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# An Empirical Model for Stereochemical Control in the Cyclization of Cyclopropanetricarboxylic Acid Esters

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## Abstract

Here, we report an empirical model for diastereoselective cyclopropanation of fumarate/maleate diesters with chloroacetate, sulfonium ylide, or ammonium ylide. With symmetrical fumarate/maleate diesters, cyclopropanation was found to proceed with a high level of diastereoselectivity in favor of the chiral isomer. In contrast, production of the *meso* isomer was observed in 38–48% diastereoselectivity when unsymmetrical fumarate/maleate was employed. An improved synthesis of (*N*-desmethy)dysibetaine CPa in both racemic and enantiomerically pure forms was furthermore achieved. Configurational analysis by experimental and calculated $^{13}$C NMR data is also reported.

**Keywords:** Cyclopropanation | Diastereoselectivity | Dysibetaine CPa

## Introduction

Cyclopropanes are an important class of carbocycles. These are 1) often found in natural products,[1] 2) used for conformational restriction in medicinal chemistry,[2] and 3) also used as an intermediate that shows unique reactivity in multi-step synthesis.[3] Many methodologies have been, therefore, developed for selective construction of cyclopropanes;[4] halomethyl-metal-mediated reactions including Simmons–Smith reaction,[5] decomposition of diazoalkane,[6] and Michael reaction followed by ring-closure.[7] A number of asymmetric syntheses of cyclopropanes have been also reported.[8]

During the course of our synthetic study of marine natural product dysibetaine CPa/CPb (Figure 1),[9] we needed to stereoselectively construct 1,2,3-trisubstituted cyclopropanes.[10] To our surprise, however, it was soon realized that stereochemical control had not been well investigated in cyclopropanations between fumarate/maleate diesters, and some Michael donors such as chloroacetate esters,[11] sulfonium ylides,[12] and ammonium ylides.[13] In this work, we found that the stereochemistry can be controlled by the combination of different ester groups, and a model is proposed, i.e., *cis*,*trans*,*trans*-chiral cyclopropane can be conveniently and selectively constructed using symmetrical fumarate diester and chloroacetate ester through 1) Michael reaction followed by 2) spontaneous cyclization without conformational change of the intermediary Michael adduct. Here, the methodology was applied to an improved, fewer-step synthesis of *rac*-(*N*-desmethyl)dysibetaine CPa.[10b] Furthermore, enantioselective synthesis of (*R*,*R*)- and (*S*,*S*)-(*N*-desmethyl)dysibetaine CPa was attempted using quinidine derivative as an organocatalyst. Results for configurational analysis of cyclopropanes, based on both experimental and calculated $^{13}$C NMR chemical shift values, are also reported herein.

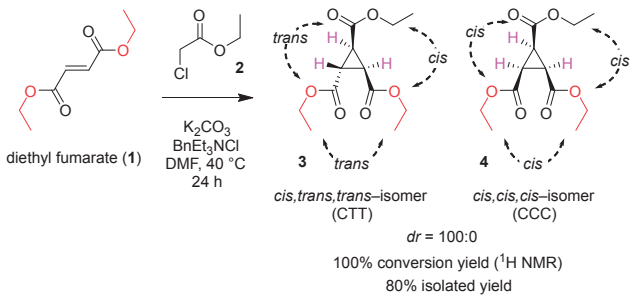

**Figure 1.** Cyclopropane natural products from Micronesian marine sponge.[9]

**Cyclopropanation of Diethyl Fumarate (1) with Ethyl Chloroacetate (2).** As has been already reported by us[10d] and another group,[11] cyclopropanation of diethyl fumarate (**1**) with ethyl chloroacetate (**2**) cleanly proceeds in 80% yield to give *cis*,*trans*,*trans*-cyclopropane (CTT) triethyl ester **3** predom-

inantly (Scheme 1). Thermodynamically, the CTT isomer **3** is obviously more stable than the *cis*,*cis*,*cis*-isomer (CCC) **4**, which indeed was not detected in this reaction.[14] In all other experiments in this paper, we did not observe such CCC isomers (see below). In this study, reactivity and stereoselectivity in the cyclopropanation of a variety of fumarate/maleate esters with chloroacetate, sulfonium ylide, or ammonium ylide were examined, as follows.

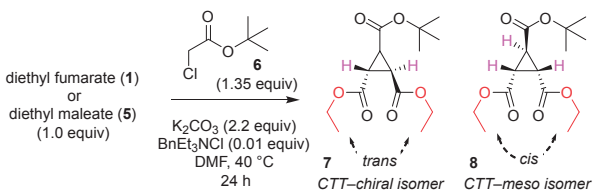
## Results

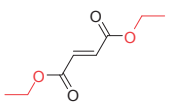
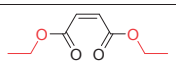
**Cyclopropanation of Diethyl Fumarate (1)/Diethyl Maleate (5) with *tert*-Butyl Chloroacetate (6).** According to the standard procedures employed in Scheme 1,[10d,11] cyclopropanation of diethyl fumarate (**1**, 1.0 equiv) with *tert*-butyl chloroacetate (**6**, 1.35 equiv) was first conducted in the presence of $K_2CO_3$ (2.2 equiv) and $BnEt_3NCl$ (0.01 equiv) in DMF at 40 °C (Table 1, run 1). After 24 h, TLC and $^1$H NMR analyses revealed that the fumarate **1** was completely consumed, and cyclopropane **7** was isolated in 85% yield after chromatographic purification. The planar structure as well as the stereochemistry of **7** was determined by spectroscopic means including $^1$H NMR analysis to be a cyclopropane with CTT-chiral configuration. No CTT-*meso* isomer **8** was detected in the reaction mixture.




**Scheme 1.** Formation of cyclopropane triethyl ester generally proceeds with exclusive CTT diastereoselectivity.[10d,11]

**Table 1.** Cyclopropanations of both fumarate and maleate with chloroacetate proceed with high CTT-chiral diastereoselectivity.




| Run | Symmetrical diester | Results [a] | Diastereoselectivity (*chiral/meso*) |
|---|---|---|---|
| 1 |  diethyl fumarate (**1**) | 100% conversion 85% isolation | **7/8** = >95:5 |
| 2 |  diethyl maleate (**5**) | 15% conversion 10% isolation | **7/8** = >95:5 |

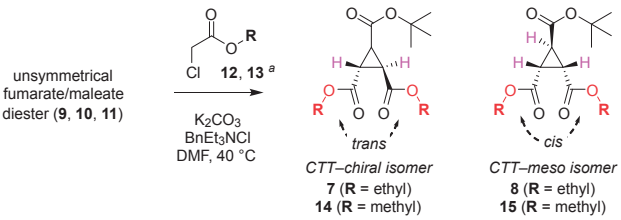
[a] Conversion yield was determined from $^1$H NMR spectrum.

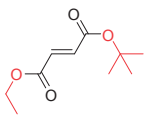
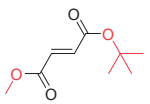
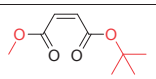
When diethyl maleate (**5**) was employed (run 2), again only CTT-chiral cyclopropane **7** was obtained, but the reaction was found to be sluggish (10% yield after 24 h).

**Cyclopropanation of "Unsymmetrical" Fumarate/Maleate Diesters (9, 10, 11) with Chloroacetates (12, 13).** Table 2 shows the results for cyclopropanation of "unsymmetrical" fumarate/maleate diesters (**9**, **10**, **11**) with ethyl chloroacetate (**12**) or methyl chloroacetate (**13**). It was found that *tert*-butyl ethyl fumarate (**9**) undergoes cyclopropanation with **12** to give a mixture of nearly comparable amounts of the CTT-chiral and CTT-*meso* cyclopropanes **7** and **8** (**7**/**8** = 52:48, run 1) in lower total yield than that in Table 1 (run 1). Generation of CTT-*meso* isomer was observed for the first time here in a series of these reactions. When sterically less demanding *tert*-butyl methyl fumarate (**10**) was employed in combination with methyl chloroacetate (**13**) (run 2), the fraction of the CTT-*meso* isomer decreased (**14**/**15** = 62:38). As had been also observed in Table 1 (run 2), only a trace amount (4.7%) of cyclopropane products was obtained in run 3, wherein the maleate **11**, isomeric to the fumarate **10** in run 2, was employed. Quite interestingly, however, the diastereoselectivity (**14**/**15** = 61:39) was found to be comparable to that in run 2. Similarly, poor yield was observed in the synthesis of cyclopropanes **7**/**8**, by reaction of *tert*-butyl ethyl maleate with ethyl chloroacetate (**12**) (data not shown in Table 2).

**Cyclopropanation with Sulfonium Ylides (16–18).** Sulfonium ylides are promising cyclopropanation reagents.[12] Gen-

**Table 2.** Cyclopropanations of "unsymmetrical" fumarate/maleate with chloroacetate provide CTT-*meso* products with 38–48% diastereoselectivity as minor products.

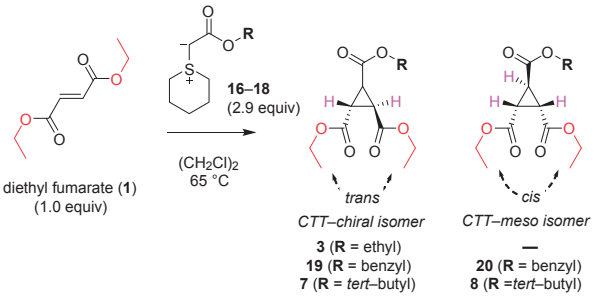



| Run | Unsymmetrical diester | **R** for chloroacetate | Results [b] | Diastereoselectivity (*chiral/meso*) |
|---|---|---|---|---|
| 1 |  *tert*–butyl ethyl fumarate (**9**) | ethyl (**12**) | 50% conversion 44% isolation | **7/8** = 52:48 |
| 2 |  *tert*–butyl methyl fumarate (**10**) | methyl (**13**) | 74% conversion 50% isolation | **14/15** = 62:38 |
| 3 |  *tert*–butyl methyl maleate (**11**) | methyl (**13**) | 4% conversion 4.7% isolation | **14/15** = 61:39 |

[a] For equivalency, see Table 1.
[b] Conversion yield was determined from $^1$H NMR spectrum.

**Table 3.** Cyclopropanations of fumarate with various sulfonium ylides proceed with acceptable CTT-chiral diastereoselectivity.




| Run | **R** for ylide | Results [a] | Diastereoselectivity (*chiral/meso*) |
|---|---|---|---|
| 1[10d,13] | ethyl (**16**) | 100% conversion<br>99% isolation | —[b] |
| 2 | benzyl (**17**) | 50% conversion<br>41% isolation | **19**/**20** = 92:8 |
| 3 | *tert*–butyl (**18**) | 100% conversion<br>91% isolation | **7**/**8** = 92:8 |

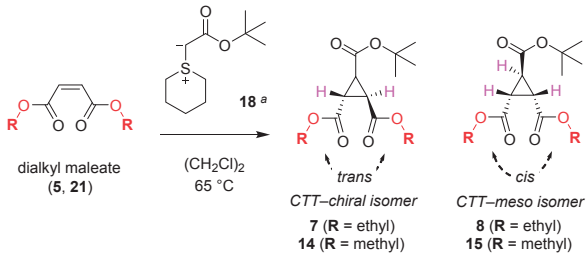
[a] Conversion yield was determined from $^1$H NMR spectrum.
[b] The diastereoselectivity for CTT/CCC isomers (**3**/**4**) were 100:0.
No chiral center is present in these molecules bearing triethyl ester.

erally, the ylide is prepared prior to use, and cyclopropanation is conducted at elevated temperature in $(CH_2Cl)_2$ without additives. Structurally complex cyclopropane with sensitive functional groups can be synthesized with sulfonium ylide-mediated cyclopropanation, owing to the high chemoselectivity. We[10d] and another group[12] have previously reported that cyclopropanation of diethyl fumarate (**1**) with ethyl sulfanylideneacetate (**16**) gives CTT cyclopropane **3** quantitatively (Table 3, run 1). The complete CTT selectivity, shown above in the chloroacetate-mediated cyclopropanations (Scheme 1, and Tables 1, 2), was again observed here in the combinations using two other sulfonium ylides **17**[10e] (run 2) and **18**[10b] (run 3). Interestingly, in both cases, the CTT-chiral isomers, **19** (run 2) and **7** (run 3), were preferably generated over the *meso* isomers in reasonable (41% yield, 92% purity) and high yields (91%, 92% purity), respectively.

Even from maleate diesters, surprisingly, the CTT-chiral isomer was found to be selectively obtained, when sulfonium ylide was employed (Table 4). Thus, *tert*-butyl sulfanylideneacetate (**18**)[10b] reacts with diethyl maleate (**5**, run 1) and dimethyl maleate (**21**, run 2)[10e] to selectively give rise to CTT-chiral cyclopropanes **7** (94% yield, 92% purity) and **14** (99% yield, 89% purity), respectively. The higher isolation yield in run 1 (94%) than that in chloroacetate-mediated reaction (Table 1, run 2, 10%) would be due to the higher reactivity of the sulfonium ylide.[15]

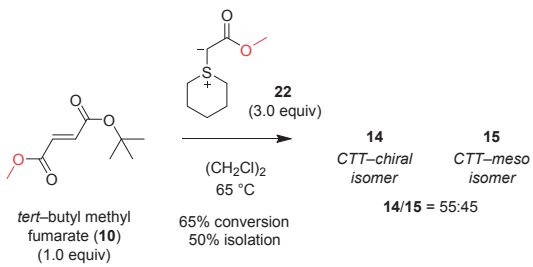
The cyclopropanation outcome of unsymmetrical diester with sulfonium ylide was comparable to that observed in the chloroacetate-mediated reaction shown above. Namely, as shown in Scheme 2, cyclopropanation of **10** using methyl sulfanylideneacetate (**22**)[10e] gave CTT-chiral isomer **14** and CTT-*meso* isomer **15** in 50% isolated yield in a ratio of 55:45, which are comparable to those shown in Table 2 (run 2).

**Table 4.** Cyclopropanations of maleate with sulfonium ylide proceed with acceptable CTT-chiral diastereoselectivity in high yield.

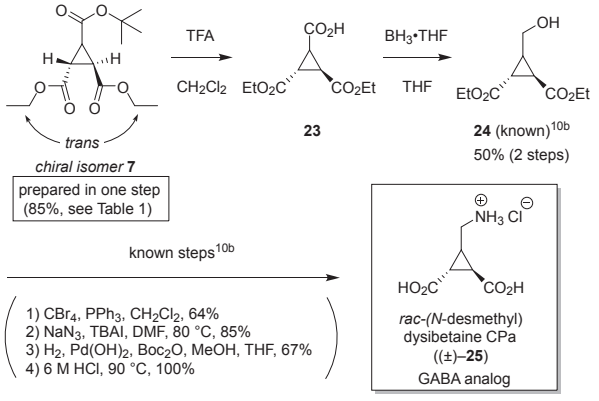



| Run | **R** for maleate | Results [b] | Diastereoselectivity (*chiral/meso*) |
|---|---|---|---|
| 1 | ethyl (**5**)<br>(diethyl maleate) | 100% conversion<br>94% isolation | **7**/**8** = 92:8 |
| 2[10e] | methyl (**21**)<br>(dimethyl maleate) | 100% conversion<br>99% isolation | **14**/**15** = 89:11 |

[a] For equivalency, see Table 3.
[b] Conversion yield was determined from $^1$H NMR spectrum.

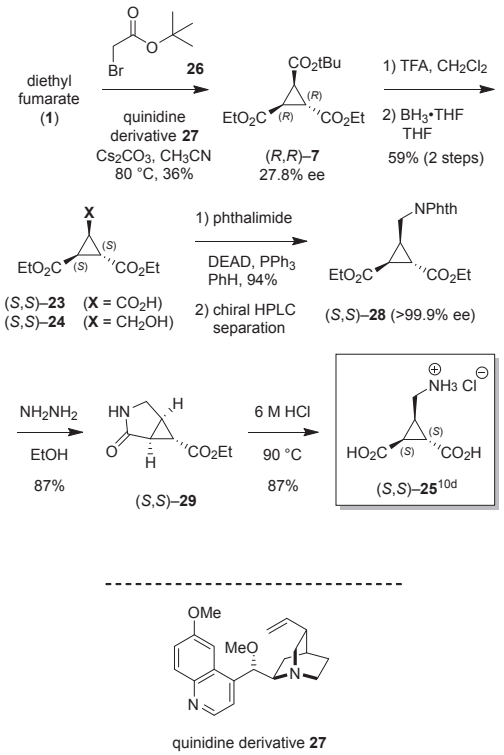



**Scheme 2.** Cyclopropanation of unsymmetrical fumarate with sulfonium ylide provides CTT-*meso* product as a minor product (45% diastereoselectivity).




**Scheme 3.** Seven-step synthesis of *rac*-(*N*-desmethyl)-dysibetaine CPa ((±)-**25**).

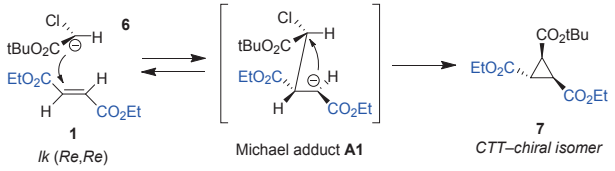
**Synthesis of *rac*-(*N*-Desmethyl)dysibetaine CPa ((±)-25) as an Application.** With the ester group-controlled cyclopropanation shown above, we decided to demonstrate natural product synthesis. Thus, synthesis of *N*-desmethyl analog **25** of dysibetaine CPa, a Micronesian sponge-derived natural product,[9] in racemic form was demonstrated in 5 steps fewer than our previous synthesis,[10b] from cyclopropane **7** (see Table 1, run 1) as follows (Scheme 3). Acidic hydrolysis of the *tert*-butyl ester of **7** by TFA, followed by chemoselective reduction




**Scheme 4.** Asymmetric synthesis of (*S*,*S*)-(*N*-desmethyl)-dysibetaine CPa hydrochloride ((*S*,*S*)-**25**). For the synthesis of natural (*R*,*R*)-congener ((*R*,*R*)-**25**), see the Experimental section.

of the generated carboxyl group ($BH_3$•THF) gave alcohol **24** in 50% yield over 2 steps. Owing to the selective cyclopropanation shown in Table 1, the three-step synthesis of alcohol **24** from diethyl fumarate (Scheme 3, 42.5% total yield) apparently improved the efficiency of our previous synthesis of (*N*-desmethyl)dysibetaine CPa ((±)-**25**),[10b] wherein a longer 8 step procedure (8.5% yield from maleic anhydride) had been required for the synthesis of alcohol **24**.

**Synthesis of Optically Pure, Both Enantiomers of (*N*-Desmethyl)dysibetaine CPa (25) by Chiral Ammonium Ylide.** We further attempted asymmetric synthesis of (*N*-desmethyl)dysibetaine CPa (**25**) by enantioselective cyclopropanation using quinidine derivative as an organocatalyst (Scheme 4). The organocatalytic reaction is mediated by chiral ammonium ylide,[16] which is empirically[16,17] expected to give cyclopropane with (*R*,*R*)-CTT-chiral configuration. Thus, diethyl fumarate (**1**) was first reacted with *tert*-butyl bromoacetate (**26**) in the presence of the quinidine derivative **27**[16] and $Cs_2CO_3$ in $CH_3CN$ at 80 °C to give cyclopropane (*R*,*R*)-**7** in 36% yield. Gratifyingly, no diastereomers other than CTT-chiral cyclopropane **7** were detected. Disappointingly, however, chiral HPLC analysis of **23**, obtained after removal of the *tert*-butyl ester, showed that the enantiomeric purity was only 27.8% ee in favor of the (*S*,*S*)-enantiomer ((*S*,*S*)-**23**) illustrated in Scheme 4. Note that (*R*,*R*)-**7** corresponds to (*S*,*S*)-**23**, that is generated after TFA treatment. All attempts to improve the efficiency were unsuccessful. For example, diethyl maleate (**5**) for the organocatalytic reaction provided (*R*,*R*)-**7** with higher enantiomeric purity (39.4% ee) but in lower yield (5%). The




**Scheme 5.** Our proposed mechanism for cyclopropanation of "symmetrical" fumarate with chloroacetate (for Table 1, run 1).

structure of the major cyclopropane (*R*,*R*)-**7** was confirmed after leading to the final product ((*S*,*S*)-**25**) with known spectroscopic properties,[10d] by the reactions illustrated in Scheme 4; the carboxylic acid (*S*,*S*)-**23**, derived from (*R*,*R*)-**7**, was reduced by $BH_3$•THF by following the procedure in the racemate synthesis shown in Scheme 3. To introduce nitrogen functionality, the alcohol (*S*,*S*)-**24** then underwent Mitsunobu reaction with phthalimide ($PPh_3$, DEAD, PhH, rt) in 94% yield. Attempts to recrystallize the phthalimide (*S*,*S*)-**28** as well as all other intermediates in order to improve the enantiomeric purity were unsuccessful, however, optical resolution of 27.8% ee of (*S*,*S*)-**28** by chiral HPLC was found to be practical to furnish (*S*,*S*)-**28** and enantiomeric (*R*,*R*)-**28** in enantiomerically pure form for each isomers (see the Supporting Information). The major and minor phthalimides (*S*,*S*)-**28** and (*R*,*R*)-**28**, were independently deprotected (hydrazine, EtOH; 6 M HCl) to provide (*S*,*S*)-(*N*-desmethyl)dysibetaine CPa ((*S*,*S*)-**25**)[10d] with unnatural configuration, and the (*R*,*R*)-congener ((*R*,*R*)-**25**, not shown in Scheme 4 but included in the Experimental section), respectively, in a stepwise manner via lactam (*S*,*S*)-**29**/(*R*,*R*)-**29**. Overall yields were 9.7% and 5.5% for (*S*,*S*)-**25** and (*R*,*R*)-**25**, respectively, for total 6 steps each.

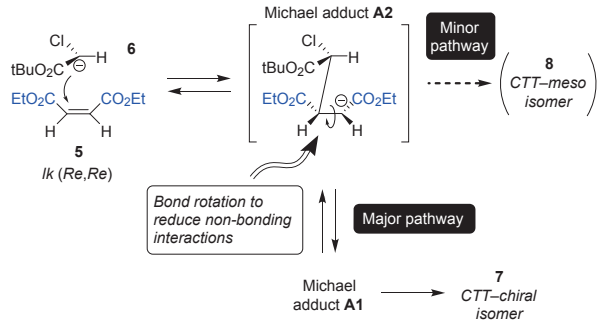
## Discussion

**Cyclopropanation Mechanisms.** Cyclopropanations using chloroacetate or sulfanylideneacetate are generally thought to proceed through Michael addition to the acceptor followed by intramolecular nucleophilic substitution ($S_N2$).[11,12,18] Based on the stereochemical outcomes observed in the present study, we deduced more detailed mechanism of these cyclopropanations, as follows. First, rapid rotation of the C–C bond in the Michael product is obviously involved prior to cyclopropane formation (e.g. run 1 vs run 2 in Table 1, see below for discussion). Second, the diastereoselectivity in the cyclopropanation seems to be, therefore, controlled by intramolecular steric repulsion between substituents in the Michael adduct. Third, the leaving groups (Cl, sulfonium, ammonium) do not play a crucial role in the diastereoselectivity.

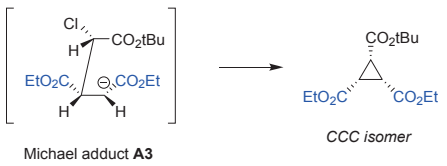
Our proposed mechanisms are shown in Schemes 5–8. The diastereoselective cyclopropanation of fumarate acceptor **1** (see Table 1, run 1) to give CTT-chiral isomer **7** can be explained by a rather simple mechanism drawn in Scheme 5. Here, the Michael adduct intermediate **A1** is generated through *Re*/*Re* face reaction (*lk* topicity) and directly cyclizes to form **7**, without large conformational change.

In contrast, as shown in Scheme 6, cyclopropanation of maleate **5** (see Table 1, run 2) seems to involve large conformational change by rotation of a C–C bond in the Michael adduct conformer **A2** generated through *Re*/*Re* face reaction

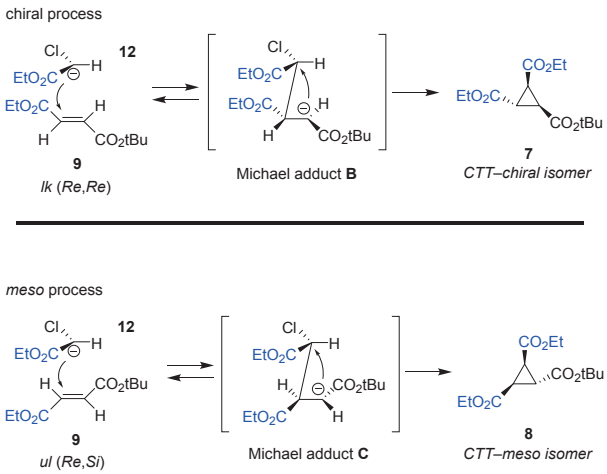

 




**Scheme 6.** Our proposed mechanism for cyclopropanation of "symmetrical" maleate with chloroacetate (for Table 1, run 2).




**Scheme 7.** The possible third Michael adduct **A3** leading to an imaginary CCC isomer.




**Scheme 8.** Our proposed mechanism for cyclopropanation of "unsymmetrical" fumarate with chloroacetate (for Table 2, run 1).

(*lk* topicity), in order to release non-bonding interactions to give rise to cyclopropane **7** predominantly via the conformer **A1**. The low yield (10%) would be due to severe interactions between sterically demanding coupling partners (the nucleophile and the (*Z*)–alkene) in the first intermolecular Michael reaction.[19]

It should be also noted here that, although we did not observe production of CCC cyclopropane in this reaction (Table 1, run 2), we cannot exclude presence of the diastereomeric Michael adduct intermediate **A3** (Scheme 7) as a precursor that bears three alkoxycarbonyl groups arranged on the same face (e.g. α face as shown in Scheme 7) in these thermodynamically equilibrated processes, since we previously observed formation of CCC cyclopropane in the cyclopropanation of cyclic imide acceptor, which obviously includes the intermediate corresponding to **A3**.[10b,14] In general, however, cyclization of **A3** is a disfavored process and is not observed, due to the steric repulsion between $CO_2$tBu and $CO_2$Et groups.

For cyclopropanation of "unsymmetrical" fumarate acceptor **9**, nonselective formation of CTT-chiral isomer **7** and CTT-*meso* isomer **8** was observed (**7**/**8** = 52:48, see Table 2, run 1). As shown in Scheme 8 (chiral/*meso* processes), this can be explained by nonstereoselective Michael addition (both *lk* and *ul* topicities) to form diastereomeric Michael adducts **B**/**C** followed by cyclization. In these processes, two Michael adducts **B**/**C** would contain the same level of unfavorable intramolecular steric interactions, between sterically demanding *tert*-butyl ester and other functional groups such as ethoxycarbonyl or chloro group.

The mechanistic discussion shown in Scheme 8 can be similarly applied to the case of methyl ester (see Table 2, run 2), from the fact that reactivity of sterically less demanding methyl ester-containing unsymmetrical fumarate **10** (50% yield) is higher than that in run 1 (44% yield). The rather higher ratio of the product **14** (**14**/**15** = 62:38) in run 2 would further indicate that the chiral process is essentially preferred over the *meso* process, which is in accord with the model in Scheme 5 for symmetrical fumarate **1**, that gives chiral cyclopropane **7** predominantly.

It is of interest to note that unsymmetrical maleate diester **11** (see Table 2, run 3) is remarkably unreactive, as compared to the fumarate diester **10** (run 2). Intermolecular steric interactions between sterically demanding maleate diester **11** and chloroacetate **13** would prevent the first Michael reaction, as judged from the fact that both components were recovered quantitatively after the reaction.

**Stereochemical Analysis by Experimental and Calculated $^{13}$C Chemical Shift Values.** Configuration of cyclopropanation products in this paper was determined on the basis of the structural symmetry as judged by the $^1$H and $^{13}$C NMR spectra.[10e] The assignments were finally confirmed by leading to dysibetaine analog (see Schemes 3 and 4).

Here, we furthermore attempted to determine the configuration of cyclopropanes in this paper by comparison of the $^{13}$C chemical shift value with those expected by density functional theory (DFT) calculation, to investigate the possibility for development of a rapid and reliable method for structural analysis of even more complex cyclopropanes. Our initial attempts, however, were not very encouraging, since $^{13}$C chemical shift values for no cyclopropanetricarboxylic acid esters (**3**, **4**, **7**, **8**, **14**, **15**, **19**, and **20** in Schemes 1–2 and Tables 1–4) in this paper were well reproduced with B3LYP/6-31G* model (Spartan '18 software; Wavefunction, Irvine, CA, U.S.A.).[20] It is now suspected that structurally flexible substituents on the cyclopropane core may interfere with precise estimation of the $^{13}$C NMR values.

We, therefore, next tried analysis of the derivatives, and found that γ-butyrolactam-fused cyclopropane **29** (see Scheme 4) showed good correlation between experimental and calculated $^{13}$C NMR values, as follows. Here, two diastereomeric candidates, (1*S*,3*S*)-**29** (correct structure) and (1*S*,3*R*)-**29a** (incorrect structure) (Figure 2), were subjected to the calculation; 1) conformational search, 2) structural optimizations with B3LYP-D3/6-31G* model, 3) calculations of the $^{13}$C NMR chemical shifts with B3LYP/6-31G* model, 4)

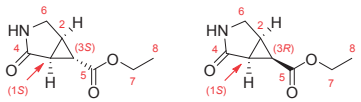



**Figure 2.** A set of diastereomers subjected to the NMR calculations for configurational analysis.

**Table 5.** Comparison of experimental and calculated $^{13}$C NMR chemical shift values of (1*S*,3*S*)-**29** (correct structure) and (1*S*,3*R*)-**29a** (incorrect structure).

| Position | Experimental[a] | Calculated[b] | |
|---|---|---|---|
| | | (1*S*,3*S*)-**29** (correct structure) | (1*S*,3*R*)-**29a** (incorrect structure) |
| 1 | 28.0 | 27.7 | 27.8 |
| 2 | 23.5 | 24.9 | 24.8 |
| 3 | 25.8 | 26.1 | 25.7 |
| 4 | 170.8 | 170.7 | 169.6 |
| 5 | 175.3 | 172.8 | 171.5 |
| 6 | 43.9 | 43.2 | 41.2 |
| 7 | 61.3 | 61.7 | 61.8 |
| 8 | 14.2 | 14.2 | 14.2 |
| RMS/ppm | | 1.05 | 1.78 |
| DP4+/% | | 99.5 | 0.5 |

[a]Experimental $^{13}$C NMR data were collected at 100 MHz in $CDCl_3$. [b]Calculated $^{13}$C NMR data were obtained employing B3LYP-D3/6-31G*//B3LYP/6-31G* model. For details, see text and the Supporting Information.

correction of the $^{13}$C NMR values on the Boltzmann weighting calculated with a single point energy calculation employing B3LYP-D3/6-31G*//B3LYP/6-31G* model to give theoretical shifts. It should be noted that parameters regarding solvents were not added in these calculations. The results are summarized in Table 5. The theoretical values obtained for C4 and C6 in (1*S*,3*S*)-**29** (correct structure) were found to agree with the experimental data, whereas (1*S*,3*R*)-**29a** (incorrect structure) shows obviously larger differences for these carbons. The correct (1*S*,3*S*)-**29** afforded smaller root mean square deviation (RMS), 1.05 ppm, than the incorrect isomer (1*S*,3*R*)-**29a** (1.78 ppm). The calculations also suggest that solvent effects are not critically operative in these models.

To give solid proof for the analysis based on the RMS values, we furthermore analyzed the $^{13}$C NMR values using DP4+ probability statistics.[21] The results, 99.5% and 0.5% probabilities for (1*S*,3*S*)-**29** and (1*S*,3*R*)-**29a**, respectively, were consistent with the fact that (1*S*,3*S*)-**29** bears correct relative configuration. These results were consistent with the observed vicinal coupling constants for (*S*,*S*)-**29** ($^3J_{H1,H2}$ = 6.1 Hz, $^3J_{H1,H3}$ = 2.7 Hz, $^3J_{H2,H3}$ = 2.7 Hz; see the Experimental section).

## Conclusion

In this paper, we reported reactivity and selectivity in the cyclopropanation of fumarate/maleate diesters in combination with chloroacetate, sulfonium ylide, or ammonium ylide. In all combinations, CTT-chiral cyclopropane was found to be predominantly provided, which allowed us to propose the reaction mechanisms for the diastereoselectivity. Based on the diastereoselective cyclopropanation, an improved racemate synthesis of (*N*-desmethyl)dysibetaine CPa ((±)-**25**), a γ-aminobutyric acid (GABA) analog of marine-derived natural cyclopropane, was achieved in fewer steps than our previous synthesis.[10b] Furthermore, asymmetric synthesis of both enantiomers of **25** has been accomplished employing cinchona alkaloid-mediated cyclopropanation followed by optical resolution by chiral HPLC. Beside the satisfactorily high diastereoselectivity, the observed poor enantioselectivity indicated the limitation of the current organocatalytic methodology.

Structurally symmetric *meso* compounds are increasingly recognized as useful intermediates for asymmetric synthesis.[22] For example, we have recently reported asymmetric synthesis of *N*-desmethyl analog of marine natural product dysibetaine CPb, employing enantioselective methanolysis of *meso*-succinic anhydride fused to cyclopropane.[10e] Regardless of the usefulness, however, *meso*-selective cyclopropanation has not yet been realized. From Scheme 2 and Table 2 in this work, some unreactive Michael acceptors under harsh reaction conditions are now expected to possibly produce *meso*-cyclopropane selectively. Experiments are currently in progress to discover conditions for *meso*-selective cyclopropanation, using acetate Michael donor with fumarate/maleate Michael acceptor.

Configuration of substituted cyclopropanes is often challenging to determine. We showed here that $^{13}$C NMR chemical shift values of γ-butyrolactam-fused cyclopropane, in combination with the DFT calculation values, are of use to determine the stereochemistry. The strategy would be applied to structurally more complex cyclopropanes whose configuration cannot be readily determined by other means.[23]

## Experimental

**General.** Details of the experimental techniques and the apparatus are summarized in our previous paper.[10b] ESI mass spectra were measured with an Exactive Focus Hybrid Quadrupole-Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, CA).

**1-(*tert*-Butyl) 2,3-Diethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (7) (Table 1, run 1):** To a stirred suspension of potassium carbonate (35.0 mg, 0.255 mmol) and benzyl triethylammonium chloride (0.264 mg, 0.00116 mmol) in DMF (0.066 mL) at 40 °C were added a solution of diethyl fumarate (**1**, 20.0 mg, 0.116 mmol) and *tert*-butyl chloroacetate (**6**, 23.6 mg, 0.157 mmol) in DMF (0.050 mL). After stirring at 40 °C for 24 h, $H_2O$ (1 mL) was added and the mixture extracted with EtOAc/hexane (1:1, 3 × 1 mL). Combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, EtOAc/hexane = 1:9) to give cyclopropane *tert*-butyl diethyl ester **7** (28.2 mg, 0.0985 mmol, 85%) as a colorless oil: IR (neat) 2981, 1727, 1639, 1370, 1308, 1150 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 7.0, 7.0 Hz, 2 H), 4.13 (dd, *J* = 7.0, 7.0 Hz, 2 H), 2.69 (t, *J* = 8.0 Hz, 1 H), 2.48 (dd, *J* = 10.0, 10.0 Hz, 1 H), 2.43 (dd, *J* = 10.0, 10.0 Hz, 1 H), 1.41 (s, 9 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.5, 166.6, 82.0,

61.5, 61.4, 29.5, 28.7, 28.0 (×3), 25.4, 14.1, 14.1; HRMS (ESI, positive) calcd for $C_{14}H_{22}O_6Na$ [$(M + Na)^+$] 309.1314, found 309.1311.

**1-(*tert*-Butyl) 2,3-Diethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (7) (Table 1, run 2):** With the same procedure as for the synthesis of **7** (Table 1, run 1), **7** (3.32 mg, 0.0116 mmol, 10%) was obtained as a colorless oil starting from diethyl maleate (**5**, 20.0 mg, 0.116 mmol), **6** (23.6 mg, 0.157 mmol), potassium carbonate (35.3 mg, 0.255 mmol), and benzyl triethylammonium chloride (0.264 mg, 0.00116 mmol). The chromatographic and spectroscopic data were identical to those of authentic sample shown above.

***tert*-Butyl Ethyl Fumarate (9):** To a stirred solution of fumaric acid monoethyl ester (3.00 g, 20.8 mmol) in *tert*-butanol (42 mL) were added $Boc_2O$ (6.80 g, 31.2 mmol) and DMAP (25.0 mg, 0.208 mmol). After stirring at 50 °C for 11 h, the mixture was concentrated under reduced pressure to remove *tert*-butanol. Then saturated aqueous $NH_4Cl$ (50 mL) was added and the mixture was extracted with $CHCl_3$ (50 mL). The extract was washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (50 g, EtOAc/hexane = 1:9) to give *tert*-butyl ester **9** (3.88 g, 19.4 mmol, 93%) as a yellow oil. The spectroscopic data were identical to those reported.[24]

**1-(*tert*-Butyl) 2,3-Diethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (7) and 1-(*tert*–Butyl) 2,3-Diethyl (1*r**,2*R**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (8) (Table 2, run 1):** With the same procedure as for the synthesis of **7** (Table 1, run 1), an inseparable mixture of **7** and **8** (**7**/**8** = 52:48, 2.44 g, 0.00852 mol, 44%) was obtained as a colorless oil starting from *tert*-butyl ethyl fumarate (**9**, 3.88 g, 0.0194 mol), **12** (4.75 g, 0.0388 mol), potassium carbonate (5.36 g, 0.0388 mol), and benzyl triethylammonium chloride (44.0 mg, 0.194 mmol). The chromatographic and spectroscopic data of CTT-chiral isomer **7** were identical to those of authentic sample shown above.

Selected data for the minor CTT-*meso* isomer **8**: $^1$H NMR (400 MHz, $CDCl_3$) δ 4.10–4.03 (m, 4 H), 2.58 (t, $J$ = 5.6 Hz, 1 H), 2.38 (d, $J$ = 5.6 Hz, 2 H), 1.37 (s, 9 H), 1.18 (t, $J$ = 6.8 Hz, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9, 167.6 (×2), 81.6, 61.2 (×2), 28.1 (×2), 27.7 (×3), 26.5, 14.0 (×2).

***tert*-Butyl Methyl Fumarate (10) and *tert*-Butyl Methyl Maleate (11):** A solution of maleic anhydride (30.0 g, 0.306 mol) in methanol (612 mL) was stirred at rt for 21 h. The mixture was then concentrated under reduced pressure to give maleic acid monomethyl ester (39.8 g, 0.306 mol) as a colorless oil, which was sufficiently pure and was used for the next reaction without purification.

To a stirred solution of maleic acid monomethyl ester (39.8 g, 0.306 mol) thus obtained above in *tert*-butanol (306 mL) were added $Boc_2O$ (86.4 g, 0.396 mol) and DMAP (374 mg, 3.06 mmol). After stirring at 50 °C for 74 h, the mixture was concentrated under reduced pressure to remove *tert*-butanol. Then saturated aqueous $NH_4Cl$ (100 mL) was added and the mixture was extracted with $Et_2O$ (2 × 150 mL). Combined extracts were washed with saturated aqueous $NaHCO_3$ (150 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (500 g, EtOAc/hexane = 1:9) to give fumarate **10** (20.0 g, 0.107 mol, 35%), maleate **11** (19.2 g, 0.103 mol, 34%), and the mixture (**10**/**11** = 46:54, 5.29 g, 0.0284 mol, 9.3%) as colorless oils. The spectroscopic data for fumarate **10**[25] and maleate **11**[26] were identical to those reported.

Maleate **11** can be quantitatively isomerized to fumarate **10** as follows. Thus, a mixture of maleate **11** (5.00 g, 0.0269 mol), NBS (5.27 g, 0.0296 mol), and AIBN (442 mg, 2.69 mmol) in $CCl_4$ (135 mL) was heated to reflux with stirring for 2 h. Insoluble materials were removed by filtration, and $H_2O$ (200 mL) was added to the filtrate. The organic layer was separated, and aqueous layer was extracted with $CCl_4$ (2 × 100 mL). The combined organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (50 g, EtOAc/hexane = 1:9) to give fumarate **10** (5.00 g, 0.0269 mol, 100%) as a colorless oil.

**1-(*tert*-Butyl) 2,3-Dimethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (14) and 1-(*tert*-Butyl) 2,3-Dimethyl (1*r**,2*R**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (15):** (Table 2, run 2) With the same procedure used for the synthesis of **7** (Table 1, run 1), an inseparable mixture of **14** and **15** (**14**/**15** = 62:38, 13.9 g, 0.0538 mol, 50%) was obtained as a colorless oil starting from *tert*-butyl methyl fumarate (**10**, 20.0 g, 0.107 mol), **13** (23.2 g, 0.214 mol), potassium carbonate (32.5 g, 0.235 mol), and benzyl triethylammonium chloride (244 mg, 1.07 mmol).

Data for an inseparable mixture of **14** and **15** (**14**/**15** = 62:38): IR (neat) 2980, 1725, 1630, 1380, 1300, 1150 cm$^{-1}$.

Selected data for the major CTT-chiral isomer **14**: $^1$H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3 H), 3.69 (s, 3 H), 2.71 (t, $J$ = 5.6 Hz, 1 H), 2.50 (dd, $J$ = 10.1, 5.6 Hz, 1 H), 2.46 (dd, $J$ = 9.8, 5.3 Hz, 1 H), 1.41 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.9, 166.5, 82.1, 52.5, 52.5, 29.5, 28.5, 27.9 (×3), 25.3.

Selected data for the minor CTT-*meso* isomer **15**: $^1$H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 6 H), 2.67 (t, $J$ = 5.6 Hz, 1 H), 2.47 (d, $J$ = 5.6 Hz, 2 H), 1.43 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9 (×2), 168.3, 82.2, 52.4 (×2), 28.0 (×2), 27.9 (×3), 26.8.

(Table 2, run 3) With the same procedure used for the synthesis of **7** (Table 1, run 1), an inseparable mixture of **14** and **15** (**14**/**15** = 61:39, 1.13 g, 4.38 mmol, 4.7%) was obtained as a colorless oil starting from *tert*-butyl methyl maleate (**11**, 17.5 g, 0.0940 mol), **13** (20.0 g, 0.188 mol), potassium carbonate (26.0 g, 0.188 mol), and benzyl triethylammonium chloride (214 mg, 0.939 mmol). The chromatographic and spectroscopic data were in good agreement with those shown above.

**1-Benzyl 2,3-Diethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (19) (Table 3, run 2):** To a stirred solution of diethyl fumarate (**1**, 10.5 mg, 0.0610 mmol) in 1,2-dichloroethane (2.6 mL) at 65 °C was added dropwise a solution of ylide **17**[10e] (44.1 mg, 0.176 mmol). The mixture was stirred for 23 h, and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.5 g, EtOAc/hexane = 1:9) to give an inseparable mixture of cyclopropane benzyl diethyl esters **19** and **20** (**19**/**20** = 92:8, 8.0 mg, 0.025 mmol, 41%) as a colorless oil: IR (neat) 2980, 1726, 1189 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 5.13 (s, 2 H), 4.15 (q, $J$ = 7.1 Hz, 2 H), 4.06 (q, $J$ = 7.1

Hz, 2 H), 2.78 (t, $J = 5.6$ Hz, 1 H), 2.57 (dd, $J = 10.0$, 5.7 Hz, 1 H), 2.52 (dd, $J = 10.0$, 5.6 Hz, 1 H), 1.26 (t, $J = 7.1$ Hz, 3 H), 1.18 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.8, 167.3, 167.3, 135.2, 128.4, 128.3, 128.3, 67.2, 61.5, 61.4, 28.5, 28.3, 25.6, 14.0, 13.9.

**1-(*tert*-Butyl) 2,3-Diethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (7) (Table 3, run 3):** With the same procedure used for the synthesis of **19** (Table 3, run 2), an inseparable mixture of cyclopropane *tert*-butyl diethyl esters **7** and **8** (**7**/**8** = 92:8, 75.8 mg, 0.265 mmol, 91%) was obtained as a colorless oil starting from diethyl fumarate (**1**, 50.0 mg, 0.290 mmol) and a solution of ylide **18**[10b] (188 mg, 0.871 mmol). The chromatographic and spectroscopic data were in good agreement with those shown above.

**1-(*tert*-Butyl) 2,3-Diethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (7) (Table 4, run 1):** With the same procedure used for the synthesis of **19** (Table 3, run 2), an inseparable mixture of cyclopropane *tert*-butyl diethyl esters **7** and **8** (**7**/**8** = 92:8, 77.9 mg, 0.272 mmol, 94%) was obtained as a colorless oil starting from diethyl maleate (**15**, 50.0 mg, 0.290 mmol) and a solution of ylide **18** (188 mg, 0.871 mmol). The chromatographic and spectroscopic data were in good agreement with those shown above.

**1-(*tert*-Butyl) 2,3-Dimethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (14) (Table 4, run 2):** With the same procedure used for the synthesis of **19** (Table 3, run 2), an inseparable mixture of cyclopropane *tert*-butyl dimethyl esters **14** and **15** (**14**/**15** = 89:11, 88.8 mg, 0.344 mmol, 99%) was obtained as a colorless oil starting from dimethyl maleate (**21**, 50.0 mg, 0.347 mmol) and a solution of ylide **18** (225 mg, 1.04 mmol). The chromatographic and spectroscopic data were in good agreement with those shown above.

**1-(*tert*-Butyl) 2,3-Dimethyl (2*S**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (14) and 1-(*tert*-Butyl) 2,3-Dimethyl (1*r**,2*R**,3*S**)-Cyclopropane-1,2,3-tricarboxylate (15) (Scheme 2):** With the same procedure used for the synthesis of **19** (Table 3, run 2), an inseparable mixture of cyclopropane dimethyl esters **14** and **15** (**14**/**15** = 55:45, 41.4 mg, 0.160 mmol, 52%) was obtained as a colorless oil starting from *tert*-butyl methyl fumarate (**10**, 57.8 mg, 0.310 mmol) and a solution of ylide **22**[10e] (162 mg, 0.930 mmol). The chromatographic and spectroscopic data were in good agreement with those shown above.

**Diethyl (1*R**,2*R**)-3-(Hydroxymethyl)cyclopropane-1,2-dicarboxylate (24) (Scheme 3):** To a stirred solution of *tert*-butyl ester **7** (1.00 g, 3.49 mmol) in $CH_2Cl_2$ (3.49 mL) at 0 °C was added TFA (3.49 mL). After stirring at rt for 1 h, the reaction mixture was concentrated under reduced pressure to give crude carboxylic acid **23** (765.9 mg) as a yellow oil.

To a stirred solution of the crude carboxylic acid **23** (765.9 mg, 3.33 mmol) thus obtained above in THF (11.9 mL) at 0 °C was added $BH_3$·THF (1.0 M in THF, 13.3 mL, 13.3 mmol). After 2 h, the reaction mixture was diluted with $CHCl_3$ (10 mL), washed with saturated aqueous $NH_4Cl$ (12 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (16 g, EtOAc/hexane = 5:5) to give alcohol **24** (375.9 mg, 1.74 mmol, 50%) as a yellowish oil. The spectroscopic data for **24** were identical to those we have reported previously.[10b]

**1-(*tert*-Butyl) 2,3-Diethyl (2*R*,3*R*)-Cyclopropane-1,2,3-tricarboxylate ((*R*,*R*)-7) (Scheme 4):** To a stirred suspension of quinidine derivative **27**[16] (47.2 mg, 0.139 mmol) and $Cs_2CO_3$ (272 mg, 0.836 mmol) in $CH_3CN$ (1.4 mL) at 80 °C was slowly added a solution of diethyl fumarate (**1**, 120 mg, 0.697 mmol) and *tert*-butyl bromoacetate (**26**, 163 mg, 0.836 mmol) in $CH_3CN$ (1.0 mL) over 6 h. After stirring for 22 h, to the mixture were added EtOAc (3 mL) and saturated aqueous $NH_4Cl$ (2 mL), and organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and combined organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (8 g, EtOAc/hexane = 8:92) to give cyclopropane (*R*,*R*)-**7** (72.0 mg, 0.251 mmol, 36%) as a yellowish oil. The spectroscopic data for (*R*,*R*)-**7** were identical to those shown above. The absolute stereochemistry was determined later by leading to known compound ((*S*,*S*)-**25**), and the enantiomeric purity was also later determined as 27.8% ee (see below).

**(2*S*,3*S*)-2,3-Bis(ethoxycarbonyl)cyclopropane-1-carboxylic Acid ((*S*,*S*)-23) and Diethyl (1*S*,2*S*)-3-(Hydroxymethyl)-cyclopropane-1,2-dicarboxylate ((*S*,*S*)-24) (Scheme 4):** According to the same procedure for the synthesis of racemic **23** and **24** shown above, deprotection of optically active *tert*-butyl ester (*R*,*R*)-**7** (3.23 g, 11.3 mmol) gave crude carboxylic acid (*S*,*S*)-**23** (2.94 g), which was then reduced to give alcohol (*S*,*S*)-**24** (1.43 g, 6.61 mmol, 59% for 2 steps) as a yellowish oil. The spectroscopic data for (*S*,*S*)-**23** and (*S*,*S*)-**24** were identical to those shown above. The enantiomeric purity was determined as 27.8% ee by chiral HPLC analysis (0.46 × 25 cm CHIRALPAK IF column, EtOH/hexane/TFA = 10:90:0.1, 1.0 mL/min, 40 °C, $t_R$ 9, 11 min) of carboxylic acid (*S*,*S*)-**23**.

**Diethyl (1*S*,2*S*)-3-((1,3-Dioxoisoindolin-2-yl)methyl)-cyclopropane-1,2-dicarboxylate ((*S*,*S*)-28) and Diethyl (1*R*,2*R*)-3-((1,3-Dioxoisoindolin-2-yl)methyl)cyclopropane-1,2-dicarboxylate ((*R*,*R*)-28):** To a stirred solution of alcohol (*S*,*S*)-**24** (517 mg, 2.39 mmol) in benzene (24.0 mL) at rt were added triphenylphosphine (941 mg, 3.59 mmol), phthalimide (704 mg, 4.78 mmol), and diethyl azodicarboxylate (2.2 M in toluene, 1.63 mL, 3.59 mmol). After 24 h, the mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (20 g, EtOAc/hexane = 29:71) to give *N*-alkyl phthalimide (*S*,*S*)-**28** (773 mg, 2.24 mmol, 94%) as a yellowish oil. Purification by chiral HPLC (0.46 × 25 cm CHIRALPAK IC column, EtOH/hexane = 10:90, 1.0 mL/min, 40 °C, $t_R$ 17 min) gave enantiomerically pure (*S*,*S*)-**28** (>99.9% ee). The enantiomer ((*R*,*R*)-**28**) eluted at $t_R$ 20 min was also collected and determined as >99.9% ee.

Data for the major *N*-alkyl (*S*,*S*)-phthalimide (*S*,*S*)-**28**: $[\alpha]_D^{22.5}$ +26.6 (*c* 0.257, $CHCl_3$); IR (neat) 2982, 1774, 1718, 1189 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2 H), 7.72–7.68 (m, 2 H), 4.25 (dd, $J = 14.2$, 7.1 Hz, 2 H), 4.13–4.08 (m, 2 H), 4.06 (dd, $J = 14.4$, 7.4 Hz, 1 H), 3.89 (dd, $J = 14.4$, 7.4 Hz, 1 H), 2.41 (t, $J = 5.3$ Hz, 1 H), 2.32 (dd, $J = 9.4$, 4.8 Hz, 1 H), 2.09 (m, 1 H), 1.30 (t, $J = 7.1$ Hz, 3 H), 1.23 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.4, 167.9 (×2), 134.0 (×2), 132.0 (×2), 123.3 (×2), 61.4, 61.2, 34.5, 27.0, 26.9, 26.4, 14.1, 14.1; HRMS (ESI, positive) calcd for $C_{18}H_{20}NO_6$ [$(M + H)^+$] 346.1285, found 346.1285.

Data for the minor *N*-alkyl (*R*,*R*)-phthalimide (*R*,*R*)-**28**: $[\alpha]_D^{22.3}$ −26.3 (*c* 0.237, $CHCl_3$). Other data were identical to those for the congener (*S*,*S*)–**28**.

**Ethyl (1*S*,5*R*,6*S*)-2-Oxo-3-azabicyclo[3.1.0]hexane-6-carboxylate ((*S*,*S*)-29):** To a stirred solution of phthalimide (*S*,*S*)-**28** (8.47 mg, 0.0245 mmol) in EtOH (0.818 mL) at rt was added hydrazine hydrate (0.00955 mL, 0.196 mmol). After 49 h, the mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (0.6 g, EtOAc/hexane = 40:60) to give butyrolactam (*S*,*S*)-**29** (3.59 mg, 0.0212 mmol, 87%) as a yellowish oil: $[\alpha]_D^{23.6}$ +79.9 (*c* 0.180, $CHCl_3$); IR (KBr) 3210, 1715, 1680, 1186 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.53 (br, 1 H), 4.14 (q, *J* = 7.1 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 1 H), 3.60 (dd, *J* = 10.9, 5.5 Hz, 1 H), 3.43 (d, *J* = 10.9 Hz, 1 H), 2.45 (ddd, *J* = 6.1, 5.5, 2.7 Hz, 1 H), 2.34 (d, *J* = 6.1 Hz, 1 H), 1.79 (dd, *J* = 2.7, 2.7 Hz, 1 H), 1.25 (br dd, *J* = 7.1, 7.1 Hz, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 175.3, 170.8, 61.3, 43.9, 28.0, 25.8, 23.5, 14.2; HRMS (ESI, positive) calcd for $C_{18}H_{12}NO_3$ $[(M + H)^+]$ 170.0812, found 170.0812.

**Ethyl (1*R*,5*S*,6*R*)-2-Oxo-3-azabicyclo[3.1.0]hexane-6-carboxylate ((*R*,*R*)-29):** According to the same procedure for the synthesis of (*S*,*S*)-**29** shown above, deprotection of phthalimide (*R*,*R*)-**28** (7.32 mg, 0.0212 mmol) gave butyrolactam (*R*,*R*)-**29** (3.35 mg, 0.0198 mmol, 93%) as a yellowish oil: $[\alpha]_D^{23.0}$ −79.3 (*c* 0.168, $CHCl_3$). Other data were identical to those for the congener (*S*,*S*)-**29**.

**(*S*,*S*)-(*N*-Desmethyl)dysibetaine CPa Hydrochloride ((*S*,*S*)-25):** A suspension of butyrolactam ethyl ester (*S*,*S*)-**29** (4.32 mg, 0.0255 mmol) in hydrochloric acid (1 M, 0.600 mL) was stirred at 70 °C for 16 h. The mixture was then concentrated by blowing air to give a residue, which was purified by column chromatography on silica gel (ODS, 0.6 g, $H_2O$) to give (*S*,*S*)-(*N*-desmethyl)dysibetaine CPa hydrochloride ((*S*,*S*)-**25**, 4.33 mg, 0.0221 mmol, 87%) as a yellow solid: $[\alpha]_D^{22.3}$ +58.4 (*c* 0.317, $H_2O$); $^1H$ NMR (400 MHz, $D_2O$) δ 3.25–3.13 (m, 2 H), 2.25 (dd, *J* = 9.3, 4.8 Hz, 1 H), 2.12 (t, *J* = 5.6 Hz, 1 H), 1.95 (m, 1 H); $^{13}C$ NMR (100 MHz, $D_2O$) δ 175.1, 173.7, 36.8, 27.3, 26.9, 24.3. Other data were identical to those reported by us.[10b]

**(*R*,*R*)-(*N*-Desmethyl)dysibetaine CPa Hydrochloride ((*R*,*R*)-25):** According to the same procedure for the synthesis of (*S*,*S*)-**25** shown above, acidic hydrolysis of butyrolactam ethyl ester (*R*,*R*)-**29** (4.86 mg, 0.0287 mmol) gave (*S*,*S*)-(*N*-desmethyl)dysibetaine CPa hydrochloride ((*R*,*R*)-**25**, 5.27 mg, 0.0269 mmol, 94%) as a yellow solid: $[\alpha]_D^{23.4}$ −58.4 (*c* 0.264, $H_2O$). Other data were identical to those for the congener (*S*,*S*)-**25** shown above, as well as those reported by us.[10b]

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## Supporting Information

Characterization data for new intermediates, HPLC profiles for chiral resolution, and $^{13}C$ NMR calculations are included. This material is available on https://doi.org/10.1246/bcsj.20190096.

## References

1 D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631.

2 a) K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ohfune, *J. Org. Chem.* **1991**, *56*, 4167. b) A. Reichelt, S. F. Martin, *Acc. Chem. Res.* **2006**, *39*, 433.

3 a) B.-L. Lu, L. Dai, M. Shi, *Chem. Soc. Rev.* **2012**, *41*, 3318. b) M. Shi, J.-M. Lu, Y. Wei, L.-X. Shao, *Acc. Chem. Res.* **2012**, *45*, 641. c) L. Jiao, Z.-X. Yu, *J. Org. Chem.* **2013**, *78*, 6842. d) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem., Int. Ed.* **2014**, *53*, 5504. e) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655. f) D. Rosa, A. Nikolaev, N. Nithiy, A. Orellana, *Synlett* **2015**, *26*, 441. g) A. P. Thankachan, K. S. Sindhu, K. K. Krishnan, G. Anilkumar, *Org. Biomol. Chem.* **2015**, *13*, 8780. h) M. A. A. Walczak, T. Krainz, P. Wipf, *Acc. Chem. Res.* **2015**, *48*, 1149. i) L. Yu, M. Liu, F. Chen, Q. Xu, *Org. Biomol. Chem.* **2015**, *13*, 8379.

4 H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.

5 H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323.

6 M. T. Rispens, E. Keller, B. de Lange, R. W. J. Zijlstra, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 607.

7 E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353.

8 a) M. P. Doyle, M. N. Protopopova, *Tetrahedron* **1998**, *54*, 7919. b) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis* **2014**, *46*, 979.

9 R. Sakai, K. Suzuki, K. Shimamoto, H. Kamiya, *J. Org. Chem.* **2004**, *69*, 1180.

10 a) M. Oikawa, S. Sasaki, M. Sakai, R. Sakai, *Tetrahedron Lett.* **2011**, *52*, 4402. b) M. Oikawa, S. Sasaki, M. Sakai, Y. Ishikawa, R. Sakai, *Eur. J. Org. Chem.* **2012**, 5789. c) M. Sakai, Y. Ishikawa, S. Takamizawa, M. Oikawa, *Tetrahedron Lett.* **2013**, *54*, 5911. d) M. Sakai, K. Tanaka, S. Takamizawa, M. Oikawa, *Tetrahedron* **2014**, *70*, 4587. e) K. Tanaka, M. Sakai, S. Takamizawa, M. Oikawa, *Chem. Lett.* **2015**, *44*, 253.

11 S. I. Kozhushkov, A. Leonov, A. de Meijere, *Synthesis* **2003**, 956.

12 V. K. Aggarwal, H. W. Smith, G. Hynd, R. V. H. Jones, R. Fieldhouse, S. E. Spey, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267.

13 C. D. Papageorgiou, S. V. Ley, M. J. Gaunt, *Angew. Chem., Int. Ed.* **2003**, *42*, 828.

14 However, we have previously found that cyclopropanation of cyclic imide gives CCC–isomer.[10b] Works are in progress to control the CTT/CCC selectivity.

15 We speculate that, because of the absence of the counter cation species, sulfonium ylide is more reactive than chloroacetate which is accompanied by sterically demanding benzyltriethylammonium cation.

16 C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley, M. J. Gaunt, *Angew. Chem., Int. Ed.* **2004**, *43*, 4641.

17 Y. Sugeno, Y. Ishikawa, M. Oikawa, *Synlett* **2014**, *25*, 987.

18 a) D. Janardanan, R. B. Sunoj, *J. Org. Chem.* **2007**, *72*, 331. b) S. S. Bhella, M. Elango, M. P. S. Ishar, *Tetrahedron* **2009**, *65*, 240. c) H. K. Hall, Jr., K. Childers, T. Centeno-Hall, C. Contreras, B. Mazel, H. Menon, V. Nguyen, J. Robertson, R. Bates, *Tetrahedron Lett.* **2012**, *53*, 4725. d) R. Herchl, M. Waser, *Tetrahedron Lett.* **2013**, *54*, 2472.

19 Another possible reason might be ascribed to the lower

reactivity of maleates in the first Michael reaction; i.e., 1,3-allylic strains in the maleic system, which would diminish conjugation at the C–C and C–O double bonds, reduce electrophilicity of the olefinic part.

20 *Tutorial and User's Guide, Spartan '18 for Windows, Macintosh and Linux*, Wavefunction Inc., **2018**.

21 N. Grimblat, M. M. Zanardi, A. M. Sarotti, *J. Org. Chem.* **2015**, *80*, 12526.

22 a) I. Atodiresei, I. Schiffers, C. Bolm, *Chem. Rev.* **2007**, *107*, 5683. b) M. D. Díaz de Villegas, J. A. Gálvez, P. Etayo, R. Badorrey, P. Lopez-Ram-de-Viu, *Chem. Soc. Rev.* **2011**, *40*, 5564. c) M. D. Díaz-de-Villegas, J. A. Gálvez, R. Badorrey, M. P. López-Ram-de-Víu, *Chem.—Eur. J.* **2012**, *18*, 13920. d) A. Enríquez-García, E. P. Kündig, *Chem. Soc. Rev.* **2012**, *41*, 7803.

23 The DP4+ methodology has been actively used for structure elucidation of complex natural products with only one set of experimental data, see; N. Grimblat, A. M. Sarotti, *Chem.—Eur. J.* **2016**, *22*, 12246.

24 B. Neises, W. Steglich, *Org. Synth.* **1985**, *63*, 183.

25 A. Matsumoto, Y. Sano, M. Yoshioka, T. Otsu, *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 291.

26 O. Meth-Cohn, C. Moore, H. C. Taljaard, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663.


 