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Facile Synthesis of (2S,1'S,2'S)-2-(Carboxycyclopropyl)glycine, an Isotype-Selective Agonist of Metabotropic Glutamate Receptors

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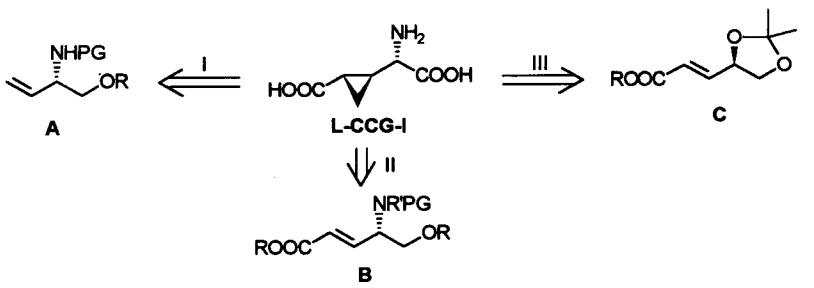
Abstract: (2S,1'S,2'S)-2-(Carboxycyclopropyl)glycine (L-CCG-I) was synthesized in 12 steps and 14% overall yield by using Sharpless's asymmetric dihydroxylation reaction and stereochemically controlled cyclopropanation as key steps. © 1997 Elsevier Science Ltd.

(2S,1'S,2'S)-2-(Carboxycyclopropyl)glycine (L-CCG-I), a conformationally constrained L-glutamate analogue, was originally synthesized by Ohfune and coworkers in 1991[1,2]. This compound was found to be an isoform-selective agonist for group II metabotropic glutamate receptors (mGluRs)[3]. As a pharmacological tool, L-CCG-I has played an important role in further understanding the functions and coupling mechanisms of in situ mGluRs in the last five years[3-6]. Recently, much attention has been paid to the modification of this compound, which has led to the discovery of several other potent and selective agonists or antagonists for mGluRs[7-12]. In order to meet the increasing requirements for chemical modification of L-CCG-I, we feel that it is necessary to develop variable synthetic protocols for this compound[13]. Herein, we describe a facile and stereoselective synthesis of L-CCG-I.

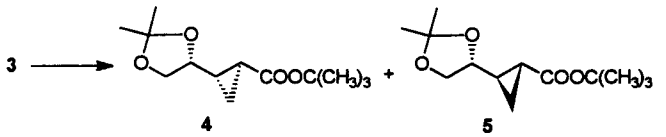
Scheme I



Our retrosynthetic analysis of L-CCG-I is shown in Scheme I. It is obvious that the key step for building this molecule is stereochemically controlled cyclopropanation. The route I has been used by Ohfune[1] to deliver L-CCG-I and the cyclopropanation step gave four stereoisomers with the desired isomer as the minor component. While the route II has also proven problematic for stereochemical control. For example, cyclopropanation of various olefins **B** under several conditions produced two isomers and the desired isomer still being the minor component[1]. We have found that the Wittig-type cyclopropanation for olefins **B** did not work[14]. On the other hand, good diastereoselectivity has been reached when isopropylidenediphenylsulfurane reacted with an olefin **C** (R = Me)[15] and the stereo configuration of cyclopropane was just the same as that of the L-CCG-I, which stimulated us to try route III.

As outlined in Scheme II, diene **1**, prepared from acrolein and 2-triphenylphosphoranylidene-*tert*-butyl acetate, was subjected to asymmetric dihydroxylation reaction[16] to produce diol **2** (85% ee determined by GC). Protection of **2** with dimethoxy propane (DMP) in refluxing benzene furnished γ-alkoxy ester **3**. Now we could try to use a ylide method to build cyclopropane ring and the results are summarized in Table 1. When we used methylene-triphenylphosphane to run the reaction, we found that no reaction occurred at lower temperature (Entry 4, Table I); while the diastereoselectivity was poor, the reaction occurred (Entry 3, Table I). After some experimentation, we found that using dimethylsulfoxonium methylide as the cyclopropanation reagent under lower reaction temperature could afford **4** in good diastereoselectivity (Entry 8). It is notable that cyclopropanation with diazomethane was not suitable in our case although good diastereofacial selectivity has been reached in some cases[17] (Entry 1).

Table 1: Stereochemically Controlled Cyclopropanation of 3

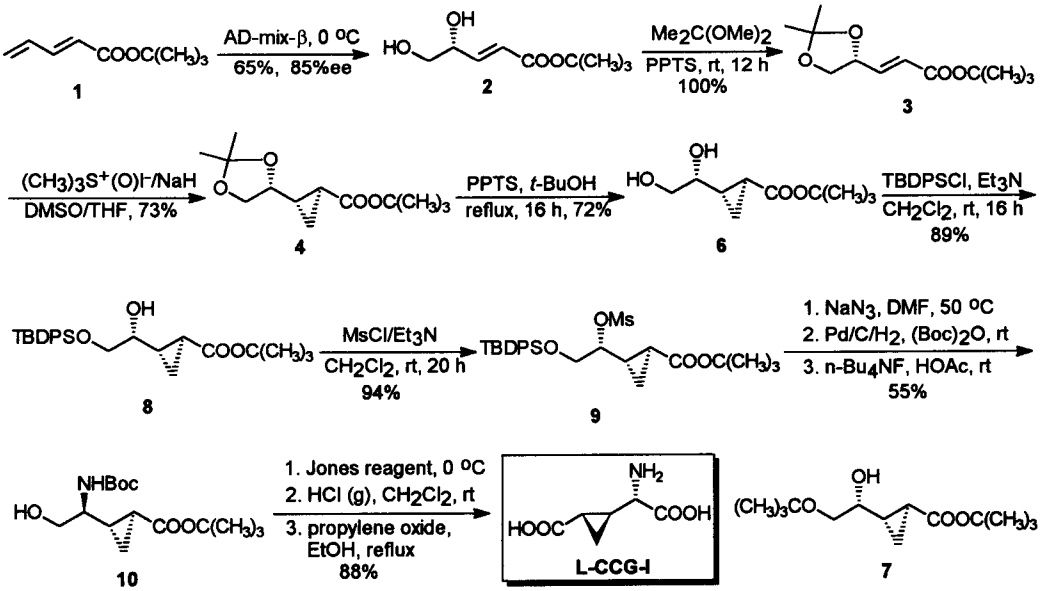


Entry	Reagent	Temperature (°C)	Time (h)	Yield (%)	5/4
1	CH_2N_2, $Pd(OAc)_2$	20	0.5	98	1.4/1
2	CH_2N_2, $Pd(OAc)_2$	-50 - 0	6	0	-
3	$Ph_3P^+CH_3I^-$, n-BuLi	20	0.5	66	1/1.3
4	$Ph_3P^+CH_3I^-$, n-BuLi	0	5	0	-
5	$(CH_3)_3S^+(O)\ I^-$, NaH	55	1	82	1/2
6	$(CH_3)_3S^+(O)\ I^-$, NaH	20	5	82	1/2
7	$(CH_3)_3S^+(O)\ I^-$, NaH	0	5	80	1/4
8	$(CH_3)_3S^+(O)\ I^-$, NaH	-30	5	73	1/19

In order to remove the isopropylidene group, compound **5** was treated with TsOH in *t*-BuOH at r.t. for 24 h., but no reaction occurred. When the reaction temperature was raised to 50 °C, in addition to the desired product **6**, a small amount of t-butyl ether **7** (**6/7**=2/1) was obtained. So pyridinium *p*-toluenesulfonate

which has lower acidity was used to afford the deprotection product **6** in 72% yield. To convert the secondary hydroxy group of **6** into amine, we had to protect the primary hydroxy group selectively. Although Chaudhary[18] reported the preparation of TBDMS ethers with kinetic preference for primary over secondary alcohols when 4-dimethylaminopyridine (DMAP) was used as a group transfer agent, we found that in our case the ratio of silylation of primary hydroxy group to secondary was only 1.5 : 1. So the more hindered *tert*-butyldiphenylsilyl chloride (TBDPSCl) was used to give the desired product **8** in 89% yield and no secondary hydroxy protection product was detected. Next, mesylation of **8** produced **9**, which was transformed to **10** by the following sequence of reactions: (i) conversion of methylsulfonyl group into azide through an S_N2 reaction; (ii) one-pot transformation of azide-group to the N-*t*-Boc derivative; (iii) removal of the TBDPS ether with 1 M $Bu_4N^+F^-$/HOAc in THF. Compound **10**[19] was found as fine crystals. Thus, recrystallization of **10** was undertaken to get optically pure product (this was confirmed by transforming **10** to L-CCG-I). Finally, Jones oxidation of **10** followed by deprotection with dry HCl in CH_2Cl_2 afforded L-CCG-I as its hydrochloride salt. Treatment of this salt with propylene oxide provided the desired L-CCG-I[20] (88% from **10**), which was identical in all respects with the reported data.

Scheme II



In conclusion, we have developed a facile synthesis of L-CCG-I by using Sharpless's asymmetric dihydroxylation reaction and stereochemically controlled cyclopropanation as key steps. The synthesis of designed analogues based on this synthetic protocol and their biological evaluation are currently underway and will be reported elsewhere in due course.

Acknowledgements: The authors are grateful to the Chinese Academy of Sciences and National Natural Science Foundation of China for their financial support.

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19. **10**: mp 81-82 °C; $[\alpha]^{16}_{D}$ = 45.8 (*c* 1.02, $CHCl_3$); IR (neat) 3490, 1720, 1367, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (m, 1H), 1.13 (m, 1H), 1.44 (s, 9H), 1.46 (s, 9H), 1.68 (m, 1H), 1.96 (m, 1H), 3.12 (br s, 1H), 3.66 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.75 (dd, *J* = 11.1, 3.3 Hz, 1H), 4.86 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 19.5, 23.4, 55.8, 65.7, 80.57, 80.59, 156.0, 172.5; HRMS calcd for $C_{14}H_{24}NO_5$ $(M\text{-}CH_3)^+$ 286.1654; found 286.1624.
20. Selected date for L-CCG-I: mp 246-249 °C, dec. [lit.[1] mp 243-247 °C, dec.]; $[\alpha]^{15}_{D}$ = 101.4 (*c* 0.21, H_2O)[lit.[1] $[\alpha]^{21}_{D}$ = 102.0 (*c* 0.50, H_2O)]; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (m, 1H), 1.30 (m, 1H), 1.67 (m, 1H), 1.75 (m, 1H), 3.20 (d, 1H, *J* = 9.8 Hz).

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