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Tandem conjugate addition–aldol cyclization of 2-formylbenzylidenemalonate with ether radicals by the mediation of dimethylzinc

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ABSTRACT

The chemoselective radical conjugate addition reaction of THF or 4,4,5,5-tetramethyl-1,3-dioxolane with 2-formylbenzylidenemalonate gave tandem conjugate addition–aldol cyclization product in one pot. The radical tandem reaction was extended to the asymmetric reaction using bis(8-phenylmenthyl) 2-formylbenzylidenemalonate as a chiral Michael acceptor to provide an enantioenriched indane derivative.

1. Introduction

Our recent report[1] indicates that carbon-centered radicals, generated directly from ethers such as THF (**1**) or acetals by the action of dimethylzinc and air,[2–4] undergo a chemoselective conjugate addition reaction[5] with 4-formyl- or 4-iminobenzylidenemalonate **2** to give the corresponding conjugate addition products **3a** with the formyl[6] or imino[7] group intact (Scheme 1).[8] We have also reported diastereoface-selective addition of acetal radicals to chiral *N*-sulfinyl imines providing a reasonably efficient methodology for the asymmetric synthesis of oxygenated chiral amine derivatives.[9] With a view of widening the applicability of the radical reaction, we investigated the conjugate addition of carbon-centered ether radicals to Michael acceptors having a pendant formyl group. Sequential conjugate addition and intramolecular aldol trapping of the resulting carbon-centered radical with the formyl group produced a cyclic indane skeleton in a single operation.[10,11] We describe herein the tandem conjugate addition of ether radicals to 2-formylbenzylidenemalonate and aldol cyclization[12,13] giving an indane skeleton, and also application to an asymmetric reaction.

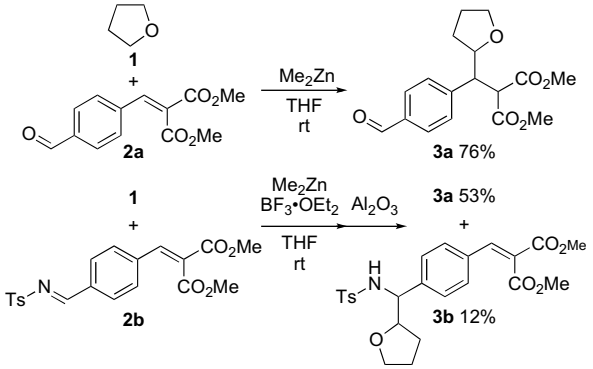
2. Results and discussions

2.1. Sequential conjugate addition–aldol cyclization

Chemoselective conjugate addition of **1** to 2-formylbenzylidenemalonate **4** would produce radical **6** or anion intermediate **8** that may attack the internal formyl carbon to give cyclized indanol skeleton **5** via **7** or **9** in a one pot sequence (Scheme 2).

Requisite benzylidenemalonate **4** was prepared in 59% yield in one step by heating a mixture of phthalaldehyde (**10**) and dimethyl malonate (**11**) in benzene under Knoevenagel conditions (Scheme 3). The reaction of **4** with THF (**1**) proceeded smoothly at room temperature for 17 h to give a mixture of four diastereomers **5** in 79% yield. The diastereomers of **5** were separated by silica gel column chromatography (ethyl acetate/toluene 1/5).

Similarly, the reaction of 4,4,5,5-tetramethyl-1,3-dioxolane (**12**) with **4** gave a 3/1 mixture of diastereomers **13** in 53% yield (Scheme 4). The diastereomers of **13** were separated by silica gel column chromatography (ethyl acetate/hexane 1/4). Recrystallization of the major diastereomer from ethyl acetate/hexane gave colorless cubes, whose X-ray diffraction undoubtedly determined the relative configuration as shown.[14] Triethylsilane reduction of the acetal and benzylic moieties of **13** gave tricyclic lactone **14** as a single diastereomer in 61% yield. The stereochemistry was tentatively



Scheme 1. Chemoselective conjugate addition of THF radical.

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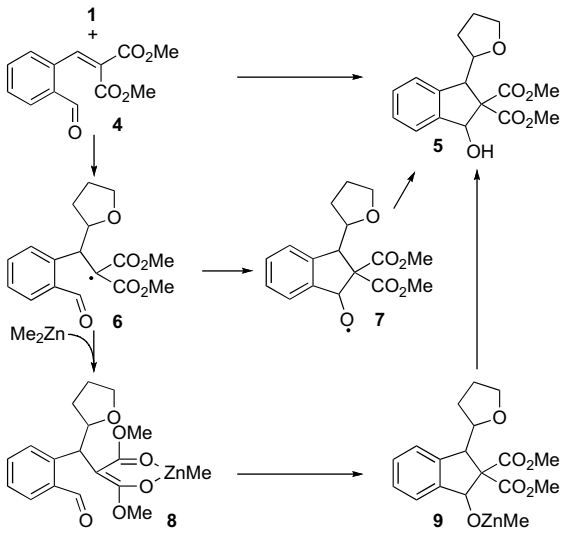
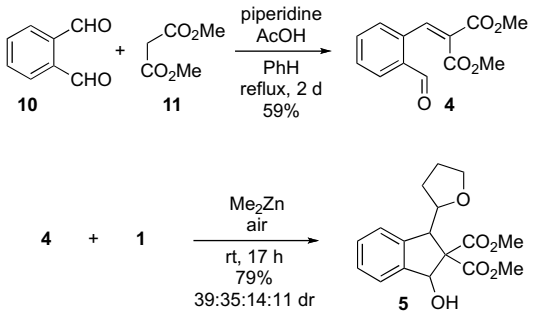
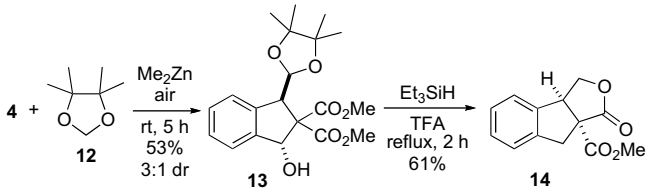


Scheme 2. Possible tandem radical conjugate addition–aldol cyclization.



Scheme 3. Synthesis and tandem reaction of 2-formylbenzylidenemalonate.

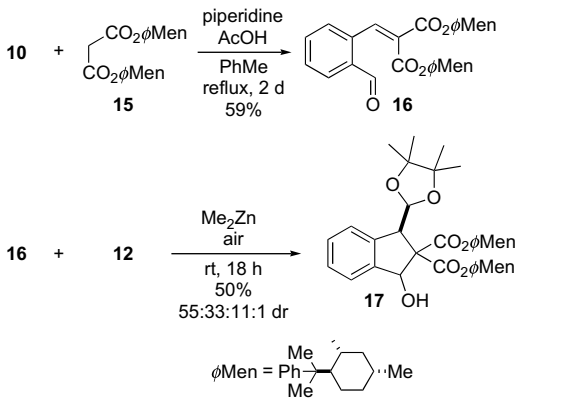
assigned based on the preferred *cis*-bicyclo[3.3.0] skeleton. Thus, two-step conversion of **4** to tricyclic lactone **14** evidently indicated the usefulness of the chemoselective radical conjugate addition of ether radicals and tandem radical conjugate addition–aldol cyclization. It is also interesting to find that 4,4,5,5-tetramethyl-1, 3-dioxolane (**12**) works as a hydroxymethyl equivalent in this two-step conversion.



Scheme 4. Tandem conjugate addition–aldol cyclization.

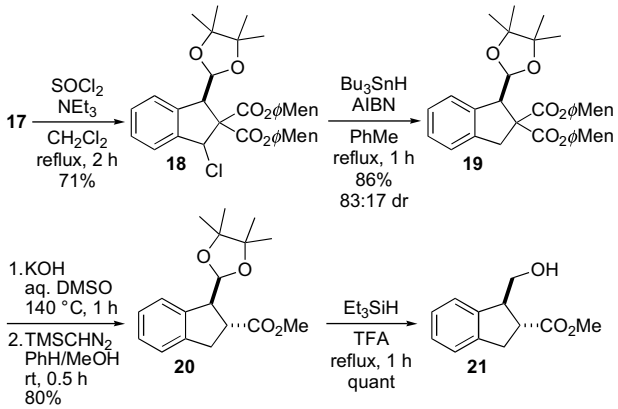
2.2. Asymmetric reaction of bis(8-phenylmenthyl) benzylidenemalonate

Extension to an asymmetric reaction was the next challenge. Bis(L-8-phenylmenthyl) 2-formylbenzylidenemalonate (**16**) was prepared in 59% yield by the condensation of **10** with bis(L-8-phenylmenthyl) malonate (**15**)[1] under Knoevenagel conditions in refluxing toluene for 2 days (Scheme 5). Tandem conjugate addition–aldol cyclization of acetal **12** was mediated by 6 equiv of dimethylzinc at room temperature for 18 h to give a 55/33/11/1 mixture of four diastereomers **17** in 50% yield.



Scheme 5. Synthesis and tandem reaction of chiral bis(8-phenylmenthyl) 2-formylbenzylidenemalonate.

Manipulation of **17** was not as easy as that of **13** because of the bulkiness of the 8-phenylmenthyl ester moieties. The hydroxy group of **17** was first reduced to give **19** in reasonably high yield by the tributyltin hydride reduction of chloride **18** (Scheme 6). The facial selectivity of the radical addition reaction was determined at this stage to be 83/17 by the integration area of ^{1}H NMR signals at 3.64 and 3.84 ppm, respectively, where one of the benzylic methylene protons of each isomer appears. Hydrolysis of phenylmenthyl ester with potassium hydroxide and subsequent methylation with trimethylsilyldiazomethane gave **20** in 80% yield. Triethylsilane reduction in trifluoroacetic acid gave chiral indane derivative **21** quantitatively. Lactonization failed to proceed because of the trans-configuration of the hydroxymethyl and ester groups in **21**. The absolute configuration was tentatively assigned as shown based on the analogy to the diastereoface differentiating radical conjugate addition of simple 8-phenylmenthyl benzylidenemalonate.[1]



Scheme 6. Conversion of tandem cyclization product **17** to **21**.

3. Summary

In summary, we have developed tandem radical conjugate addition–aldol cyclization reaction of benzylidenemalonate. In this reaction, two carbon–carbon bonds could be made in one pot, and the addition and cyclization product was transformed into tricyclic lactone. Furthermore, using 8-phenylmenthyl ester, radical tandem reaction was extended to an asymmetric reaction, which enables the formation of an enantioenriched indane skeleton.

4. Experimental section

4.1. General

Although a 1.0 M solution of dimethylzinc in hexane is easily handled and we have not experienced the spontaneous combustion, dimethylzinc is pyrophoric and there is potential danger of ignition.

All melting points were uncorrected. IR spectra were expressed in cm^{-1}. All ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured in $CDCl_3$, except for **17**, whose ^{13}C NMR spectrum was measured in C_6D_6. ^{13}C NMR peak multiplicity assignments were made based on DEPT. Chemical shifts and coupling constants were presented in part per million (δ) and hertz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Column chromatography was carried out with silica gel. A hexane solution of dimethylzinc was purchased from Kanto chemical Co., Inc. 4,4,5,5-Tetramethyl-1,3-dioxolane (**12**) was prepared according to the reported procedure.[15] Before introduction to a reaction mixture, air was passed through a drying tube filled with NaOH.

4.2. Procedure for the dimethylzinc-mediated tandem radical conjugate addition–aldol cyclization of ethers to alkylidenemalonates

*4.2.1. Dimethyl 2-(2-formylbenzylidene)malonate (**4**)*

A mixture of dimethyl malonate (**11**) (211 mg, 1.6 mmol), phthaldialdehyde (**10**) (430 mg, 3.2 mmol), piperidine (0.01 mL), and acetic acid (0.02 mL) in toluene (5 mL) was stirred at reflux for 48 h under Dean–Stark conditions. The reaction mixture was cooled to room temperature, diluted with benzene (20 mL), and then washed successively with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give pale yellow amorphous oil, which was purified by column chromatography (ethyl acetate/hexane 1/4) to give amorphous white solid (234 mg, 59%). Recrystallization from ethyl acetate gave **4** as colorless needles of mp 70–71 °C. R_f=0.40 (ethyl acetate/hexane 1/3). ^1H NMR: 3.64 (s, 3H), 3.89 (s, 3H), 7.41 (m, 1H), 7.57–7.62 (m, 2H), 7.90 (m, 1H), 8.43 (s, 1H), 10.2 (s, 1H). ^{13}C NMR: 52.3 (CH_3), 52.7 (CH_3), 129.0 (CH), 129.9 (CH), 131.1 (C), 132.9 (CH), 133.8 (CH), 134.0 (C), 135.3 (C), 142.8 (CH), 164.0 (C), 166.0 (C) 191.7 (CH). MS *m*/*z*: 249 (M+1), 248 (M^+), 189 (M−CO_2Me). IR (KBr): 2955, 1732, 1634, 1259, 1199, 1022, 762. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.82; H, 4.77.

*4.2.2. Dimethyl 1-hydroxy-3-(tetrahydrofuran-2-yl)indane-2,2-dicarboxylate (**5**)*

A dry three-neck round bottom flask was equipped with a stir bar and dimethyl 2-(2-formylbenzylidene)malonate (**4**) (248 mg, 1.0 mmol). The flask was filled with argon by evacuation and refilled three times. THF (20 mL, 250 mmol) was added at room temperature. To the stirred solution was added a 1.0 M hexane solution of dimethylzinc (6.0 mL, 6.0 mmol). The argon source was replaced with a NaOH drying tube and air was injected into the reaction mixture via an air bubbler at a rate of 0.5 mL/h. The reaction mixture was stirred for 17 h followed by quenching with saturated ammonium chloride (20 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give colorless oil. Column chromatography (ethyl acetate/toluene 1/8) gave a 39/35/14/11 diastereoisomeric mixture of **5** (252 mg, 79%) as colorless oil. The diastereomeric ratio of **5** was determined by the integration area of ^1H NMR signals at 6.05, 5.92, 5.40, and 4.91 ppm. The four diastereomers of **5** were carefully separated at most on 10 mg scale by silica gel column chromatography (ethyl acetate/toluene 1/5) of the mixture obtained above.

The major isomer was isolated as colorless solid of mp 142–143 °C. R_f=0.36 (ethyl acetate/toluene 1/5). ^1H NMR: 1.58 (m, 1H), 1.72 (m, 1H), 1.96–2.03 (m, 2H), 2.64 (d, *J*=5.8, 1H), 3.36 (m, 1H), 3.55 (m, 1H), 3.69 (s, 3H), 3.82 (s, 3H), 3.95 (d, *J*=4.0, 1H), 4.25 (ddd, *J*=4.0, 7.0, 7.0, 1H), 6.05 (d, *J*=5.8, 1H), 7.24–7.38 (m, 4H). ^{13}C NMR: 25.6 (CH_2), 28.9 (CH_2), 52.5 (CH), 52.6 (CH_3), 52.7 (CH_3), 68.2 (CH_2), 70.6 (C), 78.3 (CH), 78.9 (CH), 123.8 (CH), 125.7 (CH), 127.7 (CH), 128.0 (CH), 139.9 (C), 142.3 (C), 170.1 (C), 170.3 (C). IR (KBr): 3418, 2962, 1736, 1265, 1203, 1018, 771. FABMS *m*/*z*: 321 (M+H). FABHRMS *m*/*z*: 321.1335 (calcd for $C_{17}H_{21}O_6$: 321.1338).

The second major isomer was isolated as colorless solid of mp 109–111 °C R_f=0.25 (ethyl acetate/toluene 1/5). ^1H NMR: 1.45 (m, 1H), 1.71–1.83 (m, 3H), 3.06 (d, *J*=6.7, 1H), 3.70 (m, 1H), 3.72 (s, 3H), 3.78 (s, 3H), 3.80 (m, 1H), 4.06 (ddd, *J*=6.3, 6.3, 8.6, 1H), 4.22 (d, *J*=6.3, 1H), 5.92 (d, *J*=6.7, 1H), 7.23–7.32 (m, 3H), 7.38 (m, 1H). ^{13}C NMR: 25.9 (CH_2), 28.3 (CH_2), 52.6 (CH_3), 52.8 (CH_3), 52.9 (CH), 67.9 (CH_2), 68.7 (C), 78.2 (CH), 78.5 (CH), 123.8 (CH), 125.4 (CH), 128.0 (CH), 128.6 (CH), 139.7 (C), 141.6 (C), 170.0 (C), 170.2 (C). IR (KBr): 3370, 2953, 2928, 1732, 1435, 1229, 1063, 758. FABMS *m*/*z*: 321 (M+H). FABHRMS *m*/*z*: 321.1338 (calcd for $C_{17}H_{21}O_6$: 321.1338).

The third major isomer was isolated as colorless oil. R_f=0.42 (ethyl acetate/toluene 1/5). ^1H NMR: 1.74 (m, 1H), 1.81 (m, 1H), 2.05 (m, 1H), 2.12 (m, 1H), 3.31 (m, 1H), 3.67 (m, 1H), 3.67 (s, 3H), 3.79 (s, 3H), 3.88 (d, *J*=2.7, 1H), 4.89 (d, *J*=12, 1H), 4.91 (m, 1H), 5.40 (d, *J*=12, 1H), 7.23–7.35 (m, 3H), 7.47 (d, *J*=7.3, 1H). ^{13}C NMR: 25.7 (CH_2), 28.9 (CH_2), 52.4 (CH_3), 52.9 (CH), 53.0 (CH_3), 68.3 (C), 68.4 (CH_2), 76.6 (CH), 77.9 (CH), 124.9 (CH), 126.0 (CH), 128.3 (CH), 128.4 (CH), 139.1 (C), 143.7 (C), 168.6 (C), 170.6 (C). IR (neat): 3379, 2955, 1735, 1435, 1273, 1227, 1057, 756. FABMS *m*/*z*: 321 (M+H). FABHRMS *m*/*z*: 321.1350 (calcd for $C_{17}H_{21}O_6$: 321.1338).

The minor isomer was isolated as colorless oil. R_f=0.36 (ethyl acetate/toluene 1/5). ^1H NMR: 1.54–2.04 (m, 4H), 3.35 (m, 1H), 3.53 (m, 1H), 3.69 (s, 3H), 3.82 (s, 3H), 3.94 (d, *J*=3.7, 1H), 4.24 (m, 1H), 4.91 (d, *J*=3.7, 1H), 5.47 (d, *J*=3.1, 1H), 7.27–7.47 (m, 4H). ^{13}C NMR: 28.9, 30.1, 52.6, 53.1, 54.4, 66.0, 68.3, 79.4, 79.7, 122.7, 125.0, 125.1, 129.0, 142.0, 142.3, 167.4, 170.4. IR (neat): 3369, 2952, 2926, 1738, 1462, 1435, 1242, 1207, 1055, 756. FABMS *m*/*z*: 321 (M+H). FABHRMS *m*/*z*: 321.1335 (calcd for $C_{17}H_{21}O_6$: 321.1338).

*4.2.3. Dimethyl 1-hydroxy-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)indane-2,2-dicarboxylate (**13**)*

To a solution of **4** (248 mg, 1 mmol) in 4,4,5,5-tetramethyl-1,3-dioxolane (**12**) (36 mL, 250 mmol) was added a 1.0 M hexane solution of dimethylzinc (6.0 mL, 6.0 mmol), and the whole was stirred for 5 h at room temperature. The same work-up as for **5** gave colorless oil, which was purified by column chromatography (ethyl acetate/hexane 1/5) to give a 3/1 diastereoisomeric mixture of **13** (200 mg, 53%) as colorless oil. The diastereomeric ratio of **13** was determined by the integration area of ^1H NMR signals at 5.31 and 5.46 ppm. The two diastereomers were separated in at most 10 mg scale by column chromatography (ethyl acetate/hexane 1/4) of the mixture obtained above.

The major isomer was isolated as colorless solid, which was recrystallized from ethyl acetate/hexane to give colorless cubes of mp 140–141 °C, suitable for X-ray diffraction analysis. The relative configuration was confirmed to be (1*RS*, 3*RS*) by X-ray diffraction (Fig. 1). R_f=0.27 (ethyl acetate/hexane 1/3). ^1H NMR: 0.65 (s, 3H), 0.91 (s, 3H), 1.05 (s, 3H), 1.14 (s, 3H), 2.89 (d, *J*=6.1, 1H), 3.68 (s, 3H), 3.82 (s, 3H), 3.97 (d, *J*=4.6, 1H), 5.31 (d, *J*=4.6, 1H), 6.08 (d, *J*=6.1, 1H), 7.23–7.29 (m, 2H), 7.33–7.39 (m, 2H). ^{13}C NMR: 22.2 (CH_3), 22.3 (CH_3), 23.6 (CH_3), 23.7 (CH_3), 52.5 (CH_3), 52.8 (CH_3), 53.1 (CH), 69.0 (C), 79.2 (CH), 82.0 (C), 82.7 (C), 98.6 (CH), 123.1 (CH), 127.5 (CH), 127.8 (CH), 127.9 (CH), 138.3 (C), 141.8 (C), 169.9 (C), 170.0 (C). FABMS *m*/*z*: 379 (M+H). IR (KBr): 3549, 2955, 1736, 1265, 1218,

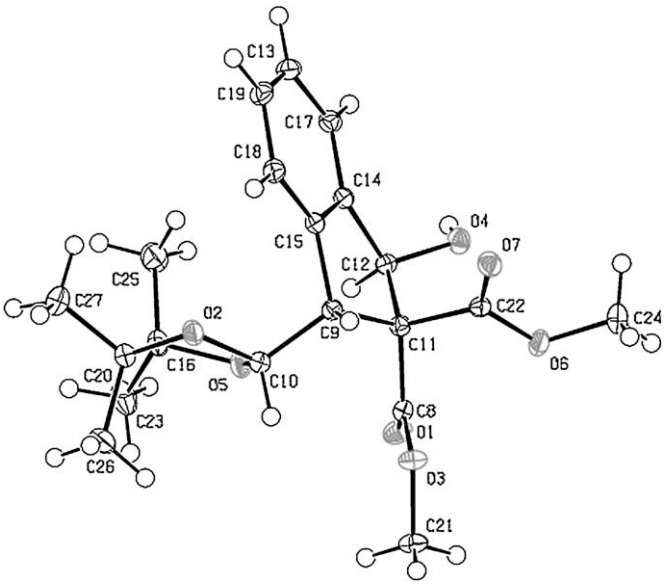


Figure 1. ORTEP (50% probability) of the major isomer of **13**.

1134. Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.27; H, 6.74.

The minor isomer was isolated as colorless oil. R_f=0.23 (ethyl acetate/hexane 1/3). ^{1}H NMR: 0.62 (s, 3H), 1.09 (s, 3H), 1.12 (s, 3H), 1.21 (s, 3H), 3.66 (s, 3H), 3.80 (s, 3H), 3.95 (d, *J*=4.6, 1H), 4.72 (d, *J*=9.2, 1H), 5.46 (d, *J*=9.2, 1H), 5.87 (d, *J*=4.6, 1H), 7.27–7.29 (m, 2H), 7.43–7.45 (m, 2H). ^{13}C NMR: 22.1 (CH_3), 22.7 (CH_3), 23.3 (CH_3), 23.8 (CH_3), 52.4 (CH_3), 53.1 (CH_3), 53.6 (CH), 66.8 (C), 78.4 (CH), 82.4 (C), 82.7 (C), 98.5 (CH), 124.7 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 139.2 (C), 142.9 (C), 168.9 (C), 170.0 (C). IR (neat): 3549, 2955, 1736, 1265, 1218, 1134. FABMS *m*/*z*: 379 (M+H). FABHRMS *m*/*z*: 379.1755 (calcd for $C_{20}H_{27}O_7$: 379.1757).

*4.2.4. Methyl 1-oxo-3,3a,8,8a-tetrahydro-1H-indeno[2,1-c]furan-8a-carboxylate (**14**)*

A mixture of **13** (71 mg, 0.18 mmol) and triethylsilane (0.31 mL, 2.0 mmol) in TFA (3 mL) was stirred under reflux for 2 h. The mixture was cooled to room temperature and then concentrated to give colorless oil (67 mg). Silica gel column chromatography (ethyl acetate/hexane 1/5) gave **14** (25.6 mg, 61%) as colorless solid, which was recrystallized from $CHCl_3$ to give colorless needles of mp 103–104 °C. R_f=0.45 (ethyl acetate/hexane 1/3). ^{1}H NMR: 3.61 (d, *J*=17, 1H), 3.77 (d, *J*=17, 1H), 3.85 (s, 3H), 4.26 (d, *J*=6.4, 1H), 4.54 (d, *J*=8.9, 1H), 4.83 (dd, *J*=6.4, 8.9, 1H), 7.22–7.30 (m, 4H). ^{13}C NMR: 39.2 (CH_2), 51.4 (CH), 53.3 (CH_3), 60.2 (C), 72.7 (CH_2), 123.7 (CH), 124.9 (CH), 128.0 (CH), 128.8 (CH), 140.1 (C), 140.3 (C), 169.3 (C), 175.8 (C). IR (KBr): 1774, 1736, 1257, 1150. MS *m*/*z*: 233 (M+1), 232 (M^+), 128 (M−CO_2H). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C 67.04; H, 5.14.

4.3. Asymmetric reaction of bis(8-phenylmenthyl) 2-formylbenzylidenemalonate

*4.3.1. Bis((1R,2R,5S)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 2-(2-formylbenzylidene)malonate (**16**)*

A mixture of bis((1*R*,2*S*,5*R*)-5-methyl-2-[2-phenylpropan-2-yl]cyclohexyl) malonate (**15**)[1] (870 mg, 1.6 mmol), phthaldialdehyde (**10**) (430 mg, 3.2 mmol), piperidine (0.01 mL), and acetic acid (0.02 mL) in toluene (5 mL) was stirred at reflux for 48 h under Dean–Stark conditions. The reaction mixture was cooled to room temperature, diluted with toluene (20 mL), and then washed successively with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give pale yellow amorphous oil, which was purified by column chromatography (ethyl acetate/hexane 1/16) to give **16** (609 mg, 59%) as white solid of mp 73–75 °C and $[\alpha]_D^{25}$ −18.2 (*c* 1.00, $CHCl_3$). R_f=0.40 (ethyl acetate/hexane 1/16). ^{1}H NMR: 0.35 (m, 1H), 0.62 (m, 1H), 0.73–1.73 (m, 13H), 0.76 (d, *J*=6.8, 3H), 0.93 (d, *J*=6.8, 3H), 1.07 (s, 3H), 1.09 (s, 3H), 1.25 (s, 3H), 1.38 (s, 3H), 2.08 (m, 1H), 4.73 (ddd, *J*=4.0, 11, 11, 1H), 5.00 (ddd, *J*=4.0, 11, 11, 1H), 6.89 (m, 1H), 7.08–7.33 (m, 10H), 7.42 (s, 1H), 7.47–7.57 (m, 2H), 7.87 (d, *J*=7.3, 1H), 9.97 (s, 1H). ^{13}C NMR: 21.6 (CH_3), 21.7 (CH_3), 23.9 (CH_3), 25.4 (CH_3), 26.6 (CH_2), 27.0 (CH_2), 27.7 (CH_3), 28.6 (CH_3), 31.0 (CH), 31.3 (CH), 34.2 (CH_2), 34.5 (CH_2), 39.7 (C), 39.9 (C), 40.5 (CH_2), 41.6 (CH_2), 50.3 (CH), 50.5 (CH), 76.0 (CH), 76.6 (CH), 124.9 (CH), 125.1 (CH), 125.5 (CH), 125.6 (CH), 127.8 (CH), 128.0 (CH), 129.4 (CH), 129.9 (CH), 130.6 (CH), 130.7 (C), 133.5 (CH), 133.6 (C), 136.3 (C), 140.2 (CH), 150.7 (C), 151.5 (C), 162.3 (C), 164.4 (C), 191.1 (CH). IR (KBr): 2955, 2924, 1728, 1705, 1258, 1219, 1057, 764, 702. FABMS *m*/*z*: 649 (M+H). FABHRMS *m*/*z*: 649.3890 (calcd for $C_{43}H_{53}O_5$: 649.3893).

*4.3.2. Bis((1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-hydroxy-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)indane-2,2-dicarboxylate (**17**)*

To a solution of **16** (648 mg, 1.0 mmol) in 4,4,5,5-tetramethyl-1,3-dioxolane (**12**) (36 mL, 250 mmol) was added a 1.0 M hexane solution of dimethylzinc (6.0 mL, 6.0 mmol), and the whole was stirred for 18 h at room temperature. The same work-up as for **5** gave colorless oil, which was purified by column chromatography (ethyl acetate/hexane 1/5) to give a 55/33/11/1 diastereoisomeric mixture of **17** (388 mg, 50%) as colorless solid of mp 73–79 °C and $[\alpha]_D^{25}$ −16.0 (*c* 1.00, $CHCl_3$). The diastereomeric ratio of **17** was determined by the integration area of ^{1}H NMR signals at 2.74, 3.79, 3.36, and 2.85 ppm.

The 55/33/11/1 diastereomeric mixture of **17**: R_f=0.38 (ethyl acetate/hexane 1/16). ^{1}H NMR: 0.07 (s, 0.03H), 0.23 (s, 0.99H), 0.27 (s, 0.33H), 0.32 (s, 1.65H), 0.23–2.47 (m, 43H), 2.61 (d, *J*=8.3, 0.01H), 2.74 (d, *J*=5.8, 0.55H), 2.78 (d, *J*=5.5, 0.11H), 2.85 (d, *J*=1.9, 0.01H), 3.36 (d, *J*=3.1, 0.11H), 3.79 (d, *J*=2.7, 0.33H), 3.91 (d, *J*=3.1, 0.55H), 4.76–5.12 (m, 2H), 4.92 (d, *J*=12, 0.33H), 5.40 (d, *J*=3.1, 0.11H), 5.42 (d, *J*=12, 0.33H), 5.59 (d, *J*=1.9, 0.01H), 5.69 (d, *J*=8.3, 0.01H), 5.74–5.76 (m, 1.1H), 6.01 (d, *J*=5.5, 0.11H), 6.14 (d, *J*=2.7, 0.33H), 6.92–7.47 (m, 14H). ^{13}C NMR (C_6D_6), *major*: 21.8 (CH_3), 22.04 (CH_3), 22.3 (CH_3), 22.6 (CH_3), 23.1 (CH_3), 24.1 (CH_3), 24.5 (CH_3), 27.6 (CH_2), 27.77 (CH_2), 30.3 (CH_3), 31.21 (CH), 31.3 (CH_3), 31.5 (CH), 34.3 (CH_2), 34.67 (CH_2), 40.5 (C), 40.6 (C), 41.85 (CH_2), 42.4 (CH_2), 50.59 (CH), 50.77 (CH), 52.4 (CH), 70.3 (C), 76.9 (CH), 77.5 (CH), 79.9 (CH), 82.29 (C), 82.6 (C), 99.1 (CH), 124.0 (CH), 125.6 (CH), 125.8 (CH), 126.2 (CH), 126.3 (CH), 127.2 (CH), 127.9 (CH), 128.22 (CH), 128.36 (CH), 128.44 (CH), 139.1 (C), 144.0 (C), 150.3 (C), 150.9 (C), 169.06 (C), 169.9 (C); *second major*: 21.9 (CH_3), 22.00 (CH_3), 22.14 (CH_3), 22.97 (CH_3), 22.99 (CH_3), 24.00 (CH_3), 26.7 (CH_3), 27.4 (CH_2), 27.5 (CH_3), 28.0 (CH_2), 30.3 (CH_3), 31.15 (CH), 31.3 (CH_3), 31.7 (CH), 34.9 (CH_2), 35.1 (CH_2), 40.3 (C), 40.9 (C), 41.77 (CH_2), 42.1 (CH_2), 50.2 (CH), 51.3 (CH), 53.1 (CH), 69.4 (C), 76.8 (CH), 77.6 (CH), 78.1 (CH), 83.0 (C), 98.3 (CH), 125.2 (CH), 125.7 (CH), 125.88 (CH), 126.02 (CH), 126.4 (CH), 127.8 (CH), 128.2 (CH), 128.30 (CH), 128.40 (CH), 128.5 (CH), 139.17 (C), 145.7 (C), 150.2 (C), 150.8 (C), 167.2 (C), 169.5 (C); *third major*: 21.7 (CH_3), 21.95 (CH_3), 22.11 (CH_3), 22.9 (CH_3), 23.0 (CH_3), 24.01 (CH_3), 24.3 (CH_3), 26.5 (CH_3), 26.9 (CH_2), 27.1 (CH_3), 27.81 (CH_2), 30.4 (CH_3), 31.1 (CH), 31.5 (CH), 34.2 (CH_2), 34.69 (CH_2), 39.9 (C), 40.7 (C), 41.5 (CH_2), 41.77 (CH_2), 50.2 (CH), 50.6 (CH), 51.0 (CH), 70.9 (C), 76.8 (CH), 77.2 (CH), 79.2 (CH), 82.0 (C), 82.32 (C), 99.3 (CH), 123.2 (CH), 125.8 (CH), 125.93 (CH), 126.3 (CH), 127.0 (CH), 127.5 (CH), 127.7 (CH), 128.30 (CH), 128.43 (CH), 128.6 (CH), 139.9 (C), 144.1 (C), 150.9 (C), 151.6 (C), 169.1 (C), 169.5 (C). IR (KBr): 3410, 2955, 1728, 1450, 1373, 1250, 1211, 1157, 1134, 1087, 972, 764, 702.

FABMS *m*/*z*: 801 (M+Na). FABHRMS *m*/*z*: 801.4721 (calcd for $C_{50}H_{66}O_7Na$: 801.4706).

4.3.3. Bis((1S,2R,5S)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-chloro-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)indane-2,2-dicarboxylate (**18**)

To a solution of **17** (222 mg, 0.28 mmol) and triethylamine (0.12 mL) in dry dichloromethane (1 mL) was added thionyl chloride (0.04 mL, 0.6 mmol) dropwise at 0 °C. After stirring for 0.5 h at 0 °C, the mixture was heated under reflux for 2 h. The mixture was cooled to 0 °C and poured into ice water. The aqueous layer was extracted with chloroform, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give dark brown oil (276 mg), which was purified by column chromatography (ethyl acetate/hexane 1/20) to give a 71/15/8/6 diastereoisomeric mixture of **18** (167 mg, 71%) as yellow solid of $[\alpha]_D^{25}$ −25.2 (*c* 1.00, $CHCl_3$). R_f=0.50 (ethyl acetate/hexane 1/16). The diastereomeric ratio of **18** was determined by the integration area of ^{1}H NMR signals at 6.08, 5.65, 6.10, and 5.72 ppm.

^{1}H NMR: 0.07 (s, 0.5H), 0.16 (s, 0.2H), 0.21 (s, 0.2H), 0.22 (s, 2.1H), 0.50–2.55 (m, 43H), 2.97 (d, *J*=7.0, 0.15H), 3.24 (d, *J*=2.8, 0.06H), 3.51 (d, *J*=7.1, 0.08H), 3.95 (d, *J*=2.8, 0.71H), 4.75–5.26 (m, 2H), 5.28 (d, *J*=7.0, 0.15H), 5.35 (d, *J*=2.8, 0.06H), 5.37 (d, *J*=7.1, 0.08H), 5.65 (s, 0.15H), 5.72 (s, 0.06H), 5.78 (d, *J*=2.8, 0.71H), 6.08 (s, 0.71H), 6.10 (s, 0.08H), 6.49–7.52 (m, 14H). ^{13}C NMR, *major isomer*: 21.67 (CH_3), 21.70 (CH_3), 21.92 (CH_3), 22.24 (CH_3), 22.9 (CH_3), 23.0 (CH_3), 23.6 (CH_3), 27.3 (CH_2), 27.48 (CH_2), 31.0 (CH_3), 31.1 (CH_3), 31.2 (CH), 31.4 (CH), 34.2 (CH_2), 34.3 (CH_2), 40.35 (C), 40.43 (C), 41.4 (CH_2), 42.2 (CH_2), 50.46 (CH), 50.50 (CH), 53.1 (CH), 64.5 (CH), 69.2 (C), 77.3 (CH), 77.5 (CH), 82.4 (C), 82.6 (C), 98.4 (CH), 124.0 (CH), 125.2 (CH), 125.3 (CH), 125.4 (CH), 125.71 (CH), 125.73 (CH), 125.8 (CH), 127.58 (CH), 127.87 (CH), 128.0 (CH), 138.7 (C), 141.4 (C), 150.3 (C), 150.53 (C), 167.5 (C), 168.7 (C); *other isomers*: 21.2 (CH_3), 21.3 (CH_3), 21.51 (CH_3), 21.54 (CH_3), 21.61 (CH_3), 21.63 (CH_3), 21.87 (CH_3), 22.02 (CH_3), 22.04 (CH_3), 22.11 (CH_3), 22.13 (CH_3), 22.21 (CH_3), 22.3 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 22.7 (CH_3), 23.5 (CH_3), 23.8 (CH_3), 24.0 (CH_3), 27.51 (CH_2), 27.4 (CH_2), 29.5 (CH_2), 31.21 (CH), 31.30 (CH), 34.1 (CH_2), 34.4 (CH_2), 34.5 (CH_2), 34.6 (CH_2), 40.5 (C), 40.6 (C), 41.0 (CH_2), 41.3 (CH_2), 41.6 (CH_2), 42.0 (CH_2), 50.0 (CH), 50.1 (CH), 50.5 (CH), 50.9 (CH), 53.7 (CH), 66.0 (CH), 68.4 (C), 68.9 (C), 70.3 (C), 76.1 (CH), 77.2 (CH), 77.9 (CH), 81.7 (C), 82.2 (C), 100.8 (CH), 123.7 (CH), 125.0 (CH), 125.2 (CH), 125.5 (CH), 125.71 (CH), 127.64 (CH), 127.92 (CH), 137.7 (C), 139.9 (C), 140.0 (C), 150.50 (C), 150.6 (C), 151.1 (C), 165.5 (C), 169.2 (C). IR (KBr): 2924, 1737, 1732, 1258, 1199, 1163, 1134, 1078, 759, 700. FABMS *m*/*z*: 797 (M+H). FABHRMS *m*/*z*: 797.4527 (calcd for $C_{50}H_{66}O_6Cl$: 797.4548).

4.3.4. Bis((1S,2R,5S)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)indane-2,2-dicarboxylate (**19**)

A mixture of **18** (166 mg, 0.21 mmol), Bu_3SnH (0.14 mL, 0.5 mmol), and AIBN (7 mg, 0.03 mmol) in toluene (2 mL) was stirred under reflux for 1 h. Concentration gave colorless oil, which was purified by silica gel column chromatography to give an 83/17 diastereoisomeric mixture of **19** (77.3 mg, 86%) as colorless solid of mp 50–55 °C and $[\alpha]_D^{25}$ −19.4 (*c* 1.17, $CHCl_3$). R_f=0.55 (ethyl acetate/hexane 1/16). The diastereomeric ratio of **19** was determined by the integration area of ^{1}H NMR signals at 3.64 and 3.84 ppm.

^{1}H NMR, *major*: 0.47 (s, 3H), 0.65–2.17 (m, 43H), 3.37 (d, *J*=16, 1H), 3.64 (d, *J*=16, 1H), 4.05 (d, *J*=4.0, 1H), 4.82 (m, 1H), 4.98 (m, 1H), 5.72 (d, *J*=4.0, 1H), 7.07–7.38 (m, 14H); *minor*: 0.63 (s, 3H), 0.65–2.23 (m, 43H), 3.32 (d, *J*=16, 1H), 3.84 (d, *J*=16, 1H), 4.07 (d, *J*=4.6, 1H), 4.82 (m, 1H), 4.98 (m, 1H), 5.28 (d, *J*=4.6, 1H), 7.07–7.38 (m, 14H). ^{13}C NMR *major*: 21.7 (CH_3), 21.79 (CH_3), 22.3 (CH_3), 22.7 (CH_3), 23.18 (CH_3), 23.35 (CH_3), 23.38 (CH_3), 23.69 (CH_3), 27.4 (CH_2), 27.75 (CH_2), 30.8 (CH_3), 30.9 (CH_3), 31.13 (CH), 31.30 (CH), 34.2 (CH_2), 34.4 (CH_2), 39.2 (CH_2), 40.29 (C), 40.5 (C), 41.3 (CH_2), 41.4 (CH_2), 50.1 (CH), 50.3 (CH), 53.3 (CH), 64.78 (C), 76.69 (CH), 76.8 (CH), 81.9 (C), 82.15 (C), 99.1 (CH), 123.5 (CH), 125.3 (CH), 125.38 (CH), 125.6 (CH), 125.8 (CH), 125.9 (CH), 127.3 (CH), 127.89 (CH), 127.92 (CH), 128.01 (CH), 139.3 (C), 142.3 (C), 149.9 (C), 150.6 (C), 168.6 (C), 170.8 (C). ^{13}C NMR *minor*: 21.75 (CH_3), 22.1 (CH_3), 22.5 (CH_3), 22.6 (CH_3), 23.24 (CH_3), 23.66 (CH_3), 23.8 (CH_3), 27.7 (CH_2), 27.84 (CH_2), 30.5 (CH_3), 31.09 (CH_3), 31.1 (CH), 31.27 (CH), 31.6 (CH_3), 34.3 (CH_2), 38.6 (CH_2), 39.6 (CH_2), 40.26 (C), 40.7 (C), 41.0 (CH_2), 41.5 (CH_2), 50.2 (CH), 50.6 (CH), 54.6 (CH), 64.76 (C), 76.73 (CH), 76.9 (CH), 81.8 (C), 82.20 (C), 98.8 (CH), 123.4 (CH), 125.1 (CH), 125.44 (CH), 125.7 (CH), 126.0 (CH), 127.6 (CH), 128.00 (CH), 128.1 (CH), 140.0 (C), 141.1 (C), 150.0 (C), 150.8 (C), 169.0 (C), 170.7 (C). IR (KBr): 2924, 1720, 1458, 1373, 1250, 1157, 1065, 972, 764, 702. FABMS *m*/*z*: 763 (M+H). FABHRMS *m*/*z*: 763.4930 (calcd for $C_{50}H_{67}O_6$: 763.4938).

4.3.5. Methyl 1-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)indane-2-carboxylate (**20**)

A mixture of **19** (84 mg, 0.11 mmol) and 4 M aq KOH (0.4 mL, 2 mmol) in DMSO (2 mL) was stirred at 140 °C for 2 h, and then diluted with 2 mL of ice water and 2 mL of diethyl ether. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give pale yellow oil. Silica gel column chromatography (ethyl acetate/hexane 1/12) recovered L-8-phenylmenthol (51 mg, quant) as colorless oil. In turn, the combined aqueous layers were acidified with 10% HCl (2 mL) at 0 °C and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting crude oil in benzene (3.5 mL) and MeOH (0.5 mL) was treated with 1 M hexane solution of $TMSCHN_2$ at room temperature. The mixture was stirred until gas evolution ceased, and subsequently concentrated to give colorless oil (98.3 mg). Silica gel column chromatography (ethyl acetate/hexane 1/10) gave **20** (26.7 mg, 80%) as colorless oil of $[\alpha]_D^{25}$ −46.1 (*c* 1.33, $CHCl_3$). R_f=0.31 (ethyl acetate/hexane 1/15). ^{1}H NMR: 1.18 (s, 3H), 1.19 (s, 3H), 1.20 (s, 3H), 1.21 (s, 3H), 3.15 (m, 1H), 3.23–3.29 (m, 2H), 3.72 (s, 3H), 3.77 (dd, *J*=6.1, 6.4, 1H), 5.11 (d, *J*=6.4, 1H), 7.16–7.19 (m, 3H), 7.44 (m, 1H). ^{13}C NMR: 22.2 (CH_3), 22.3 (CH_3), 23.9 (CH_3), 24.1 (CH_3), 36.0 (CH_2), 45.4 (CH), 51.8 (CH_3), 54.3 (CH), 81.9 (C), 82.4 (C), 102.2 (CH), 124.2 (CH), 125.7 (CH), 126.6 (CH), 127.4 (CH), 141.0 (C), 142.2 (C), 175.9 (C). IR (neat): 2982, 2951, 1738, 1442, 1369, 1221, 1163, 1134, 750. FABMS *m*/*z*: 305 (M+H). FABHRMS *m*/*z*: 305.1721 (calcd for $C_{18}H_{25}O_4$: 305.1753).

4.3.6. Methyl 1-(hydroxymethyl)indane-2-carboxylate (**21**)

A mixture of **20** (26 mg, 0.08 mmol) and triethylsilane (0.08 mL, 0.8 mmol) in TFA (0.5 mL) was stirred under reflux for 1 h. The mixture was cooled to room temperature and then concentrated to give colorless oil (27.8 mg). Silica gel column chromatography (ethyl acetate/hexane 1/12) gave **21** (20.6 mg, quant) as colorless oil of $[\alpha]^{25}_D$ −39.2 (*c* 0.95, $CHCl_3$). R_f=0.33 (ethyl acetate/hexane 1/15). ^{1}H NMR: 3.15 (ddd, *J*=7.6, 8.0, 9.5, 1H), 3.26 (dd, *J*=7.6, 16, 1H), 3.30 (dd, *J*=9.5, 16, 1H), 3.75 (s, 3H), 3.98 (ddd, *J*=5.5, 7.1, 7.6, 1H), 4.62 (dd, *J*=7.1, 11, 1H), 4.69 (dd, *J*=5.5, 11, 1H), 7.19–7.28 (m, 4H). ^{13}C NMR: 35.2 (CH_2), 47.0 (CH), 47.1 (CH), 52.2 (CH_3), 69.5 (CH_2), 123.7 (CH), 124.8 (CH), 127.2 (CH), 128.1 (CH), 139.8 (C), 141.5 (C), 174.5 (C). IR (neat): 3395, 2955, 1790, 1736, 1218, 1165, 756. FABMS *m*/*z*: 207 (M+H). FABHRMS *m*/*z*: 207.1062 (calcd for $C_{12}H_{15}O_3$: 207.1021).

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