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# Stereochemically Controlled Cyclopropanation of (*S*)-Glyceraldehyde Acetonide-Derived Olefins. Synthesis of (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-Dicarboxycyclopropyl)glycine

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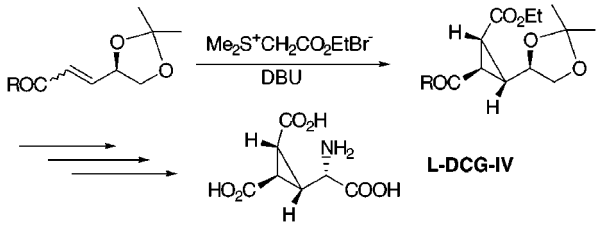
## ABSTRACT




**The reactions of ethyl (dimethylsulfuranylidene)acetate or other related sulfonium ylides with olefins 1 derived from (*S*)-glyceraldehyde acetonide provide cyclopropanation products in good to excellent diastereoselectivity. On the basis of 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 receptors, is developed.**

The 1,2,3-trisubstituted cyclopropane subunit can be found in many natural and synthetic compounds with important biological activities.[1] Although the enantioselective construction of cyclopropanes has attracted significant attention in the past two decades,[2] few examples have been reported for synthesizing enantiopure 1,2,3-trisubstituted cyclopropanes.[1,2] In connection with our efforts on the development of selective modulators for metabotropic glutamate receptors (mGluRs),[3] we recently reported that the olefin **1a** reacted with dimethylsulfoxonium methylide at −30 °C to provide the cyclopropanation product **2** in 93% diastereoselectivity[3a] (Scheme 1). This result stimulated us to try the reaction of the olefins **1a**−**g** with the sulfoxonium ylide possessing a suitable electron-withdrawing group to provide 1,2,3-trisubstituted cyclopropanes diastereoselectively. The studies thus undertaken are reported herein.

Initially, we tried the reaction of **1b** with ethyl (dimethylsulfuranylidene)acetate (EDSA) generated in situ by treatment of ethyl dimethylsulfonium acetate bromide with DBU.[4]

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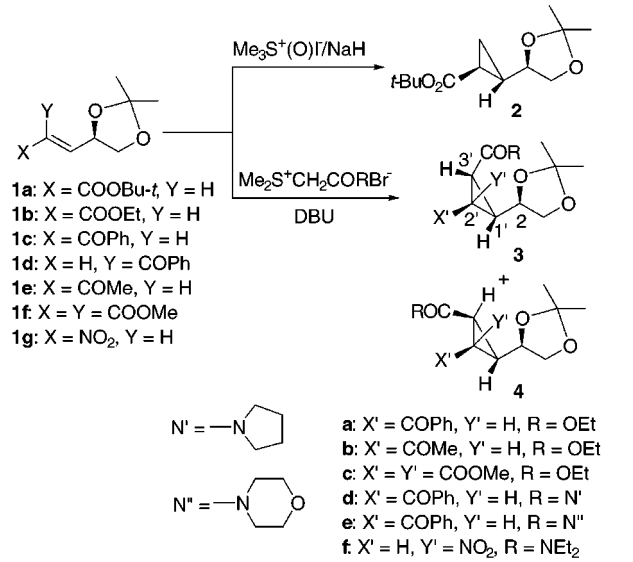
**Scheme 1**




It was found that this reaction did not occur under various conditions such as different reaction temperatures and solvents. However, when enone **1c** was used to replace **1b**, the reaction worked well to give cyclopropanation products in high yields. After ether-extract workup, two fractions were separated by column chromatography. The major fraction was a mixture of two isomers in a ratio of 10:1 determined by $^1$H NMR. These products could be recrystallized to deliver a pure isomer. Its structure was assigned to be (2*R*,1′*R*,2′*R*′3′*R*)-**3a** by a single-crystal X-ray analysis. 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*)-**4a** by its NOESY spectra. To check whether any products with (1′*S*,2′*S*)-configuration formed during the reaction, we tried to identify the minor isomer in major fraction. After the major fraction was treated with TsOH in methanol, two lactones were isolated and the structure of minor product **6a** was assigned as (2*R*,3*S*,4*S*,5*S*) by the NOESY experiment indicated in Figure 1, which implied that the minor isomer in

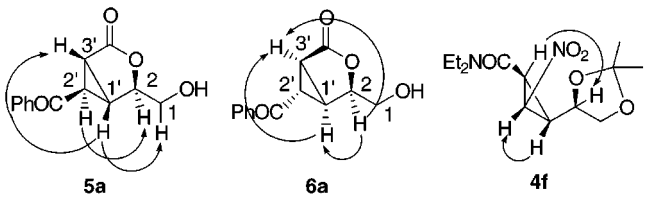



**Figure 1.** NOE correlations of lactones **5a** and **6a** and compound **4f**.

the major fraction should have the (2*R*,1′*S*,2′*S*,3′*S*)-configuration. This result showed that when the cyclopropane ring formed, the diastereoselectivity for 1′- and 2′-chiral centers was about 10:1.

Encouraged by above results, we checked the reaction of other olefins and the results are summarized in Table 1. From *cis*-olefin **1d** the reaction still provided **3a** as the major

**Table 1.** Cyclopropanation Reaction of the Olefins **1** with EDSA[a]

| entry | olefin | temp (°C) | time (h) | yield[b] (%) |
|---|---|---|---|---|
| 1 | **1b** | 20 | 10 | |
| 2 | **1c** | −20 | 4 | **3a** (74)[c] **4a**(10) |
| 3 | **1d** | −20 | 4 | **3a** (95)[c] **4a**(4) |
| 4 | **1d** | −40 | 6 | **3a** (96)[c] **4a**(1) |
| 5 | **1d** | −78 | 10 | **3a** (95)[c] **4a**(0.5) |
| 6 | **1e** | 0 | 3 | **3b** (45) **4b** (18) |
| 7 | **1f** | 0 | 3 | **3c** (41) **4c** (37) |
| 8 | **1c** | 0 | 10 | **3d** (34) **4d** (25) |
| 9 | **1c** | −20 | 10 | **3e** (53) **4e** (37) |
| 10[d] | **1 g** | −40 | 3 | **4f** (62) |

[a] Reaction condition: olefin **1** (1 mmol), sulfonium salt (1 mmol), DBU (1 mmol), toluene (1 mL). [b] Isolated yield. [c] Containing 10% (2*R*,1′*S*,2′*S*,3′*S*)-isomer. [d] Reaction was carried out in methylene chloride.

product and the selectivity was even better than that of *trans*-olefin **1c** (compare entries 2 and 3). Lowering the reaction temperature could inhibit the formation of **4a** thereby enhancing the selectivity of this reaction (entries 3, 4, and 5). The methyl ketone **1e** did not give as satisfactory a result as that of the phenyl ketone **1c** (entry 6). The diester **1f**, in contrast with the monoester **1a**, could react with EDSA to provide the corresponding cyclopropanation products (entry 7). In this case the diastereoselectivity in the formation of 1′- and 2′-chiral centers was better than that of the enone **1c** because only two isomers, **3c** and **4c**, were observed by $^1$H NMR. Changing the sulfonium ylides also enhanced the diastereoselectivity in the formation of 1′- and 2′-chiral centers. For example, when the enone **1d** reacted with the pyrrolidine or morpholine-derived ylides, two pure diastereomers **3** and **4** (determined by $^1$H NMR) were isolated (entries 8 and 9). Interestingly, nitroalkene **1g** also worked for this reaction and gave the corresponding cyclopropane products **4f** in 62% yield, together with a small amount of unidentified isomers (entry 10). In this reaction the major product was **4f** in which the nitro group was *cis* to the acetonide group and its structure was confirmed by its NOESY spectra (Figure 1). The purity of **4f** should greater than 97% because no other isomer was found by $^1$H NMR spectra. It was noted that **4f** should be a useful intermediate for synthesizing cyclopropyl analogues of cyclobut-G, a broad spectrum antiviral agent.[1j]

On the basis of this cyclopropanation reaction, we developed a new synthetic route for (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (L-DCG-IV), an isotype-selective agonist of metabotropic glutamate receptor.[3j,5] As

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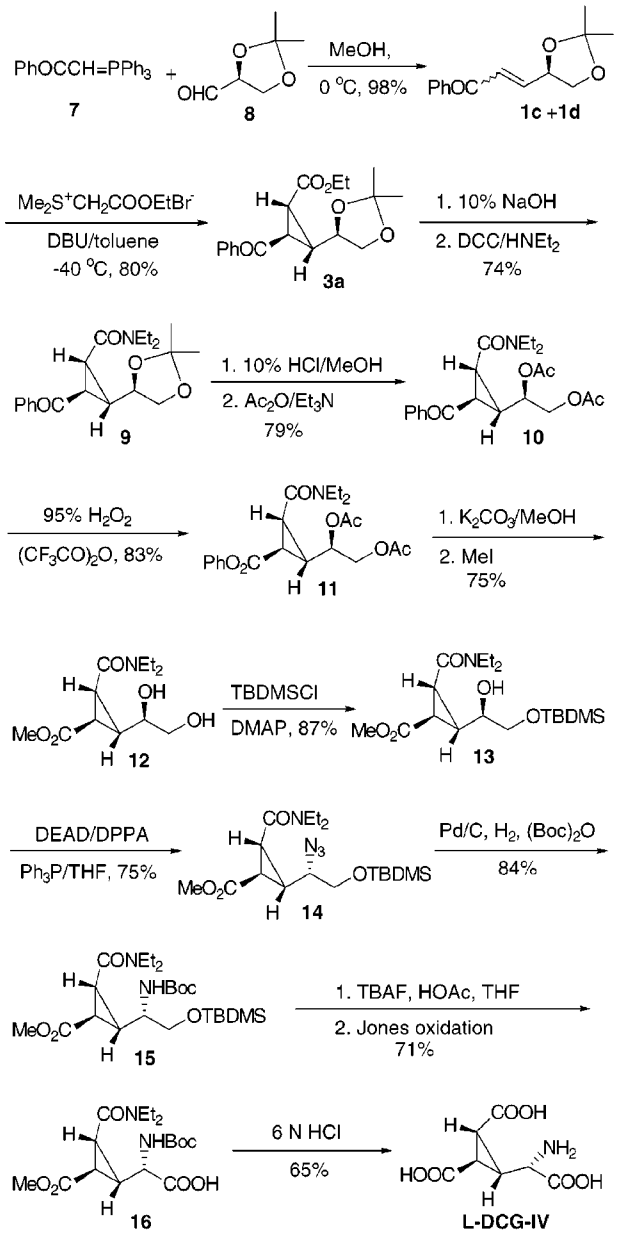
**Scheme 2**




outlined in Scheme 2, after the Wittig reaction products **1c** and **1d** were obtained in a ratio of 1:1, the mixture was directly used to react with EDSA at −40 °C to produce **3a** in about 80% yield after simple recrystallization. To avoid the lactonization in a later stage, the ester group of **3a** had to be converted into an amide group. Thus, hydrolysis of **3a** followed by coupling with diethylamine provided amide **9**. Now it was considered to transform the ketone moiety into the corresponding ester by the Baeyer−Villiger oxidation.[6] Many conditions were checked to directly oxidize **9**, and it was found that these reactions were complicated partly because its acetonide group was unstable under the acidic conditions. Thus, the protecting group for diol had to be changed. Accordingly, the acetonide group of **9** was removed under the action of hydrochloride/methanol and the resultant diol was reprotected with the acetyl group to yield the diacetate **10**. Treatment of **10** with trifluoroperacetic acid[7] that was in situ prepared by mixing 95% hydrogen peroxide and trifuoroacetic anhydride afforded the oxidation product **11** in 83% yield. Next, the ester **11** was treated with potassium carbonate in methanol to remove two acetyl protecting groups and transform the phenyl ester into the corresponding potassium salt. The generated salt was then reacted with iodomethane to provide diol **12**. After the primary alcohol of **12** was protected with silyl ether, the generated monoalcohol **13** was subjected to Mitsunobu reaction[8] to afford azide **14**. Finally, the azide **14** was converted into the corresponding amine by the hydrogenation catalyzed by Pd/C, which was trapped in situ with di-*tert*-butyl dicarbonate to provide **15** in 84% yield. After the deprotection of **15** with TBAF/HOAc, the resultant alcohol was oxidized with the Jones reagent to afford the acid **16**. Heating a mixture of **16** in 6 N HCl at 100 °C for 24 h removed all the protecting groups to give the crude L-DCG-IV as a hydrochloride salt, which was purified by ion-exchange column (Dowex-50WX4) to furnish L-DCG-IV as its ammonium salt. Its spectral data were the same as those reported.[1i]

In conclusion, we have developed a convenient method for synthesizing chiral 1,2,3-trisubstituted cyclopropanes. Its efficiency was demonstrated by the total synthesis of L-DCG-IV using this reaction. It is obvious that the present method would be useful for synthesizing other related compounds.[1]

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**Supporting Information Available:** Experimental details for the synthesis and product characterizations and X-ray structure of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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