Pergamon

Tetrahedron 56 (2000) 7447–7456

TETRAHEDRON

Synthesis of (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-Dicarboxycyclopropyl)-glycine via the Stereochemically Controlled Cyclopropanation of (*S*)-Glyceraldehyde Acetonide-Derived Enones

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Received 18 May 2000; revised 7 July 2000; accepted 27 July 2000

Abstract—The reaction of ethyl dimethylsulfonium acetate bromide with aromatic enones **5a** or **5b** derived from (*S*)-glyceraldehyde acetonide under the action of DBU provides cyclopropanation products in excellent yield and good diastereoselectivity (10/1). High geometry-selectivity (>95/1) can be reached when the reaction is carried out at lower temperature in toluene. The *cis*-enone **5a** gives better geometry-selectivity than *trans*-enone **5b**. The ylides with amide groups can also be used for cyclopropanation reaction but neither the yields nor the geometry-selectivity are satisfactory. Based on this reaction a new synthetic protocol for (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (L-DCG-IV), an isotype-selective agonist of metabotropic glutamate, is developed.

Introduction

As a major neurotransmitter in excitatory synaptic pathways of the mammalian central nervous system (CNS), L-glutamate plays an important role in many integrative brain functions.[1] In order to have better knowledge of the conformational requirements of L-glutamate for activating each glutamate receptor subtype, Ohfune and co-workers synthesized four diastereomers of L-2-(carboxycyclopropyl)glycine (L-CCG-I–IV), conformationally restricted analogs in which a cyclopropyl group fixes the glutamate chain in either an extended or a folded form.[2] Among these compounds, (2*S*,1′*S*,2′*S*)-2-(2′-carboxycyclopropyl)glycine (L-CCG-I) could selectively activate the mGluRs with a similar potency as L-glutamate.[1c,2] By further modification of L-CCG-I, Ohfune found that (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (L-DCG-IV), an analog of L-CCG-I with a third carboxylic group at 3′-position which is geometrically *trans* to 2′-carboxylic group,[3] was about 10 times more potent than L-CCG-I for activating group II mGluRs and also possessed better subtype-selectivity for mGluRs.[4] Although this compound was also found to be a potent agonist for NMDA receptor,[5] it has been widely utilized for investigating the functions of individual mGluR subtype.[6] As a continuing effort to develop efficient synthesis of mGluR modulators, as well as discovery of new mGluRs ligands,[7] we have reported a facile synthesis of L-CCG-I using stereochemically controlled cyclopropanation as a key step (Scheme 1).[7a] Herein, we wish to report the total synthesis of L-DCG-IV by employing the similar strategy.[8]

Results and Discussion

Originally, L-CCG-IV was synthesized from the Garner's aldehyde derived from D-serine and the key step was an intramolecular cyclopropanation.[3] Our retrosynthetic analysis of L-DCG-IV is shown in Scheme 1, the key intermediate **6** could be prepared by an intermolecular cyclopropanation reaction of an enone **5** with a suitable sulfonium ylide. It was expected that the sulfonium ylide with an electron withdrawing group would attack the enone **5** in a similar substrate-induced diastereoselectivity (from *si* face) as dimethylsulfoxonium methylide thereby giving the desired stereochemistry for synthesizing the target molecule. From the intermediate **6**, it would be possible to transform the acetonide moiety to the α-amino acid moiety by using the similar method for synthesizing L-CCG-I.[7a]

Initially, we tried the reaction of ethyl dimethylsulfonium acetate bromide[9] with olefin **5d** (R′=OMe) to obtain the desired cyclopropanation product (Eq. (1)). It was found that this reaction did not occur under various conditions using different bases and solvents. Recently, Pedregal and co-workers reported a stereoselective cyclopropanation

Keywords: cyclopropanation; aromatic enones; *S*-glyceraldehyde.
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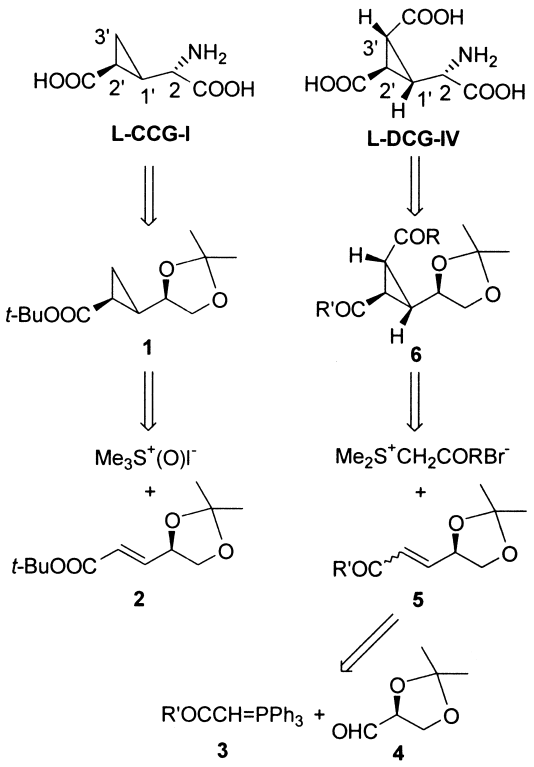
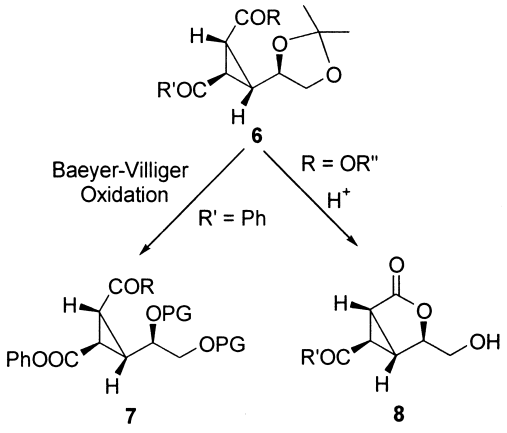
PII: S0040-4020(00)00677-3



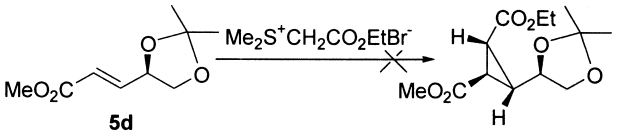
Scheme 1.

reaction of enones with ethyl (dimethylsulfuranylidene)-acetate (EDSA) generated in situ by treatment of ethyl dimethylsulfonium acetate bromide with DBU,[10] which stimulated us to employ the similar strategy to build our desired cyclopropane ring. As shown in Schemes 1 and 2, we planned to use aromatic ketones **5** (R′=Ph) to obtain the corresponding cyclopropanation product **6**. It was expected that in this case the ketone moiety could be converted into a carboxylate group by Baeyer–Villiger oxidation to give ester **7**. In the course of synthesizing L-DCG-VI, another factor we had to consider was that if the COR substituent of **6** was an ester group, lactonization would occur spontaneously to give **8** when its acetonide moiety was subjected to deprotection under the acidic condition. This lactonization would obviously cause major problems for further transformations. To solve this problem, it was intended to



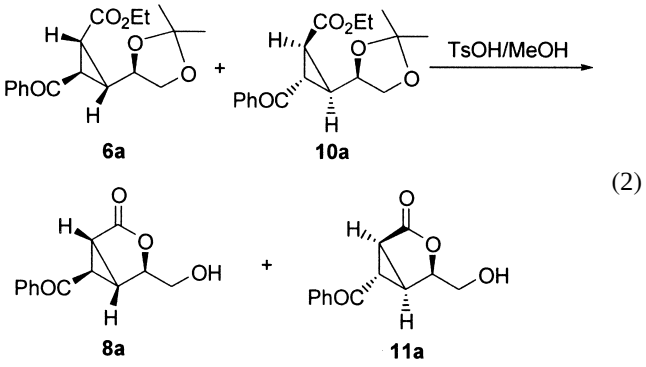
Scheme 2.

use the more stable amide as a substituent at this position.



(1)

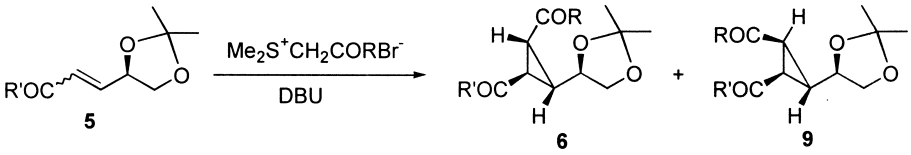
With these ideas in mind, we undertook the studies of the cyclopropanation reactions by varying olefins, sulfur ylides, as well as reaction conditions to get an optimized result. The results are summarized in Table 1. The reaction of the aromatic enone **5a** with ethyl dimethylsulfonium acetate bromide worked well to give cyclopropanation products under the action of DBU in high yield. By column chromatography two fractions were separated. The major fraction was a mixture of two isomers in a ratio of 10/1 determined by ^{1}H NMR, which could be recrystallized to deliver a pure isomer. Its structure was assigned to be (2*R*,1′*R*,2′*R*′3′*R*)-**6a** by a single crystal X-ray analysis (Fig. 1). *It meant that the stereochemistry of the three newly created stereogenic centers is all in correct form for synthesizing* L*-DCG-IV as we have expected!* This result implied that the sulfur ylide attacked predominantly the enone **5a** from the *Re* face as predicted. The minor fraction also contained two isomers in a ratio of 20/1 and the major isomer was assigned to be (2*R*,1′*R*,2′*R*,3′*S*)-**9a** by its NOESY spectra. As shown in Fig. 2, marked NOE correlations between 2′-H and 3′-H were observed, which indicated that the carboxylate group and the ketone group are on the same side and *trans* to the acetonide group. To check whether any products formed through the attack of the sulfur ylide from *Si* face, we tried to identify the minor isomer in major fraction. After the mixture was treated with TsOH in methanol (Eq. (2)), two lactones were separated by column chromatography. By the NOE analysis as indicated in Fig. 2, the structure of the lactone **11a** could be assigned as (2*R*,3*S*,4*S*,5*S*), which implied that the minor isomer **10a** should have the (2*R*,1′*S*,2′*S*,3′*S*)-configuration. This result manifested that when the cyclopropane ring formed the diastereoselectivity was about 10/1.

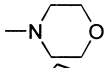


(2)

As shown in Table 1, either the *trans*-olefin **5b** or the *cis*-olefin **5a** could provide **6a** as the major diastereomer and the geometry of the olefins only influenced slightly the ratio of two mixtures (compare entries 1 and 2), which indicated that the same intermediate probably formed during the course of each reaction. A lower reaction temperature inhibited the

Table 1. Cyclopropylation of enones **5** with sulfonium ylides. Reaction condition: enone **5** (1 mmol), sulfonium salt (1 mmol), DBU (1 mmol), solvent (1 mL)



Entry	Enone **5**		R	Solvent	Temperature (°C)	Time (h)	Products (yield (%))[a]	
	R′	Geometry						
1	Ph	*Z* (**5a**)	OEt	Toluene	0	3	**6a** (87)[b]	**9a** (7)
2	Ph	*E* (**5b**)	OEt	Toluene	0	3	**6a** (73)[b]	**9a** (10)
3	Ph	*Z* (**5a**)	OEt	Toluene	−20	4	**6a** (95)[b]	**9a** (4)
4	Ph	*E* (**5b**)	OEt	Toluene	−20	6	**6a** (74)[b]	**9a** (10)
5	Ph	*Z* (**5a**)	OEt	Toluene	−40	6	**6a** (96)[b]	**9a** (1)
6	Ph	*Z* (**5a**)	OEt	Toluene	−78	10	**6a** (95)[b]	**9a** (0.5)
7	Ph	*Z* (**5a**)	OEt	Toluene	25	1	**6a** (73)[b]	**9a** (14)
8	Ph	*E* (**5b**)	OEt	Toluene	25	1	**6a** (80)[b]	**9a** (14)
9	Ph	*E* (**5b**)	OEt	Benzene	25	1	**6a** (74)[b]	**9a** (21)
10	Ph	*Z* (**5a**)	OEt	CH_3CN	−20	3	**6a** (78)[b]	**9a** (11)
11	Ph	*Z* (**5a**)	OEt	$CHCl_3$	−40	8	**6a** (73)[b]	**9a** (5)
12	Ph	*E* (**5b**)	OMe	Toluene	0	3	**6b** (72)[b]	**9b** (9)
13	Ph	*E* (**5b**)	$OC(CH_3)_3$	Toluene	0	10	**6c** (52)	**9c** (8)
14	Ph	*E* (**5b**)		Toluene	0	10	**6d** (53)	**9d** (9)
15	Ph	*E* (**5b**)		Toluene	0	10	**6e** (34)	**9e** (25)
16	Ph	*E* (**5b**)		Toluene	−20	10	**6e** (0)	**9e** (0)
17	Ph	*E* (**5b**)	NEt_2	Toluene	0	10	–	–
18	Ph	*E* (**5b**)	NEt_2	CH_3CN	0	10	**6f** (21)	**9f** (18)[c]
19	Ph	*E* (**5b**)	NEt_2	$CHCl_3$	−78	15	**6f** (37)	**9f** (13)[d]
20	CH_3	*E* (**5c**)	OEt	Toluene	0	3	**6g** (45)	**9g** (18)
21		*E*+*Z* (**5e**)[e]	OEt	CH_3CN	25	10	**6h** (25)	**9h** (12)[f]
22	Ph	*E*+*Z* (**5a**+**5b**)	Me	Toluene	0	10	**6i** (34)	**9i** (38)[g]

[a] Isolated yield.
[b] Containing inseparable 10% (2*S*,1′*S*,2′*S*′3′*S*)-isomer.
[c] Compound **12** was isolated in 17% yield.
[d] Compound **12** was isolated in 13% yield.
[e] R′CO═CN.

formation of **9a** thereby enhancing the geometry-selectivity of this reaction. For example, when the reaction of **5a** with EDSA was carried out below −40°C, it gave exclusively **6a** and its (2*R*,1′*S*,2′*S*,3′*S*)-isomer **10a**. However, the ratio of **6a** to **10a** did not change in a wide temperature range (entries 2, 3, 5 and 6), which indicated that the attack of the EDSA to the olefin from *si* face or *re* face was independent on the reaction temperature. Among the solvents tested, toluene was found to be the best one for either reaction yield or geometry-selectivity (compare entries 3, 10 and 11).

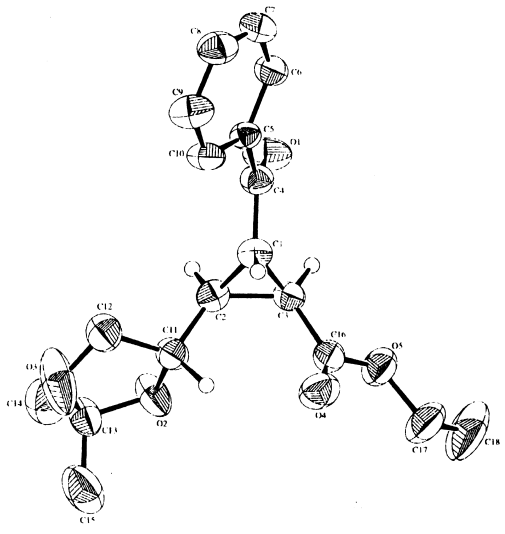


Figure 1. X-Ray structure of **6a**.

Besides the EDSA, the ylides with amide substituents could also react with enone **5b** to afford the corresponding cyclopropanation products. In these cases, neither the reaction yields nor geometry-selectivity were as good as those of EDSA. However, better diastereoselectivity could be obtained. When the reaction was carried out in toluene, only two isomers were isolated as determined by ^{1}H NMR. The structure of each product was assigned by comparing its ^{1}H NMR spectrum with that of **6a** or **9a**. For example, the obvious similarity of the chemical shifts of protons in cyclopropane ring between **6c**–**6f** and **6a** indicated that they all had (2*R*,1′*R*,2′*R*′3′*R*)-configuration. This conclusion was further supported by their reactions under acidic conditions. Treatment of **6c**–**6f** with hydrochloride in methanol gave the same product **8a**. While similarity in the ^{1}H NMR spectra between **9c**–**9f** and **9a** demonstrated that they all had (2*R*,1′*R*,2′*R*,3′*S*)-configuration. When the reaction was run in the polar solvents, another isomer **12** was

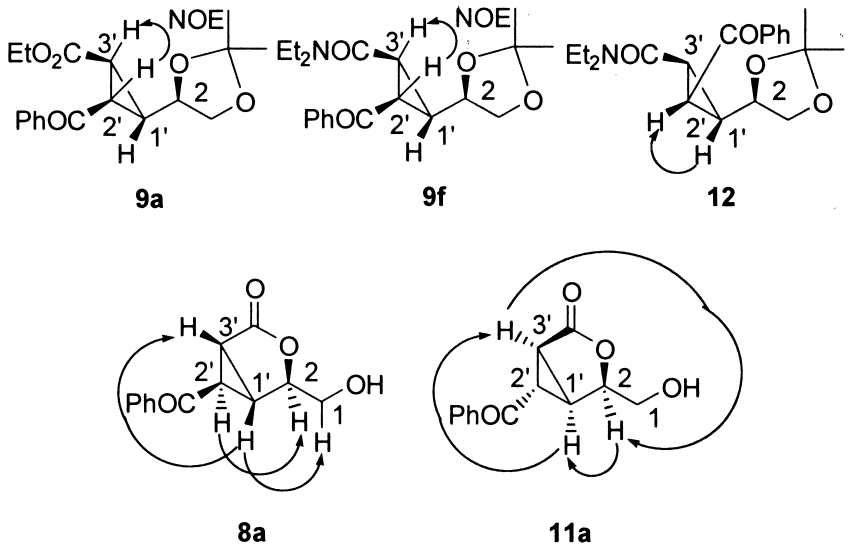
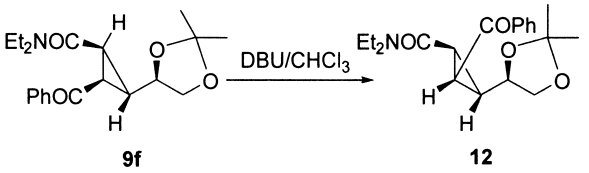


Figure 2. NOE correlations of compounds **9a**, **9f**, **8a**, **11a** and **12**.

also isolated and its structure was assigned by the NOE experiments. This isomer might result from the isomerization of **9f** because we found that the treatment of **9f** with DBU in chloroform for 6 h could provide a mixture of **9f** and **12** (Eq. (3)). This result was consistent with that of the Pedregal's report.[10] As mentioned before, lowering the reaction would be of benefit for either the reaction yield or the geometry-selectivity. However, when these sulfonium salts with amide substituents were used at the lower temperature, it was found that the reaction in toluene did not take place at all due to their poor solubility (entries 16 and 17). Although the reaction of **5b** with the diethylamine-derived ylide could occur at −78°C in chloroform, either the reaction yield or the geometry-selectivity was still found unsatisfactory (entry 19). Thus, these results led us to prepare the desired **6f** indirectly when we processed the total synthesis of L-CCG-IV (as indicated in Scheme 4). In addition, it was found that the methyl ketone **5c** did not give as satisfactory result as that of the phenyl ketone **5b** (entry 20).

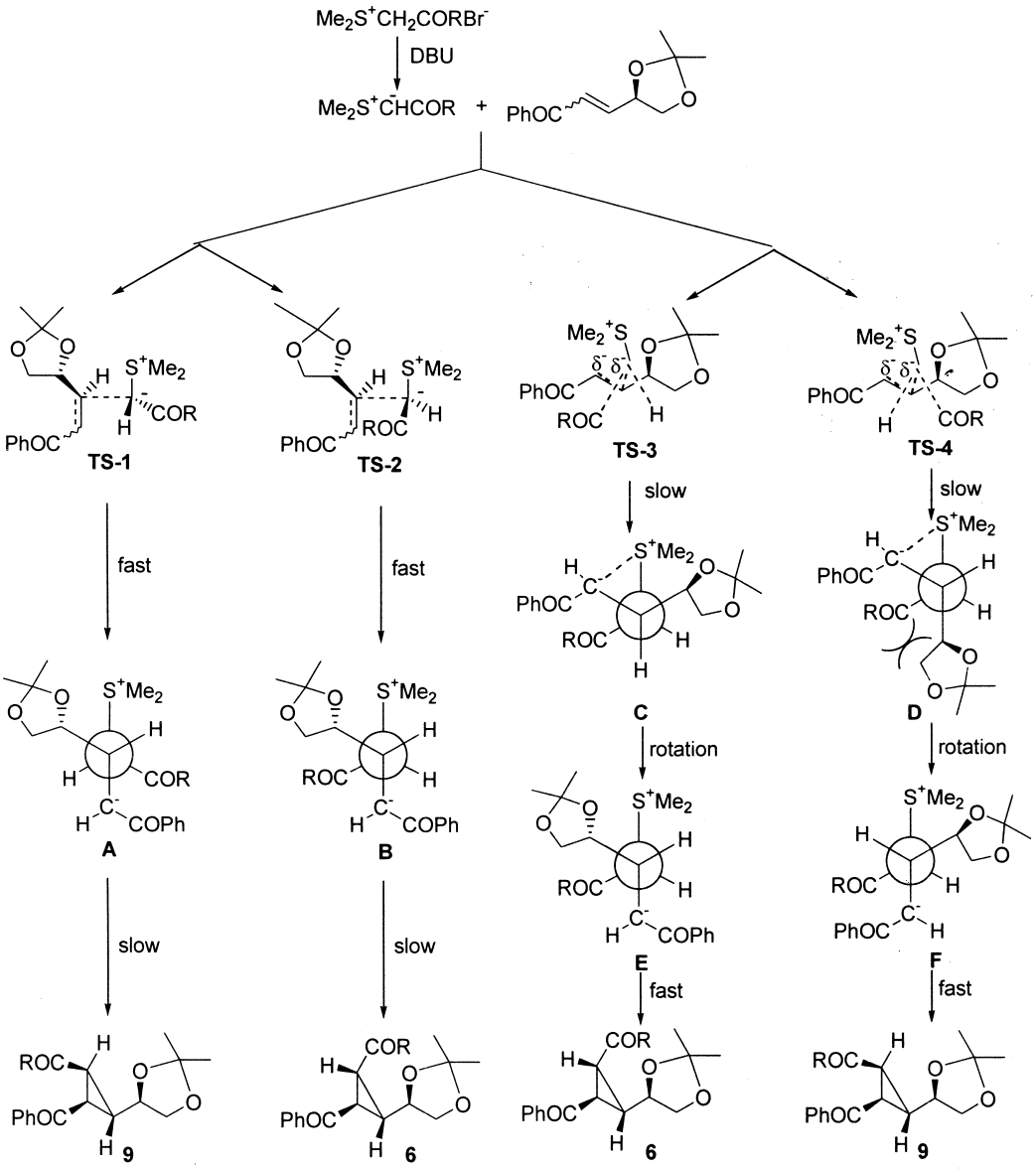


(3)

Although the reaction of ethyl dimethylsulfonium acetate bromide with the α,β-unsaturated ester **5d** failed to give the corresponding cyclopropanation products, the α,β-unsaturated nitrile **5e** under the similar condition provided us the desired cyclopropanes **6h** and **9h** in moderate yield (entry 21). In addition, the sulfonium yield derived from acetone also worked for this reaction and gave diketone cyclopropanes **6i** and **9i** (entry 22). It is notable in these two cases no other diastereomers were detected, which is similar with the cases when the ylides with amide substituents were used (entries 14–19)

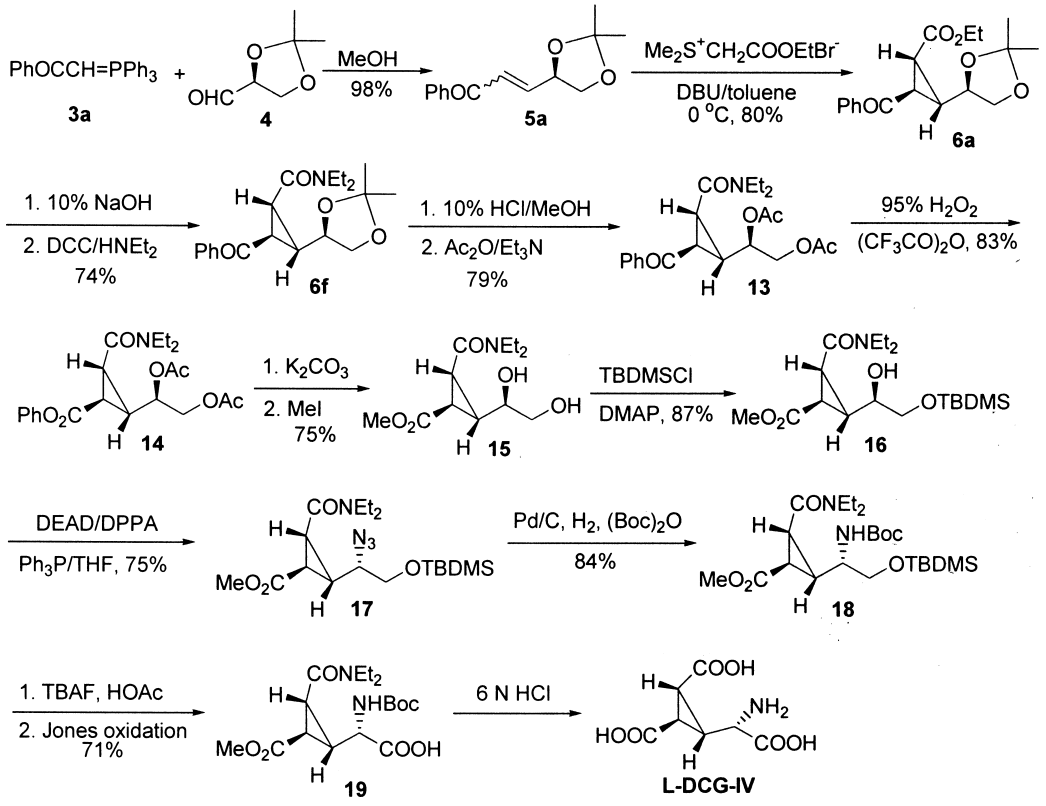
A possible mechanism for the present reaction is discussed in Scheme 3. It is known that the mechanism of ylide cyclopropanation is through the Michael addition and the subsequent elimination–cyclization.[11] If the Michael addition was the fast step and the elimination–cyclization was the slow step, the geometry of the reaction products would be controlled by the stability of intermediates **A** or **B** which was formed through **TS-1** and **TS-2**, respectively. It is obviously that the intermediate **A** is the more stable one because in the intermediate **B** two bulky groups are crowded at one side.[11] Thus, in this case the compound **9** should be the major product. This is not in agreement with the above experimental results. However, if the elimination–cyclization was the fast step and the Michael addition was the slow step, the stereochemistry of the cyclopropanation products would depend on the ratio of intermediates **C** and **D** which benefit from electrostatic attraction, and was formed through transition states **TS3** and **TS4**, respectively.[11] Because of the bigger steric hindrance between acetonide group and the COR group in the intermediate **D**, this intermediate is not so stable in comparison with the intermediate **C**. Thus, in this case **6** should be the major product, which agreed with the above experimental results. Therefore it was concluded that the predominant formation of (2*R*,1′*R*,2′*R*′3′*R*)-isomer was due to the fact that the Michael addition step was the rate-determining step in the present reaction.

Based on the above investigations, we started the total synthesis of L-CCG-IV according to the reaction sequence as outlined in Scheme 4. (*S*)-Glyceraldehyde acetonide **4**, could be prepared in large scale according to the known procedure,[12] and was reacted with the ketone ylide **3a** derived from 2-bromoacetophenone to afford olefins **5a** and **5b** in a ratio of 1/1. Since it has been found that both **5a** and **5b** could react with EDSA to give **6a** as the major product, the Wittig reaction products **5a** and **5b** were not separated and were directly used for next step. The reaction of the mixture of **5a** and **5b** with EDSA at −40°C worked well to produce **6a** in about 80% yield after simple recrystallization. Compound **6a** was then hydrolyzed with 10% NaOH to transfer the ester to the corresponding acid, which was further coupled with diethylamine under the

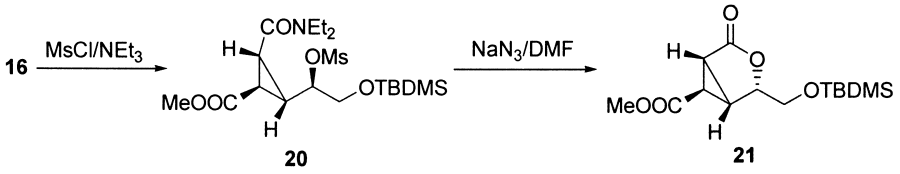


Scheme 3.

action of DCC to provide the amide **6f**. Now it was necessary to transform the ketone moiety into the corresponding ester by the Baeyer–Villiger oxidation.[13] Many conditions were checked to directly oxidize **6f** and it was found that these reactions were complicated partly because the acetonide group was unstable under the acidic conditions. Thus, the protecting group for diol had to be changed. Accordingly, the acetonide group of **6f** was removed under the action of hydrochloride/methanol and the resultant diol was reprotected with the acetyl group to yield the diacetate **13**. Treatment of **13** with trifluoroperacetic acid[14] that was in situ prepared by mixing 95% hydrogen peroxide and trifuoroacetic anhydride afforded the Baeyer–Villiger oxidation product **14** in 83% yield. It is notable this reaction did not work at all if hydrogen peroxide at lower concentration (such as 80% H_2O_2) was used. Next, the ester **14** was treated with potassium carbonate in methanol to remove the two acetal protecting groups and transform the phenyl ester to the corresponding potassium salt. The generated salt was then reacted with iodomethane to provide diol **15**. Unlike the synthesis of L-CCG-I,[7a] the primary hydroxy group of the diol **15** could be selectively protected with TBDMS group without difficulty. After the alcohol **16** was obtained, it was expected to be possible to convert the free hydroxy group into the amino group according to the similar reaction sequence for synthesizing L-CCG-I.[7a] Unfortunately, although the alcohol **16** could be transformed into the mesylate **20** by reacted it with methanesulfonic chloride carefully, it was found that the reaction of **20** with sodium azide in DMF gave the lactonization product **21** as a sole product (Scheme 5). In fact it was found that the mesylate **20** could spontaneously convert into **21** even in DMF without any base assistance. Other amination methods such as direct reaction of **20** with amines or ammonia gave similar results. Fortunately, after some experimentation, we found that the Mistunobu's procedure worked well for our desired transformation.[15] Thus, reacting the alcohol **16** with DPPA under the action of DEAD and



Scheme 4.



Scheme 5.

triphenylphosphine at room temperature for 24 h produced the azide **17** in 75% yield. Finally, the azide **17** was converted to the corresponding amine by the hydrogenation catalyzed by Pd/C, which was trapped in situ with di-*tert*-butyl dicarbonate to provide **18** in 84% yield.[7a] After the deprotection with TBAF/HOAc, the resultant alcohol was subjected to the Jones oxidation to afford the acid **19**. Heating a mixture of **19** in 6N HCl at 100°C for 24 h removed all the protecting groups to give the crude L-DCG-IV as hydrochloride salt, which was purified by ion-exchange column (Dowex-50 W×4) to furnish L-DCG-IV as its ammonium salt. Its spectral data were the same as those reported.[3]

In conclusion, we have developed a stereochemically controlled reaction for synthesizing the enantiopure 1,2,3-trisubstituted cyclopropane. Its efficiency was demonstrated by the total synthesis of L-DCG-IV using this reaction. It is obviously that the present method would be useful for synthesizing other important 1,2,3-trisubstituted cyclopropane derivatives.[16]

Experimental

(*R*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-1-phenyl-prop-2*Z*-en-1-one 5a and (*R*)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-1-phenyl-prop-2*E*-en-1-one 5b. To a solution of (*S*)-glyceraldehyde acetonide **4** (6.4 g, 49 mmol) in methanol (20 mL) was added ylide **3a** (20.6 g, 54.1 mmol) at 0°C. After it was stirred for 10 h with cooling by ice-water, the solvent was evaporated by rotavapor and the residual oil was chromatographed (1/10 ethyl acetate/petroleum ether as eluent) to give **5a** (5.5 g, 48%) and **5b** (5.7 g, 50%). **5a:** pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J=7.9 Hz, 2H), 7.54 (t, J=7.8 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 6.97 (dd, J=11.5, 1.5 Hz, 1H), 6.49 (dd, J=11.6, 6.6 Hz, 1H), 5.37 (m, 1H), 4.53 (dd, J=8.4, 7.2 Hz, 1H), 3.69 (dd, J=8.3, 6.8 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H); MS m/z 232 (M^+); HRMS found m/z 232.1091 (M^+), $C_{14}H_{16}O_3$ requires 232.1096. **5b:** pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J=7.9 Hz, 2H), 7.55 (t, J=7.8 Hz, 1H), 7.48 (t, J=7.8 Hz, 2H), 7.18 (dd, J=15.3, 1.1 Hz, 1H), 6.99 (dd, J=15.3,

5.3 Hz, 1H), 4.79 (m, 1H), 4.23 (dd, *J*=8.2, 6.6 Hz, 1H), 3.72 (dd, *J*=8.3, 7.3 Hz, 1H), 1.48 (s, 3H), 1.38 (s, 3H); MS *m/z* 232 (M^+); HRMS found *m/z* 232.1093 (M^+), $C_{14}H_{16}O_3$ requires 232.1096.

General procedure for cyclopropanation reaction

The enone **5a** (9.48 mmol) and a suitable sulfonium salt (10.5 mmol) was dissolved in toluene (8 mL). The resulting solution was cooled with ice-water and DBU (1.57 mL, 10.5 mmol) was added in a dropwise manner. The resultant mixture was stirred at indicated temperature (Table 1) until TLC showed disappearance of the enone, and then ethyl acetate (40 mL) was added to dilute the solution. After the organic layer was separated, it was washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated and the residual oil was chromatographed (1/4–1/2 ethyl acetate/petroleum ether as eluent) to afford the corresponding cyclopropanation products.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, ethyl ester 6a. mp 78.2°C; $[\alpha]_D^{14}=-31.3$ (*c* 1.35, $CHCl_3$); IR (neat) 3053, 1721, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J*=8.4 Hz, 2H), 7.59 (dd, *J*=8.4, 8.0 Hz, 1H), 7.49 (t, *J*=8.3 Hz, 2H), 4.32 (dt, *J*=9.3, 6.4 Hz, 1H), 4.20 (q, *J*=7.3 Hz, 2H), 3.73 (dd, *J*=8.0, 6.3 Hz, 1H), 3.24 (dd, *J*=5.6, 4.7 Hz, 1H), 2.59 (dd, *J*=9.3, 4.7 Hz, 1H), 2.20 (ddd, *J*=9.4, 9.4, 5.9 Hz, 1H), 1.44 (s, 3H), 1.33 (s, 3H), 1.29 (t, *J*=7.3 Hz, 3H); MS *m/z* 319 ($M^+ + H^+$); HRMS found *m/z* 318.1489 (M^+), $C_{18}H_{22}O_5$ requires 318.1467.

(1*S*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, ethyl ester 9a. $[\alpha]_D^{17}=+74$ (*c* 0.25, $CHCl_3$); IR (neat) 3053, 1721, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (t, *J*=8.0 Hz, 2H), 7.56 (t, *J*=7.9 Hz, 1H), 7.48 (d, *J*=8.0 Hz, 2H), 4.22 (m, 2H), 3.99 (q, *J*=7.1 Hz, 2H), 3.76 (dt, *J*=9.0, 4.8 Hz, 1H), 2.92 (dd, *J*=9.1, 6.2 Hz, 1H), 2.45–2.34 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.04 (t, *J*=7.1 Hz, 3H); MS *m/z* 319 ($M^+ + H^+$); HRMS found *m/z* 318.1489 (M^+), $C_{18}H_{22}O_5$ requires 318.1467.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, *tert*-butyl ester 6c. $[\alpha]_D^{14}=-15.6$ (*c* 0.5, $CHCl_3$); IR (neat) 3061, 1718, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J*=8.1 Hz, 2H), 7.61 (t, *J*=8.0 Hz, 1H), 7.49 (t, *J*=8.1 Hz, 2H), 4.23 (dt, *J*=9.3, 6.1 Hz, 1H), 4.12 (dd, *J*=8.0, 6.0 Hz, 1H), 3.69 (t, *J*=7.7 Hz, 1H), 3.21 (t, *J*=5.3 Hz, 1H), 2.53 (dd, *J*=9.5, 4.7 Hz, 1H), 2.15 (ddd, *J*=9.5, 9.3, 5.5 Hz, 1H) 1.50 (s, 9H), 1.45 (s, 3H), 1.31 (s, 3H); MS *m/z* 347 ($M^+ + H^+$). HRMS found *m/z* 346.1771 (M^+), $C_{20}H_{26}O_5$ requires 346.1778.

(1*S*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, *tert*-butyl ester 9c. $[\alpha]_D^{17}=-14.2$ (*c* 0.5, $CHCl_3$); IR (neat) 3053, 1721, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J*=8.2 Hz, 2H), 7.54 (t, *J*=8.1 Hz, 1H), 7.46 (t, *J*=8.1 Hz, 2H), 4.19 (m, 2H), 3.78 (m, 1H), 2.83 (dd, *J*=9.6, 6.6 Hz, 1H), 2.39–2.28 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.19 (s, 9H); MS *m/z* 347 ($M^+ + H^+$). HRMS found *m/z* 346.1769 (M^+), $C_{20}H_{26}O_5$ requires 346.1778.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, morpholino amide 6d. $[\alpha]_D^{17}=-42.8$ (*c* 0.25, $CHCl_3$); IR (neat) 3059, 1720, 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.1 Hz, 2H), 7.59 (t, *J*=8.0 Hz, 1H), 7.49 (t, *J*=8.0 Hz, 2H), 4.08 (dd, *J*=7.9, 6.0 Hz, 1H), 4.00 (m, 1H), 3.89–3.70 (m, 6H), 3.60 (m, 2H), 3.48 (t, *J*=4.8 Hz, 1H), 3.35 (m, 1H), 2.59 (dd, *J*=9.2, 4.5 Hz, 1H), 2.22 (ddd, *J*=9.4, 9.2, 5.3 Hz, 1H), 1.43 (s, 3H), 1.30 (s, 3H); MS *m/z* 360 ($M^+ + H^+$); HRMS found *m/z* 359.1728 (M^+), $C_{20}H_{25}NO_5$ requires 359.1733.

(1*S*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, morpholino amide 9d. $[\alpha]_D^{17}=+51$ (*c* 1.9, $CHCl_3$); IR (neat) 3063, 1724, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J*=8.0 Hz, 2H), 7.61 (t, *J*=7.9 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 2H), 4.01 (m, 1H), 3.89–3.53 (m, 10H), 3.39 (dd, *J*=9.5, 5.1 Hz, 1H), 2.88 (t, *J*=5.4 Hz, 1H), 2.15 (m, 1H), 1.48 (s, 3H), 1.33 (s, 3H); MS *m/z* 360 ($M^+ + H^+$); HRMS found *m/z* 359.1731 (M^+), $C_{20}H_{25}NO_5$ requires 359.1733.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, diethyl amide 6f. $[\alpha]_D^{14}=-62.7$ (*c* 2.3, $CHCl_3$); IR (neat): 1672, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J*=7.8 Hz, 2H), 7.59 (t, *J*=8.0 Hz, 1H), 7.43 (t, *J*=7.9 Hz, 2H), 4.05 (dd, *J*=7.8, 6.0 Hz, 1H), 3.93 (m, 1H), 3.73–3.53 (m, 3H), 3.46 (t, *J*=5.1 Hz, 1H), 3.31 (dt, *J*=14.6, 7.3 Hz, 1H), 3.17 (dt, *J*=14.4, 7.1 Hz, 1H), 2.58 (dd, *J*=9.4, 4.5 Hz, 1H), 2.18 (ddd, *J*=9.5, 9.4, 5.5 Hz, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 1.23 (t, *J*=7.3 Hz, 3H), 1.10 (t, *J*=7.3 Hz, 3H); MS *m/z* 346 ($M^+ + H^+$); HRMS found *m/z* 345.1940 (M^+), $C_{20}H_{27}NO_4$ requires 345.1949.

(1*S*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, diethyl amide 9f. $[\alpha]_D^{17}=+69.8$ (*c* 1.0, $CHCl_3$); IR (neat): 1672, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*=7.8 Hz, 2H), 7.57 (t, *J*=8.0 Hz, 1H), 7.47 (t, *J*=7.9 Hz, 2H), 4.01 (m, 1H), 3.70 (dd, *J*=8.1, 5.9 Hz, 1H), 3.64–3.31 (m, 6H), 2.88 (t, *J*=5.3 Hz, 1H), 2.19 (ddd, *J*=9.5, 9.4, 5.7 Hz, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 1.25 (t, *J*=7.3 Hz, 3H), 1.10 (t, *J*=7.3 Hz, 3H); MS *m/z* 346 ($M^+ + H^+$); HRMS found *m/z* 345.1940 (M^+), $C_{20}H_{27}NO_4$ requires 345.1949.

(1*S*,2*S*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanecarboxylic acid, diethyl amide 12. $[\alpha]_D^{17}=-5.1$ (*c* 1.0, $CHCl_3$); IR (neat): 1672, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*=7.8 Hz, 2H), 7.53 (t, *J*=8.0 Hz, 1H), 7.44 (t, *J*=7.9 Hz, 2H), 4.23 (m, 1H), 4.17 (dd, *J*=8.0, 6.2 Hz, 1H), 3.78 (dd, *J*=7.9, 6.6 Hz, 1H), 3.54–3.38 (m, 2H), 3.24–3.06 (m 2H), 3.01 (dd, *J*=9.0, 5.9 Hz, 1H), 2.49 (dd, *J*=6.1, 5.9 Hz, 1H), 2.34 (dd, *J*=8.9, 6.3 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 1.12 (t, *J*=7.3 Hz, 3H), 0.96 (t, *J*=7.3 Hz, 3H); MS *m/z* 346 ($M^+ + H^+$); HRMS found *m/z* 345.1940 (M^+), $C_{20}H_{27}NO_4$ requires 345.1949.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-

4-yl)]-cyclopropanenitrile 6h. $[\alpha]_D^{20}=+8.6$ (*c* 1.03, $CHCl_3$); IR (neat): 2251, 1675, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30–4.10 (m, 4H), 3.69 (dd, *J*=7.7, 6.0 Hz, 1H), 2.21 (d, *J*=8.5 Hz, 2H), 1.99 (dd, *J*=14.2, 7.6 Hz, 1H), 1.46 (s, 3H), 1.29 (s, 3H). 1.27 (t, *J*=7.6 Hz, 3H); MS *m*/*z* 238 (M^+-H^+); Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24, H, 7.16, N, 5.85, found: C, 60.45, H, 7.14, N, 5.74.

(1*S*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropanenitrile 9h. $[\alpha]_D^{20}=-23.4$ (*c* 0.89, $CHCl_3$); IR (neat): 2255, 1674, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30–4.09 (m, 4H), 3.65 (dd, *J*=7.6, 5.4 Hz, 1H), 2.19 (d, *J*=8.3 Hz, 2H), 1.98 (t, *J*=7.6 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 238 (M^+-H^+); Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24, H, 7.16, N, 5.85, found: C, 60.19, H, 7.26, N, 5.56.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropyl methyl ketone 6i. $[\alpha]_D^{20}=+114$ (*c* 1.11, $CHCl_3$); IR (neat): 1695, 1670, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J*=8.4 Hz, 2H), 7.60 (dd, *J*=8.4, 8.0 Hz, 1H), 7.47 (t, *J*=8.3 Hz, 2H), 4.16 (m, 2H), 3.70 (m, 1H), 3.39 (t, *J*=4.8 Hz, 1H), 2.87 (dd, *J*=9.3, 4.7 Hz, 1H), 2.43 (s, 3H), 2.32 (dt, *J*=9.2, 5.2 Hz, 1H), 1.48 (s, 3H), 1.29 (s, 3H); MS *m*/*z* 273 (M^+-Me); Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81, H, 6.99, found: C, 70.82, H, 7.01.

(1*S*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-cyclopropyl methyl ketone 9i. $[\alpha]_D^{17}=-97$ (*c* 1.0, $CHCl_3$); IR (neat): 1698, 1670, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J*=8.0 Hz, 2H), 7.59 (t, *J*=7.9 Hz, 1H), 7.48 (t, *J*=8.0 Hz, 2H), 4.05 (m, 1H), 3.71 (dd, *J*=8.1, 6.1 Hz, 1H), 3.07 (dd, *J*=8.2, 6.3 Hz, 1H), 3.32 (dd, *J*=8.6, 4.8 Hz, 1H), 3.08 (t, *J*=5.1 Hz, 1H), 2.40 (s, 3H), 2.18 (dt, *J*=9.4, 5.5 Hz, 1H), 1.42 (s, 3H), 1.31 (s, 3H); MS *m*/*z* 273 (M^+-Me); Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81, H, 6.99, found: C, 70.55, H, 6.99.

Synthesis of 6f from 6a

To a solution of **6a** (2.4 g, 7.5 mmol) in 95% ethanol (10 mL) was added NaOH (300 mg, 7.5 mmol). The mixture was stirred at 0°C for 10 h and then ethanol was removed by rotavapor. The residue was added brine (10 mL) and NaH_2PO_4 until pH=5, and extracted with methylene chloride (3×30 mL). After the combined organic layers were dried over Na_2SO_4 and concentrated, the residual oil was chromatographed eluting with 1/1 ethyl acetate/petroleum ether to provide 2.15 g of acid.

The above acid (2.1 g, 7.1 mmol) was dissolved in CH_2Cl_2 (20 mL). To this stirring solution was added HOBt (1.0 g, 7.4 mmol) and $HNEt_2$ (0.92 mL, 8.8 mmol). The mixture was cooled in ice bath and then a solution of DCC (1.5 g, 7.4 mmol) in CH_2Cl_2 (5 mL) was added in a dropwise manner. After the resulting solution was stirred at room temperature overnight, it was diluted with methylene chloride (30 mL) and then washed with aqueous NH_4Cl, and dried over Na_2SO_4. The solvent was removed by rotavapor and the residual oil was chromatographed to afford **6f** (1.93 g, 74%). Its ^1H NMR spectra was identical with that of **6f** prepared by direct cyclopropanation.

(1*R*,2*R*,3*R*)-2-Benzoyl-3-[(*R*)-1,2-diacetoxyethyl]-cyclopropanecarboxylic acid, diethyl amide 13. A mixture of **6f** (1.9 g, 5.6 mmol) in MeOH (30 mL) and 10% aqueous HCl (10 mL) was stirred overnight. After the solution was concentrated, the residue was diluted with methylene chloride (70 mL), and washed by aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, and concentrated to dryness to give 1.6 g of crude diol as an oil, which was dissolved in CH_2Cl_2 (10 mL). To this stirring solution was added DMAP (10 mg, 0.08 mmol), triethylamine (2.17 mL), and Ac_2O (1.48 mL, 15.9 mmol) with cooling by ice-water. After stirring was continued for 1 h at the same temperature, the solution was diluted with methylene chloride (50 mL), washed with aqueous NH_4Cl, and dried over Na_2SO_4. The crude product was purified by chromatography eluting with ethyl acetate/petroleum ether (1/2) to afford **13** (1.72 g, 79%) as an oil. $[\alpha]_D^{18}=-78.2$ (*c* 0.55, $CHCl_3$); IR (neat) 1746, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*=8.5 Hz, 2H), 7.55 (t, *J*=8.4 Hz, 1H), 7.47 (t, *J*=8.4 Hz, 2H), 5.00 (dt, *J*=9.5, 4.7 Hz, 1H), 4.31 (dd, *J*=11.9, 3.8 Hz, 1H), 4.14 (dd, *J*=11.9, 5.0 Hz, 1H), 3.62–3.49 (m, 3H), 3.30 (dt, *J*=14.6, 7.2 Hz, 1H), 3.20 (dt, *J*=14.4, 7.1 Hz, 1H), 2.56 (dd, *J*=9.2, 4.5 Hz, 1H), 2.31 (m, 1H), 2.00 (s, 3H), 1.92 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H), 1.07 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 389 (M^+); HRMS found *m*/*z* 389.1814 (M^+), $C_{21}H_{27}NO_6$ requires 389.1838.

(1*R*,2*R*,3*R*)-2-[(*R*)-1,2-Diacetoxyethyl]-3-diethylcarbamoyl-cyclopropane-carboxylic acid, phenyl ester 14. To a solution of $(CF_3CO)_2O$ (1.2 mL, 8.5 mmol) in methylene chloride (1 mL) was added 95% H_2O_2 (0.35 mL, 8.4 mmol) at 0°C. After the mixture was stirred for 10 min, a suspension solution of **13** (440 mg, 1.13 mmol) and Na_2HPO_4 (600 mg, 4.2 mmol) in CH_2Cl_2 (5 mL) was added. The resultant solution was stirred at room temperature overnight and then refluxed for 0.5 h. The cooled solution was diluted with CH_2Cl_2 (50 mL), washed by saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. After removal of solvent, the residual oil was chromatographed eluting with ethyl acetate/petroleum ether (1/2) to afford **14** (380 mg, 83%) as a pale yellow oil. $[\alpha]_D^{14}=-32.8$ (*c* 2.8, $CHCl_3$); IR (neat) 1746, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J*=8.0 Hz, 2H), 7.25 (t, *J*=8.0 Hz, 1H), 7.11 (d, *J*=8.1 Hz, 2H), 4.93 (dt, *J*=10.0, 4.4 Hz, 1H), 4.41 (dd, *J*=11.9, 4.2 Hz, 1H), 4.28 (dd, *J*=11.9, 4.5 Hz, 1H), 3.65–3.51 (m, 2H), 3.30 (dt, *J*=14.6, 7.2 Hz, 1H), 3.22 (dt, *J*=14.4, 7.1 Hz, 1H), 2.81 (t, *J*=5.1 Hz, 1H), 2.53 (dd, *J*=9.9, 4.6 Hz, 1H), 2.20 (ddd, *J*=9.9, 9.7, 5.6 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 1.24 (t, *J*=7.2 Hz, 3H), 1.09 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 406 (M^++H^+); HRMS found *m*/*z* 406.1839 (M^++H^+), $C_{21}H_{28}NO_7$ requires 406.1866.

(1*R*,2*R*,3*R*)-2-[(*R*)-1,2-Dihydroxyethyl]-3-diethylcarbamoyl-cyclopropane-carboxylic acid, methyl ester 15. To a solution of **14** (440 mg, 1.1 mmol) in anhydrous MeOH (5 mL) was added K_2CO_3 (340 mg, 2.5 mmol). The resultant mixture was stirred at room temperature overnight before iodomethane (3 mL) was added. The stirring was continued for 12 h and then the solvent was removed by rotavapor. The residue was partitioned between methylene chloride (50 mL) and water (10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography of the residual oil afforded **15** (210 mg,

75%) as a pale yellow oil. $[\alpha]_D^{17}=+53.3$ (*c* 1.2, $CHCl_3$); IR (neat) 1731, 1621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (m, 1H), 3.70 (s, 3H), 3.60–3.30 (m, 6H), 2.36 (dd, *J*=9.1, 5.2 Hz, 1H), 2.29 (t, *J*=5.3 Hz, 1H), 1.93 (m, 1H) 1.25 (t, *J*=7.2 Hz, 3H), 1.11 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 260 ($M^+ + H^+$); HRMS found *m*/*z* 259.1414 (M^+), $C_{12}H_{21}NO_5$ requires 259.1420.

(1*R*,2*R*,3*R*)-2-[(*R*)-1-*tert*-Butyldimethylsiloxy-2-hydroxyethyl]-3-diethyl-carbamoyl-cyclopropanecarboxylic acid, methyl ester 16. A solution of **15** (150 mg, 0.58 mmol), *tert*-butyldimethylsilyl chloride (104 mg, 0.69 mmol), DMAP (52 mg, 0.43 mmol), and triethylamine (0.25 mL, 1.8 mmol) in methylene chloride (2 mL) was stirred for 12 h. The solution was partitioned between methylene chloride (20 mL) and brine (20 mL). After the organic layer was concentrated, the residual oil was chromatographed (1/3 ethyl acetate/petroleum as eluent) to afford **16** (188 mg, 87%) as a pale yellow oil. $[\alpha]_D^{17}=-48.6$ (*c* 0.70, $CHCl_3$); IR (neat) 1733, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.64 (d, *J*=5.5 Hz, 2H), 3.62–3.29 (m, 5H), 2.38 (d, *J*=7.2 Hz, 2H), 1.95 (m, 1H), 1.24 (t, *J*=7.1 Hz, 3H), 1.12 (t, *J*=7.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); MS *m*/*z* 374 ($M^+ + H^+$); HRMS found *m*/*z* 373.2280 (M^+), $C_{18}H_{35}NO_5Si$ requires 373.2284.

(1*R*,2*R*,3*R*)-2-[(*S*)-1-*tert*-Butyldimethylsiloxy-2-azido-ethyl]-3-diethyl-carbamoyl-cyclopropanecarboxylic acid, methyl ester 17. To a solution of **16** (180 mg, 0.48 mmol) in anhydrous THF (8 mL) was added triphenylphosphine (633 mg, 2.4 mmol), diethyl azodicarboxylate (0.93 mL, 2.4 mmol), and diphenylphosphoryl azide (0.50 mL, 2.4 mmol) at −20°C, respectively. After the stirring was continued for 6 h at the same temperature, the reaction solution was warmed to room temperature and then stirred overnight. The solvent was removed via rotavapor and the residual oil was directly loaded on a silica gel column and then eluted with 1/5 ethyl acetate/petroleum ether to provide **17** (144 mg, 75%) of as a yellow oil. $[\alpha]_D^{24}=-13.9$ (*c* 1.0, $CHCl_3$); IR (neat) 2114, 2004, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.66 (m, 1H), 3.60–3.20 (m, 6H), 2.58 (t, *J*=5.1 Hz, 1H), 2.40 (dd, *J*=9.6, 4.8 Hz, 1H), 1.97 (m, 1H), 1.28 (t, *J*=7.1 Hz, 3H), 1.10 (t, *J*=7.1 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); MS *m*/*z* 399 ($M^+ + H^+$); HRMS found *m*/*z* 398.2344 (M^+), $C_{18}H_{34}N_4O_4Si$ requires 398.2349.

(1*R*,2*R*,3*R*)-2-[(*S*)-1-*tert*-Butyldimethylsiloxy-2-(*tert*-butoxycarbonyl)amino-ethyl]-3-diethyl-carbamoyl-cyclopropanecarboxylic acid, methyl ester 18. A suspension of 10% Pd/C (20 mg) in ethyl acetate (2 mL) was vigorously stirred under hydrogen atmosphere until the uptake of hydrogen ceased. To this was added a mixture of azide **17** (130 mg, 0.30 mmol) and di-*tert*-butyl dicarbonate (260 mg, 1.16 mmol) in ethyl acetate (1 mL). The resulting solution was stirred under H_2 (1 atm) at rt until disappearance of the azide as monitored by TLC. The solution was filtered and the filtrate was concentrated in vacuo to give the crude product. The crude product was purified by column chromatography on silica gel (1/4 ethyl acetate/petroleum ether as eluent) to give **18** (120 mg, 84%) as a pale yellow oil. $[\alpha]_D^{22}=-20.8$ (*c* 0.75, $CHCl_3$); IR (neat) 3378, 1714, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (br s, 1H), 3.75 (m, 1H), 3.69 (s, 3H), 3.63–3.15 (m, 6H), 2.71 (m, 1H), 2.34 (dd, *J*=9.6, 4.9 Hz, 1H), 2.03 (m, 1H), 1.48 (s, 9H), 1.26 (t, *J*=7.1 Hz, 3H), 1.08 (t, *J*=7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); MS *m*/*z* 473 ($M^+ + H^+$); HRMS found *m*/*z* 472.2942 (M^+), $C_{23}H_{44}N_2O_6Si$ requires 472.2967.

(1*R*,2*R*,3*R*)-2-[(*S*)-*N*-*tert*-Butoxycarbonylglycine]-3-diethyl-carbamoyl-cyclopropanecarboxylic acid, methyl ester 19. To a solution of **18** (100 mg, 0.21 mmol) in THF (5 mL) was added tetrabutylammonium fluoride hydrate (266 mg, 1 mmol) and HOAc (0.1 mL, 1.7 mmol) at 0°C. The resulting solution was stirred at rt for 4 h and poured into saturated $NaHCO_3$ solution (10 mL). The mixture was extracted with methylene chloride three times and the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and then concentrated. The crude product was purified by column chromatography on silica gel (1/3 ethyl acetate/petroleum ether as eluent as eluent) to provide alcohol (75 mg), which was dissolved in acetone (7 mL). This resultant solution was cooled with ice-water and Jones reagent (80 μL) was added. After the reaction mixture was stirred at the same temperature for 3 h it was allowed to warm to rt. The reaction was quenched with 2-propanol and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give an oily residue. This oil was purified by column chromatography (1/3 ethyl acetate/petroleum as eluent) to afford **19** (50 mg, 71%). $[\alpha]_D^{20}=+23.3$ (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (br d, *J*=6.9 Hz, 1H), 4.42 (dd, *J*=11.0, 7.1 Hz, 1H), 3.74 (s, 3H), 3.51–3.34 (m, 4H), 2.59 (t, *J*=5.5 Hz, 1H), 2.42 (dd, *J*=8.5, 6.2 Hz, 1H), 1.83 (m, 1H), 1.43 (s, 9H), 1.23 (t, *J*=7.2 Hz, 3H), 1.16 (t, *J*=7.1 Hz, 3H); MS *m*/*z* 372 (M^+); HRMS found *m*/*z* 372.1901 (M^+), $C_{17}H_{28}N_2O_7$ requires 372.1897.

L-DCG-IV. A mixture of **19** (50 mg, 0.14 mmol) and 6N HCl (2 mL) was heated in a sealed tube at 80°C for 24 h. The cooled solution was concentrated to dryness and the residue was purified with DOWEX-50 W (elution with 1% NH_3) to give L-DCG-IV (20 mg, 65%) of as an ammonium salt. $[\alpha]_D^{20}=-19.6$ (*c* 0.56, H_2O) [lit.[3] $[\alpha]_D^{20}=-20.2$ (*c* 0.44, H_2O)]; ^1H NMR (300 MHz, D_2O) δ 3.94 (d, *J*=9.9 Hz, 1H), 2.17 (dd, *J*=9.5, 4.9 Hz, 1H), 2.05 (t, *J*=5.6 Hz, 1H), 1.86 (ddd, *J*=9.9, 9.5, 5.3 Hz, 1H).

Acknowledgements

We thank the Chinese Academy of Sciences, National Natural Science Foundation of China (grant 29725205), and Qiu Shi Science & Technologies Foundation for their financial support.

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