, **29**, 365; (*b*) C. J. Wakins, P. Kroggsgaard-Larsen and T. Honore, *Trends Pharmacol. Sci.*, 1990, **11**, 25.
2 (*a*) G. L. Collingridge and T. V. P. Bliss, *Trends Neurosci.*, 1987, **10**, 288; (*b*) D. V. Madison, R. C. Malenka and R. A. Nicoll, *Annu. Rev. Neurosci.*, 1991, **14**, 379; (*c*) H. Kaba, Y. Hayashi, T. Higuchi and S. Nakanishi, *Science*, 1994, **265**, 262.
3 (*a*) B. Meldrum and J. Garthwaite, *Trends Pharmacol. Sci.*, 1990, **11**, 379; (*b*) L. W. Olney, *Annu. Rev. Pharmacol. Toxicol.*, 1999, **30**, 47; (*c*) D. W. Choi and S. M. Rothman, *Annu. Rev. Neurosci.*, 1990, **13**, 171.
4 (*a*) J. P. Pin and R. Duvoisin, *Neuropharmacology*, 1995, **34**, 1; (*b*) T. Knopfel, R. Kuhn and H. Allegier, *J. Med. Chem.*, 1995, **38**, 1417.
5 Z. A. Bortolotte, Z. I. Beshir, C. H. Davies and G. L. Collingridge, *Nature*, 1994, **368**, 740.
6 C. Pawloski-Dahm and F. J. Gordon, *Am. J. Physiol.*, 1992, **262**, 1611.
7 G. Riedel, W. Wetzel and K. G. Reymann, *Neurosci. Lett.*, 1994, **167**, 141.
8 A. I. Sacaan, F. P. Bymaster and D. D. Schoepp, *J. Neurochem.*, 1992, **59**, 245.
9 (*a*) H. Shinozaki, Y. Ohfune, K. Watanabe, P. Li and H. Takeuchi, *Tetrahedron Lett.*, 1988, **29**, 1181; (*b*) K. Shimamato, M. Ishida, H. Shinozaki and Y. Ohfune, *J. Org. Chem.*, 1991, **56**, 4167; (*c*) K. Shimamato and Y. Ohfune, *Synlett*, 1993, **12**, 919.
10 D. Ma and Z. Ma, *Tetrahedron Lett.*, 1997, **38**, 7599.
11 (*a*) D. K. Mohapatra and A. Datta, *J. Org. Chem.*, 1998, **63**, 642; (*b*) V. Sundararaman, D. K. Mohapatra and A. Datta, *Tetrahedron Lett.*, 1998, **39**, 1075; (*c*) V. Sundararaman, D. K. Mohapatra and A. Datta, *Tetrahedron Lett.*, 1998, **39**, 5667; (*d*) D. K. Mohapatra, *Synth. Commun.*, 1999, **29**, 4261.
12 T. Morikawa, H. Sasaki, A. Shibuya and T. Taguchi, *J. Org. Chem.*, 1994, **59**, 103.
13 A. B. Charette, S. Prescott and C. Brochu, *J. Org. Chem.*, 1995, **60**, 1081 and references therein.
14 Compound **4**: [a]$_D$: −63.8 (*c* = 2.0, CHCl₃); IR (neat): 1742, 1698 cm⁻¹; ¹H NMR (CDCl₃): δ 1.30 (t, *J* = 6.98 Hz, 3H, CH₃), 1.38–1.70 (m, 15H, 2 × CH₃ and *t*-Bu), 3.80 (dd, *J* = 3.68, 9.2 Hz, 1H, OCH₂), 4.07 (dd, *J* = 5.00, 9.20 Hz, 1H, OCH₂), 4.20 (q, *J* = 6.80 Hz, 1H, OCH₂CH₃), 4.32–4.60 (br m, 1H, NCH), 5.87 (br d, *J* = 15.80 Hz, 1H, COCH=CH), 6.80 (dd, *J* = 8.70, 15.80 Hz, 1H, COCH=CH); FABMS: 230 (MH⁺). Compound **2**: [a]$_D$: −21.59 (*c* = 0.75, CHCl₃); IR (neat): 3400–3200, 1692 cm⁻¹; ¹H NMR (CDCl₃): δ 0.86 (m, 1H, CH-cyclopropyl), 1.21 (m, 1H, CH-cyclopropyl), 1.47–1.70 (m, 17H, 2 × CH-cyclopropyl, *t*-Bu and 2 × CH₃), 3.30 (m, 1H, NCH), 3.55 (m, 1H, OCH₂), 3.66 (m, 1H, OCH₂), 3.92 (m, 2H, CH₂OH); FABMS: 260 (MH⁺). Compound **1**: [a]$_D$: −32.45 (*c* = 1.2, CHCl₃); IR (neat): 1742, 1723, 1682 cm⁻¹; ¹H NMR (CDCl₃): δ 1.05 (m, 1H, CH-cyclopropyl), 1.24 (m, 1H, CH-cyclopropyl), 1.44 (s, 9H, *t*-Bu), 1.72 (m, 2H, CH₂-cyclopropyl), 3.69 (2 × s, 3H, OCH₃), 3.78 (2 × s, 3H, OCH₃), 3.90–4.15 (m, 1H, NCH), 5.14 (br m, 1H, NHBoc); ¹³C NMR (CDCl₃): δ 173.4, 171.6, 155.4, 80.0, 54.8, 52.3, 28.0, 23.9, 17.8, 12.8, 12.0; FABMS: 288 (MH⁺). HPLC column, CHIRAL CEL (OD); mobile phase, 10% propan-2-ol in *n*-hexane; flow rate, 1 mL min⁻¹; UV detection at 225 nm.