A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers

DOAJ Seal

Arkivoc **2021**, part viii, 0-0

to be inserted by editorial office

Diastereoselective photochemical radical addition of a cyclic ether to olefins: addition of THF radicals to dialkyl maleates

Mamiko Hayakawa, Tadashi Aoyama, and Akihiko Ouchi*

Department of Materials and Applied Chemistry, College of Science and Technology, Nihon University, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan

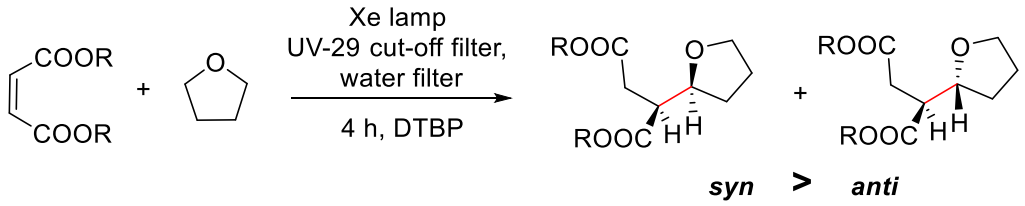
Email: ouchi.akihiko@nihon-u.ac.jp

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

The diastereoselectivity of the addition reaction of a THF radical to dialkyl maleates, the stereochemistry of the carbon atoms at *both* sides of the newly formed C-C bonds, has still not been established; both the presence and absence of diastereoselectivity have been reported in previous studies and its origin has not been discussed. We have obtained clear evidence for the presence of diastereoselectivity in the addition reaction, in which the diastereoselectivity increases with an increase in the bulkiness of the alkyl groups. DFT calculations on the maleates showed the presence of one or two stable conformations, which depend on the bulkiness of the alkyl groups.

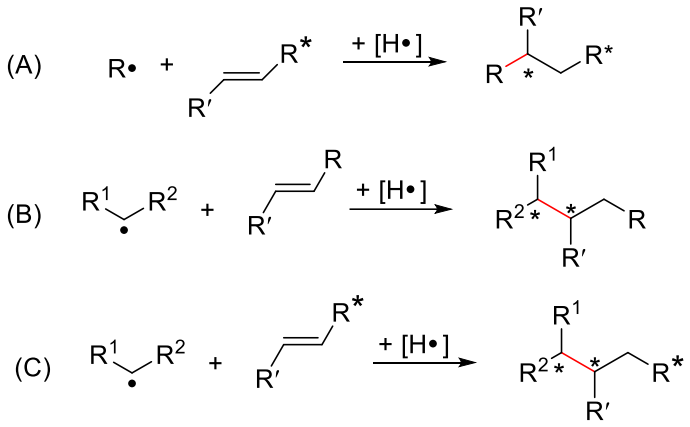


Keywords: Diastereoselective photochemical reaction, carbon radical addition reaction, THF, maleic acid dialkyl ester, steric effect

 ©**AUTHOR(S)**

Introduction

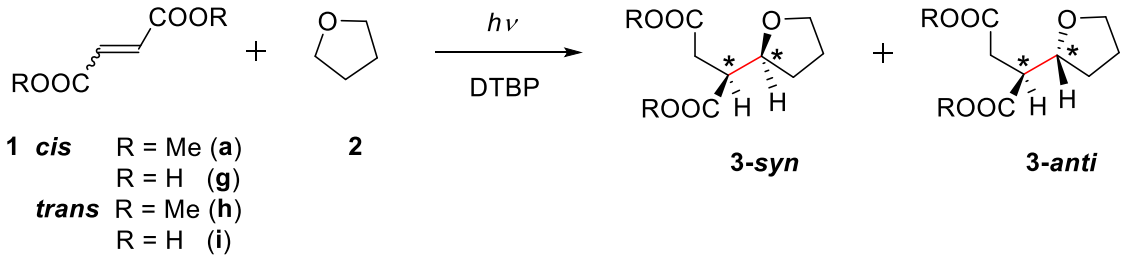
Diastereoselective reactions have been developed in order to introduce new asymmetric centers into a molecule, and these reactions have been also studied in the carbon radical addition reaction of olefins.[1–4] A typical reaction is the addition of a carbon radical to an asymmetric olefin, which generates an asymmetric carbon atom via the formation a new C-C bond in the olefin due to the steric effects of the original asymmetric center in the olefin (Scheme 1A).[5–11] If the addition of carbon radicals to non-asymmetric olefins proceeds diastereoselectively (Scheme 1B), i.e. the selective formation of one of the two sets of enantiomers, the introduction of two new asymmetric carbon atoms using a single reaction will be accomplished by the combination of reactions A and B (Scheme 1C). Therefore, the development of reactions that correspond to Scheme 1B is essential for realizing the reactions outlined in Scheme 1C.



Scheme 1. Diastereoselective carbon radical addition reactions of olefins: (A) Addition to asymmetric olefins, (B) addition to non-asymmetric olefins, and (C) addition to asymmetric olefins in combination with reaction type B. The asymmetric carbons are indicated using asterisks (*).

In the course of our study on the photochemical C-C bond formation reactions between cyclic ethers and olefins, we discovered an interesting diastereoselective photochemical addition of THF (**2**) to dimethyl maleate (**1a**)(Scheme 2), which corresponds to the reaction shown in Scheme 1B. The diastereomeric ratio (*d.r.*), **3a-*syn*/3a-*anti***, was found to be 1.6/1.0; the *syn* and *anti* isomers were assigned according to the literature.[12] In contrast, the *d.r.* was very small during the addition of **2** to maleic acid (**1g**, 0.9/1.0 *d.r.*), dimethyl fumarate (**1h**, 0.9/1.0 *d.r.*), and fumaric acid (**1i**, 0.8/1.0 *d.r.*).[12] However, previous studies on the addition reaction of a THF radical to **1a**, using an Ir photoredox catalyst [13] and radical initiator ($PhCOCO_2H$)[14] have been reported to show no diastereoselectivity (1/1 *d.r.*), which are inconsistent with our results. In the latter report, the reaction was also conducted using other dialkyl esters of maleic acid (cf. Scheme 2); although no diastereoselectivity (50/50 *d.r.*) was observed in the reactions with R = *n*-Pr, *iso*-Pr (**1e**), *sec*-Bu, allyl, methoxyethyl, and *p*-chlorobenzyl groups, those with R = Et (60/40 *d.r.*), benzyl (80/20 *d.r.*), *p*-methylbenzyl (60/40 *d.r.*), and *p-tert*-butylbenzyl (60/40 *d.r.*) showed diastereoselectivity.[14]

 ©**AUTHOR(S)**



Scheme 2. The addition of a THF radical to various olefins (**1**). The asterisks (*) show the carbon atoms where the two new asymmetric centers were generated.

On the other hand, the addition of a THF radical to olefins **4**–**7** using eosin Y as a photocatalyst showed no diastereoselectivity,[15] but that to **8** using neutral eosin Y and a Rh catalyst [16] showed a small amount of diastereoselectivity (57/43 *d.r.*) (Figure 1).

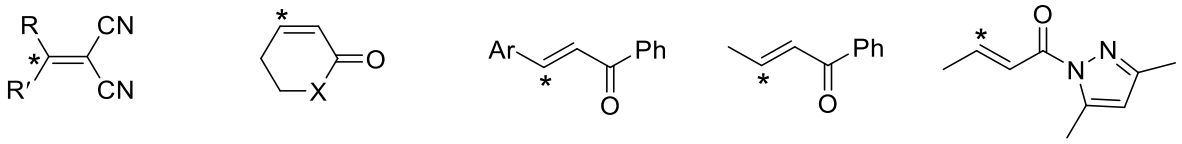


Figure 1. The olefins used for the addition of a THF radical. The asterisks (*) shows the carbon atoms where a new stereo-center was expected to be formed during the addition reaction.

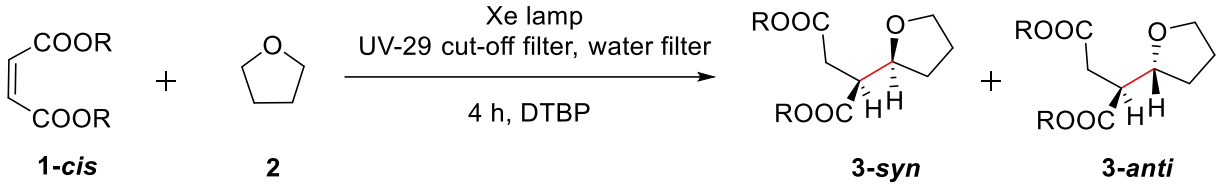
As demonstrated in the literature, the diastereoselectivity of the addition reaction of a THF radical to olefins has still not been established and the origin of the diastereoselectivity has not been considered until now. In this paper, we report clear evidence for the presence of the diastereoselectivity during the addition of a THF radical to dialkyl maleates and that the origin of the diastereoselectivity is the steric effect of the R groups.

Results and Discussion

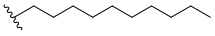
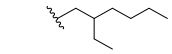
The reactions between THF (**2**) and various maleic acid esters bearing different R groups (**1a**–**f**) have been conducted and the results are summarized in Table 1. The photolyses were performed using a radical initiator, di-*tert*-butyl peroxide (DTBP), and >290 nm light at room temperature under a nitrogen atmosphere.[12] The yields of the *syn*- and *anti*-isomers for each product were determined using NMR spectroscopy with naphthalene as an internal standard. The *syn*- and *anti*- isomers were isolated using column chromatography.

 ©**AUTHOR(S)**

Table 1. Diastereomeric ratio (*d.r.*) of **3** (**3-*syn*/3-*anti***) during the addition of THF (**2**) to maleic acid dialkyl esters (**1a-f**). [a]



1-*cis* **2** **3-*syn*** **3-*anti***

Entry	**1-*cis*** R		Yield [b] **3-*syn*/3-*anti*** (%)	*d.r.* [b] *syn*/*anti* ratio
1	Me	**1a**	60/35	1.7/1.0
2	Bu	**1b**	65/35 (62/34) [c]	1.8/1.0 (1.8/1.0) [c]
3		**1c**	60/28 (57/24) [c]	2.1/1.0 (2.4/1.0) [c]
4		**1d**	66/32 (59/29) [c]	2.0/1.0 (2.0/1.0) [c]
5	*iso*-Pr	**1e**	63/31 (60/29) [c]	2.0/1.0 (2.1/1.0) [c]
6	*tert*-Bu	**1f**	67/29 (65/25) [c]	2.3/1.0 (2.6/1.0) [c]

[a] Photolysis condition, substrates: **1** (0.2 mmol) and DTBP (0.1 mmol) in THF (10 mL), light source: 500-W xenon short-arc lamp fitted with an 18-cm water filter and a UV-29 cut-off filter (2.0 $mW \cdot cm^{-2}$), irradiation time: 4 h, N_2 atm, room temp. [b] The yield and *syn*/*anti* ratio were determined by NMR spectroscopy using naphthalene as an internal standard. The NMR ratios are the average of two independent runs, whose experimental errors were < 5%.[18] [c] Yield of isolated products **3-*syn*** and **3-*anti*** isomers and their *syn*/*anti* ratio.

As seen in Table 1, the reactions proceed in high yield for all R groups and the *d.r.* of the addition product (**3**) increased with an increase in the length of the alkyl chain R: Me (**1a**, 1.7/1.0 *d.r.*) < Bu (**1b**, 1.8/1.0 *d.r.*) < decyl (**1c**, 2.1/1.0 *d.r.*) (Entries 1–3). The increase in the *d.r.* was also observed when the carbon adjacent to the alkoxy oxygen was varied from a *primary*, *secondary*, and *tertiary*: Bu (**1b**, 1.8/1.0 *d.r.*) < *iso*-Pr (**1e**, 2.0/1.0 *d.r.*) < *tert*-Bu (**1f**, 2.3/1.0 *d.r.*) (Entries 2, 5, and 6). The introduction of an alkyl side chain at the second carbon atom from the alkoxy oxygen did not show any significant effect on the *d.r.*: decyl (**1c**, 2.1/1.0 *d.r.*) ≈ 2-ethylhexyl (**1d**, 2.0/1.0 *d.r.*) (Entries 3 and 4). These results indicate that the steric effect of the R groups is an important factor for determining the *d.r.* (*syn/anti* ratio), in which the *d.r.* increases with an increase in the bulkiness of the R groups.

Figure 2 shows the stable ground state conformations of substrate olefins **1a**–**1g** obtained using DFT calculations;[17] the detailed conformations and energies for each olefin are shown in the Supplementary Material. Fumaric acid (**1i**) and its dimethyl ester (**1h**), which show no diastereoselectivity in the addition reaction, have a planar conformation (Conformer 3). On the other hand, maleic acid (**1g**) and its dimethyl ester (**1a**) showed two stable conformers with similar energies (Conformers 1 and 2). Conformer 1 has normal conjugation between the π-electron systems in the olefin and one of the ester groups, but that of the other ester is twisted out from the conjugated π-electron system. In the case of conformer 2, the π-electron systems of the two ester groups are both slightly twisted out from the π-electron system of the olefin, but considerable conjugation of the π-electron systems is maintained between the olefin and the two ester groups. The presence and absence of diastereoselectivity in the reactions of **1a** and **1g**, respectively, are probably due to the difference in the bulkiness between R = Me and H. As for linear alkyl groups, olefins **1b** and **1c** exhibited

 ©AUTHOR(S)

two stable conformations, conformers 1 and 2 with the same energy, which were also obtained from our DFT calculations. Linear R groups seem to have interactions similar to that of the Me groups. However, R = 2-ethylhexyl (**1d**), *iso*-Pr (**1e**), and *tert*-Bu (**1f**) only have conformer 1 as their stable conformation.

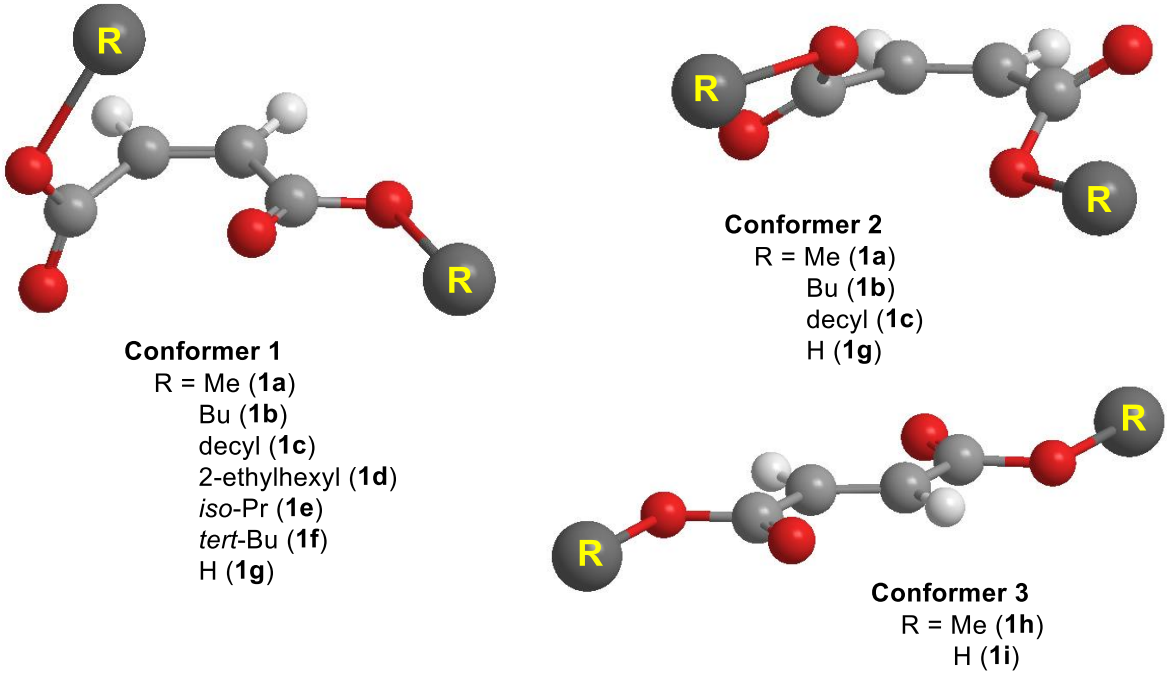


Figure 2. The stable ground state conformations of substrate olefins calculated using DFT calculations utilizing the B3LYP functional.[17]

These results indicate that the steric bulkiness near the carbon atom adjacent to the alkoxy oxygen atom seems to have a considerable effect on the conformation of the olefins via the interaction between the two R groups. However, it is still not clear which of the two isomers are responsible for determining the *d.r.* of the obtained products. The reactions of **1d**–**f** indicate that conformer 1 is responsible for determining the *d.r.* because their stable conformation is only conformer 1. On the other hand, **1c** with conformers 1 and 2 as its stable form, has a similar *d.r.* as those of **1d** and **1e**, which have only conformer 1 as their stable form. Conformers 1 and 2 of **1c** have the same energy so that both conformers are expected to exist in the same ratio, and if conformer 2 is not responsible for determining the *d.r.*, the *d.r.* of **1c** should be smaller than those of **1d** and **1e**. Therefore, these results indicate that conformer 2 is also responsible for determining the *d.r.* of the reaction adducts.

In contrast to previous reports (*vide supra*),[13,14] clear evidence for the presence of diastereoselectivity was observed during the addition of **2** to olefin **1** in our study. The difference in the results between previous reports and our study is not clear at the moment as no explanation of the diastereoselectivity has been given in the previous reports.[14] However, a comparison of the reaction procedures suggests that the difference in the reaction temperature may be the reason for the different *d.r.* Therefore, we have conducted our reaction using **1a** and **2** at 50 °C, but the *d.r.* (*syn*/*anti* ratio) was found to be 61/38, which was almost the same as the *d.r.* obtained at room temperature. This result indicates that the reaction temperature was not a factor for determining the *d.r.* of the reaction, and the reason for the difference in the result is still not clear at the moment.

 ©**AUTHOR(S)**

Conclusions

The addition reactions of carbon radicals to olefins have been reported, but the stereochemistry of the carbon atoms on *both* sides of the newly formed C-C bond have not been studied in detail. In particular, the diastereoselectivity during the addition of a THF (**2**) radical to dialkyl maleates (**1**), a fundamental reaction, has not been established; both the presence and absence of diastereoselectivity has been reported in the literature. Our systematic study has shown a diastereoselective reaction took place during the addition of a THF radical to dialkyl maleates (**1a**–**f**), whose *d.r.* increased with the bulkiness of the alkyl groups. DFT calculations on **1a**–**f** showed the presence of one or two stable conformations that depend on the bulkiness of the alkyl groups.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX400 spectrometer with $CDCl_3$ as solvent. As internal standards, TMS (δ 0.0 ppm) in $CDCl_3$ were used for ^{1}H NMR, and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR analyses. IR spectra were recorded on a JASCO FT/IR-4700 spectrometer. MS spectra were recorded on a Shimadzu GCMS-QP2010 plus spectrometer. HRMS spectra were recorded on an Agilent G1969 LC/MDS TOF mass spectrometer. Olefins **1a, 1b, 1d, 1f**, THF (**2**) and DTBP were purchased and used as bought. Olefins **1c** [19] and **1e** [20] were synthesized according to the reported procedures.

General procedure for the photolysis [12] A THF (**2**) (10 mL) solution of olefin (**1a**-**f**) (0.2 mmol) and DTBP (0.1 mmol) was introduced into a quartz cylindrical cell (diameter: 3 cm) equipped with a three-way stopcock. The three-way stopcock was connected to the cell, a nitrogen source, and small vacuum pump. The solution was evacuated to about 50 mmHg under sonication for 5 s and nitrogen was then introduced into the cell; this cycle was repeated 10 times to remove oxygen efficiently from the solution. The photolysis was conducted using a 500-W xenon lamp (USHIO Optical Modulex SX-UI500XQ) fitted with an 18-cm water filter and a cut-off filter (Toshiba UV-29) under a nitrogen atmosphere. The irradiated light intensity was 2.0 mW/cm^2, which was measured by an Ushio UIT-150-A Ultraviolet Radiometer equipped with a UVD-S365 photo detector. After photolysis, THF was removed in vacuo at 40–50 °C / < 70 Torr (most of the products were volatile under reduced pressure) and the consumption of the olefin and the products yield were determined by NMR spectroscopy using a precise amount of naphthalene as an internal standard. The isolation of the products was conducted using silica gel column chromatography.

2-(Tetrahydro-2-furanyl) butanedioic acid 1,4-dimethyl ester (3a-*cis*). [12–14] Dimethyl maleate (**1a**-***cis***, 28.87 mg, 0.20 mmol) and DTBP (14.76 mg, 0.10 mmol) in THF (**2**, 10 mL). Yield of **3a**: quantitative % (*syn* / *anti* = 61 / 39) (conversion: 100 %) (NMR, $CDCl_3$).

2-(Tetrahydro-2-furanyl) butanedioic acid 1,4-dibutyl ester (3b). Dibutyl maleate (**1b**, 45.61 mg, 0.20 mmol) and DTBP (14.68 mg, 0.10 mmol) in THF (**2**, 10 mL). Yield of **3b**: quantitative % (*syn* / *anti* = 65 / 35) (conversion: 100 %) (NMR, $CDCl_3$). Eluent for chromatography: hexane/ethyl acetate (50/1 → 0/1).

3b-*syn*. 37.29 mg (62 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.92 (t, *J* 7.4 Hz, 3 H), 0.93 (t, *J* 7.4 Hz, 3 H), 1.32-1.44 (m, 4 H), 1.54-1.72 (m, 5 H), 1.83-1.97 (m, 3 H), 2.46 (dd, *J* 4.0, 16.6 Hz, 1 H), 2.76 (dd, *J* 10.0, 16.6 Hz, 1

 ©**AUTHOR(S)**

H), 3.10 (ddd, *J* 4.0, 6.4, 10.0 Hz, 1 H), 3.74 (ddd, *J* 6.8, 6.8, 8.4 Hz, 1 H), 3.86 (ddd, *J* 6.4, 6.4, 8.4 Hz, 1 H), 4.04-4.17 (m, 5 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 13.7 (×2), 19.1 (×2), 25.7, 28.4, 30.6 (×2), 32.5, 46.1, 64.6, 64.7, 68.4, 78.9, 171.9, 172.8 ppm. IR (KBr disk): 3451, 2960, 2874, 1736, 1465, 1392, 1259, 1168, 1068, 1023, 947, 756, 665 cm^{-1}. MS, m/z (relative intensity): 41 (35), 42 (5), 43 (31), 44 (10), 55 (8), 56 (11), 71 (100), 129 (7), 227 (1). HRMS: *m/z* calcd. For $C_{16}H_{28}O_5$ +Na: 323.1834; found: 323.1833.

3b-*anti*. 21.00 mg (34 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.92 (t, *J* 7.4 Hz, 3 H), 0.93 (t, *J* 7.4 Hz, 3 H), 1.38 (tq, *J* 7.4, 7.4 Hz, 2 H), 1.38 (tq, *J* 7.4, 7.4 Hz, 2 H), 1.55-1.66 (m, 4 H), 1.69-1.79 (m, 1 H), 1.82-2.04 (m, 3 H), 2.69 (dd, *J* 4.8, 16.4 Hz, 1 H), 2.78 (dd, *J* 9.6, 16.4 Hz, 1 H), 2.89 (ddd, *J* 4.8, 8.0, 9.6 Hz, 1 H), 3.73 (ddd, *J* 6.8, 7.2, 7.2 Hz, 1 H), 3.81 (ddd, *J* 6.4, 6.8, 8.0 Hz, 1 H), 3.99 (ddd, *J* 6.8, 7.2, 7.2 Hz, 1 H), 4.03-4.16 (m, 4 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 13.7 (×2), 19.08, 19.11, 25.6, 29.7, 30.58, 30.61, 33.5, 46.9, 64.5, 64.7, 68.0, 78.8, 172.3, 172.9 ppm. IR (KBr disk): 2959, 2937, 2873, 1737, 1464, 1415, 1390, 1357, 1260, 1166, 1121, 1066, 1024, 963 cm^{-1}. MS, m/z (relative intensity): 41 (41), 42 (8), 43 (32), 44 (7), 56 (17), 57 (8), 71 (100), 129 (7), 171 (5), 185 (5), 227 (2). HRMS: *m/z* calcd. For $C_{16}H_{28}O_5$ +Na: 323.1834; found: 323.1832.

2-(Tetrahydro-2-furanyl) butanedioic acid 1,4-didecyl ester (3c). Didecyl maleate (**1c**, 79.56 mg, 0.20 mmol) and DTBP (14.85 mg, 0.10 mmol) in THF (**2**, 10 mL). Yield of **3c**: 89 % (*syn* / *anti* = 60 / 29) (conversion: 100 %) (NMR, $CDCl_3$). Eluent for chromatography: hexane/ethyl acetate (50/1 → 0/1).

3c-*syn.* 40.20 mg (57 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, *J* 6.6 Hz, 6 H), 1.20-1.38 (m, 28 H), 1.56-1.72 (m, 5 H), 1.84-1.97 (m, 3 H), 2.46 (dd, *J* 4.8, 16.4 Hz, 1 H), 2.76 (dd, *J* 10.0, 16.4 Hz, 1 H), 3.10 (ddd, *J* 4.8, 6.4, 10.0 Hz, 1 H), 3.74 (ddd, *J* 6.4, 6.4, 6.8 Hz, 1 H), 3.86 (ddd, *J* 6.4, 6.4, 8.4 Hz, 1 H), 4.00-4.18 (m, 5 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 14.1 (×2), 22.7 (×2), 25.7, 25.9 (×2), 28.4, 28.6 (×2), 29.25 (×2), 29.30 (×2), 29.5 (×4), 31.9 (×2), 32.5, 46.1, 64.9, 65.0, 68.4, 78.9, 171.9, 172.7 ppm. IR (KBr disk): 2954, 2925, 2855, 1737, 1466, 1413, 1358, 1259, 1165, 1069, 920, 733 cm^{-1}. MS, m/z (relative intensity): 41 (19), 43 (43), 44 (8), 55 (14), 57 (15), 71 (100), 129 (8), 171 (8), 269 (7). HRMS: *m/z* calcd. For $C_{28}H_{52}O_5$ +Na: 491.3712; found: 491.3712.

3c-*anti.* 24.31 mg (24 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, *J* 6.8 Hz, 6 H), 1.26-1.35 (m, 28 H), 1.56-1.67 (m, 4 H), 1.69-1.79 (m, 1H), 1.83-2.03 (m, 3 H), 2.69 (dd, *J* 4.8, 16.4 Hz, 1 H), 2.78 (dd, *J* 9.2, 16.4 Hz, 1 H), 2.89 (ddd, *J* 4.8, 7.6, 9.2 Hz, 1 H), 3.73 (ddd, *J* 6.4, 7.2, 7.2 Hz, 1 H), 3.79 (ddd, *J* 7.2, 7.6, 8.0 Hz, 1 H), 4.01 (ddd, *J* 6.4, 7.0, 7.0 Hz, 1H), 4.01-4.15 (m, 4 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 14.1 (×2), 22.7 (×2), 25.6, 25.9 (×2), 28.5, 28.6, 29.2, 29.26, 29.30 (×2), 29.5 (×4), 29.7, 31.9 (×2), 33.5, 46.9, 64.8, 65.0, 68.0, 78.8, 172.3, 172.9 ppm. IR (KBr disk): 2954, 2925, 2855, 1735, 1466, 1164, 1067, 913, 771, 736 cm^{-1}. MS, m/z (relative intensity): 41 (19), 43 (41), 44 (10), 55 (13), 57 (13), 71 (100), 129 (8), 171 (8), 269 (7). HRMS: *m/z* calcd. For $C_{28}H_{52}O_5$ +Na: 491.3712; found: 491.3712.

2-(Tetrahydro-2-furanyl) butanedioic acid 1,4-bis(2-ethylhexyl) ester (3d). Bis(2-ethylhexyl) maleate (**1d**, 68.18 mg, 0.20 mmol) and DTBP (14.63 mg, 0.10 mmol) in THF (**2**, 10 mL). Yield of **3d**: 96 % (*syn* / *anti* = 62/ 34) (conversion: 100 %) (NMR, $CDCl_3$). Eluent for chromatography: hexane/ethyl acetate (50/1 → 0/1).

3d-*syn.* 48.62 mg (59 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, *J* 7.2 Hz, 6H), 0.89 (t, *J* 7.2 Hz, 6H), 1.21-1.41 (m, 16 H), 1.51-1.62 (m, 2 H), 1.63-1.72 (m, 1 H), 1.84-1.96 (m, 3 H), 2.47 (dd, *J* 4.4, 16.8 Hz, 1 H), 2.77 (dd, *J* 10.2, 16.8 Hz, 1 H), 3.14 (ddd, *J* 4.4, 6.4, 10.2 Hz, 1 H), 3.73 (ddd, *J* 7.2, 7.2, 8.0, 1 H), 3.86 (ddd, *J* 6.4, 6.4, 8.0, 1 H), 3.92-4.13 (m, 5 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 10.89, 10.92, 10.94, 14.0 (×2), 23.0, 23.66, 23.68, 25.7, 28.3, 28.8, 28.9, 30.29, 30.34, 32.3, 38.64, 38.66, 38.68, 46.0, 67.1, 68.4, 78.8, 172.0, 172.7 ppm. IR (KBr disk): 2956, 2926, 2859, 1732, 1462, 1381, 1259, 1164, 1067, 1023, 773, 729, 676, 583, 556, 507 cm^{-1}. MS, m/z (relative intensity): 41 (49), 42 (11), 43 (47), 55 (37), 57 (60), 70 (24), 71 (100), 129 (15), 171 (10), 301 (0.1). HRMS: *m/z* calcd. For $C_{24}H_{44}O_5$ +Na: 435.3086; found: 435.3087.

3d-*anti.* 23.84 mg (29 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, *J* 6.4 Hz, 6H), 0.90 (t, *J* 6.8 Hz, 6H), 1.20-1.42 (m, 16 H), 1.50-1.63 (m, 2 H), 1.69-1.79 (m, 1H), 1.82-2.03 (m, 3H), 2.70 (dd, *J* 5.0, 16.8 Hz, 1 H), 2.79 (dd,

 ©AUTHOR(S)

J 9.2, 16.8 Hz, 1 H), 2.90 (ddd, *J* 5.0, 8.0, 9.2 Hz, 1 H), 3.72 (ddd, *J* 6.8, 6.8, 7.0 Hz, 1 H), 3.81 (ddd, *J* 6.8, 6.8, 8.0 Hz, 1 H), 3.91-4.07 (m, 5 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 10.88, 10.92, 10.95, 14.0, 23.0 (×2), 23.66, 23.69, 25.6, 28.8, 28.9, 29.7, 30.29, 30.32, 33.5, 38.62, 38.68, 46.9, 67.0, 67.2, 68.0, 78.8, 172.3, 173.0 ppm. IR (KBr disk): 2956, 2927, 2859, 1732, 1461, 1259, 1161, 1066, 1024, 773 cm^{-1}. MS, m/z (relative intensity): 41 (51), 42 (10), 43 (49), 44 (16), 55 (38), 56 (13), 57 (61), 70 (25), 71 (100), 129 (17), 207 (12), 342 (0.1). HRMS: *m/z* calcd. For $C_{24}H_{44}O_5$ +Na: 435.3086; found: 435.3086.

2-(Tetrahydro-2-furanyl) butanedioic acid 1,4-diisopropyl ester (3e). [14] Diisopropyl maleate (**1e**, 68.07 mg, 0.20 mmol) and DTBP (14.79 mg, 0.10 mmol) in THF (**2**, 10 mL). Yield of **3e**: 96 % (*syn* / *anti* = 64 / 32) (conversion: 100 %) (NMR, $CDCl_3$). Eluent for chromatography: hexane/ethyl acetate (50/1 → 0/1).

3e-*syn.* 32.80 mg (60 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 1.22 (d, *J* 6.4 Hz, 3 H), 1.226 (d, *J* 6.4 Hz, 3 H), 1.234 (d, *J* 6.4 Hz, 3 H), 1.25 (d, *J* 6.4 Hz, 3 H), 1.62-1.72 (m, 1 H), 1.83-1.96 (m, 3 H), 2.42 (dd, *J* 4.4, 16.4 Hz, 1 H), 2.71 (dd, *J* 10.0, 16.4 Hz, 1 H), 3.07 (ddd, *J* 4.4, 6.4, 10.0 Hz, 1 H), 3.73 (ddd, *J* 6.8, 7.2, 8.0 Hz, 1 H), 3.86 (ddd, *J* 6.4, 6.8, 8.0 Hz, 1 H), 4.08 (ddd, *J* 6.8, 6.8, 6.8 Hz, 1 H), 5.00 (dq, *J* 6.4, 6.4 Hz, 1 H), 5.05 (dq, *J* 6.4, 6.4 Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 21.7, 21.76 (×2), 21.79, 25.7, 28.2, 32.7, 46.1, 67.97, 68.04, 68.3, 78.8, 171.4, 172.1 ppm. IR (KBr disk): 2979, 2931, 2874, 1731, 1468, 1374, 1263, 1173, 1107, 1068 cm^{-1}. MS, m/z (relative intensity): 41 (29), 43 (54), 71 (100), 129 (9), 171 (15), 229 (0.1). HRMS: *m/z* calcd. For $C_{14}H_{24}O_5$ +Na: 295.1521; found: 295.1521.

3e-*anti.* 15.60 mg (29 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 1.216 (d, *J* 6.4 Hz, 3 H), 1.223 (d, *J* 6.4 Hz, 3 H), 1.24 (d, *J* 6.4 Hz, 3 H), 1.25 (d, *J* 6.4 Hz, 3 H), 1.69-1.80 (m, 1 H), 1.81-2.03 (m, 3 H), 2.66 (dd, *J* 5.2, 16.4 Hz, 1 H), 2.73 (dd, *J* 9.2, 16.4 Hz, 1 H), 2.83 (ddd, *J* 5.2, 8.4, 9.2 Hz, 1 H), 3.73 (ddd, *J* 7.2, 7.2, 7.2 Hz, 1 H), 3.80 (ddd, *J* 6.8, 6.8, 8.4 Hz, 1 H), 3.96 (ddd, *J* 7.2, 7.2, 7.2 Hz, 1 H), 4.99 (dq, *J* 6.4, 6.4 Hz, 1 H), 5.04 (dq, *J* 6.4, 6.4 Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 21.69, 21.73 (×2), 21.8, 25.6, 29.6, 34.0, 47.1, 67.8, 68.0, 68.1, 77.3, 171.6, 172.3 ppm. IR (KBr disk): 2979, 2937, 2874, 1731, 1468, 1374, 1262, 1172, 1108, 1067 cm^{-1}. MS, m/z (relative intensity): 41 (46), 42 (20), 43 (79), 45 (47), 71 (100), 129 (10), 171 (16), 213 (1). HRMS: *m/z* calcd. For $C_{14}H_{24}O_5$ +Na: 295.1521; found: 295.1521.

2-(Tetrahydro-2-furanyl) butanedioic acid 1,4-di-*tert*-butyl ester (3f). Di-*tert*-butyl maleate (**1f**, 45.59 mg, 0.20 mmol) and DTBP (14.75 mg, 0.10 mmol) in THF (**2**, 10 mL). Yield of **3f**: 96% (*syn* / *anti* = 67 / 29) (conversion: 100%) (NMR, $CDCl_3$). Eluent for chromatography: hexane/ethyl acetate (50/1 → 0/1).

3f-*syn.*.38.79 mg (65 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 1.44 (s, 9 H), 1.45 (s, 9 H), 1.58-1.74 (m, 1 H), 1.81-1.93 (m, 3 H), 2.34 (dd, *J* 4.4, 16.6 Hz, 1 H), 2.60 (dd, *J* 10.0, 16.6 Hz, 1 H), 2.99 (ddd, *J* 4.4, 6.4, 10.0 Hz, 1 H), 3.73 (ddd, *J* 6.8, 6.8, 7.2 Hz, 1H), 3.85 (ddd, *J* 6.4, 6.8, 8.0 Hz, 1 H), 4.07 (ddd, *J* 6.4, 6.4, 7.2 Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 25.8, 28.0 (×7), 33.4, 46.8, 68.3, 78.9, 80.5, 80.6, 171.2, 171.8 ppm. IR (KBr disk): 2978, 2931, 2874, 1730, 1457, 1392, 1367, 1257, 1150, 1068, 848 cm^{-1}. MS, m/z (relative intensity): 41 (100), 43 (9), 56 (40), 57 (32), 71 (37), 188 (1.4). HRMS: *m/z* calcd. For $C_{16}H_{28}O_5$ +Na: 323.1834; found: 323.1833.

3f-*anti.* 14.76 mg (25 %); colorless oil. ^{1}H-NMR ($CDCl_3$): δ =1.44 (s, 9 H), 1.45 (s, 9 H), 1.70-1.82 (m, 1 H), 1.82-2.02 (m, 3 H), 2.55-2.66 (m, 2 H), 2.72 (ddd, *J* 0.8, 6.4, 8.0 Hz, 1 H), 3.72 (ddd, *J* 6.8, 7.3, 8.8 Hz, 1 H), 3.79 (ddd, *J* 6.4, 6.8, 8.0 Hz, 1 H), 3.92 (ddd, *J* 6.0, 6.8, 7.3 Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 25.7, 27.99 (×3), 28.03 (×3), 29.7, 35.2, 48.0, 67.9, 79.1, 80.4, 80.7, 171.5, 172.1 ppm. IR (KBr disk): 2978, 2931, 2869, 1729, 1458, 1367, 1257, 1147, 1067, 848 cm^{-1}. MS, m/z (relative intensity): 40 (11), 41 (100), 44 (12), 55 (17), 56 (39), 57 (33), 71 (38), 118 (5), 171 (7), 188 (1.5). HRMS: *m/z* calcd. For $C_{16}H_{28}O_5$ +Na: 323.1834; found: 323.1833.

Acknowledgements

 ©AUTHOR(S)

This work was supported by JSPS KAKENHI Grant Number JP17K05953 (A.O.) and Mayekawa Houonkai Foundation (M. H.). We thank Professor Masako Takada for the use of her Gaussian system.

Supplementary Material

Experimental details, structure and energy of the stable conformers of maleic acid and its dialkyl esters (**1a**–**g**) obtained by DFT calculations, and ^{1}H NMR and ^{13}C NMR spectra of **3b–f-*syn*/*anti***.

References and Notes

1. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, **1986**. https://doi.org/10.1002/9783527615230
2. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**.

3. Zard, S. Z. *Radical Reactions in Organic Synthesis*, Oxford University Press, Oxford, **2003**.

4. Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*, Elsevier, Oxford, **2004**.

5. Paquette, L. A.; Pansegrau, P. D.; Wiederman, P. E.; Springer, J. P. *J. Org. Chem.* **1988**, *53*, 1461-1466. https://doi.org/10.1021/jo00242a021
6. Hoffmann, N., *Tetrahedron: Asymmetry* **1994**, *5*, 879–886. https://doi.org/10.1016/S0957-4166(00)86239-4
7. Mase, N.; Watanabe, Y.; Toru, T., *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2957–2965. https://doi.org/10.1246/bcsj.71.2957
8. Pyne, S. G.; Schafer, K., *Tetrahedron* **1998**, *54*, 5709–5720. https://doi.org/10.1016/S0040-4020(98)00259-2
9. Graalfs, H.; Fröhlich, R.; Wolff, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 1057–1073. https://doi.org/10.1002/(SICI)1099-0690(199905)1999:5<1057::AID-EJOC1057>3.0.CO;2-A
10. Campari, G.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1891–1906. https://doi.org/10.1016/S0957-4166(00)00138-5
11. Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822–7829. https://doi.org/10.1021/jo049156y
12. Hayakawa, M.; Shimizu, R.; Omori, H.; Shirota, H.; Uchida, K.; Mashimo, H.; Xu, H.; Yamada, R.; Niino, S.; Wakame, Y.; Liu, C.; Aoyama, T.; Ouchi, A. *Tetrahedron* **2020**, *76*, 131557. https://doi.org/10.1016/j.tet.2020.131557
13. Rohe, S.; Morris, A. O.; McCallum, T.; Barriault, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 15664–15669. https://doi.org/10.1002/anie.201810187
14. Papadopoulos, G. N.; Kokotou, M. G.; Spiliopoulou, N.; Nikitas, N. F.; Voutyritsa, E.; Tzaras, D. I.; Kaplaneris. N.; Kokotos, C. G. *ChemSusChem* **2020**, *13*, 5934–5944. https://doi.org/10.1002/cssc.202001892
15. Fan, X.-Z.; Rong, J.-W.; Wu, H.-L.; Zhou, Q.; Deng, H.-P.; Tan, J. D.; Xye, C.-W.; Wu, L.-Z.; Tao, H.-R.; Wu, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 8514–8518.

 ©**AUTHOR(S)**

https://doi.org/10.1002/anie.201803220
16. Kuang, Y.; Wang, K.; Shi, X.; Huang, X.; Meggers, E.; Wu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 16859–16863.
https://doi.org/10.1002/anie.201910414
17. Stable conformations were calculated by B3LYP/6-31++G(d,p) using Gaussian 16; Gaussian 16, Revision A.03, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

18. See Supplementary Material.
19. Kim, J.; Han, S.-P.; Kim, J.; Kim, Y.-J. *Bull. Korean Chem. Soc.* **2011**, *32*, 915-920.
https://doi.org/10.5012/bkcs.2011.32.3.915
20. Kaplaneris. N.; Bisticha, A.; Papadopoulos, G. N.; Limnios, D.; Kokotos, C. G. *Green Chem.* **2017**, *19*, 4451-4456.
https://doi.org/10.1039/C7GC01903C

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)