Concise and Practical Total Synthesis of (+)-Abscisic Acid

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ABSTRACT: (+)-Abscisic acid 1 was obtained in a concise total synthesis from ethyl 2,6,6-trimethyl-4-oxocyclohex-2-en-1-carboxylate (2) with 41% overall yield in seven steps. A hydroxyl group was stereoselectively introduced by Sharpless asymmetric epoxidation; then, the side chain was appended with dimethyl 2-(propan-2-ylidene)malonate (7); subsequently, selective decarboxylation of diacid 8 established the Z-configuration of the conjugated acid 1.

INTRODUCTION

Abscisic acid (ABA) 1 is a plant hormone, which down-regulates metabolic pathways to survive various environmental stress factors such as extreme temperatures, drought, salinity, and similar inconveniences.1 It induces abscission of leaves, stomatal closure, bud dormancy, and so forth thereby slowing down plant growth to respond and adapt to the environmental changes.2 ABA has also been found in mammals.3 Even though anti-inflammatory and antidiabetic effects are reported in these cases. It is worth noting that superb 97% enantiomeric excess was obtained by Sharpless asymmetric epoxidation13 of the cyclic allylic alcohol (entries 6 and 7). Z-Enyne was extensively used as a nucleophile to the cyclohexanones since the first report by Mayer15 to establish the required Z-configuration of the double bond.11,12 Reformatsky reaction of 4-bromo-3-methyl-2-butenolic ester followed by lactonization was effectively utilized for appendage of the required dienyl acid to the cyclohexanecarbaldehyde.14

Ethyl 2,6,6-trimethyl-4-oxocyclohex-2-ene-1-carboxylate (2), an essential starting material for the cyclic allylic alcohol in the Sharpless asymmetric epoxidation (entries 6 and 7), has been a useful building block for the synthesis of xanthophylls: rhodoxanthin, zeaxanthin, and violaxanthin.14 The first synthesis of 2 appeared in the literature more than a century ago through condensation of ethyl acetoacetate and isopropylideneacetoacetate ester 4 under Na in EtOH.17 This method was evaluated as a long and complicated procedure by Rubinstein, who claimed a better preparation method of 2 by BF3·OEt2-mediated reaction of acetoacetic ester with acetone or directly with mesityl oxide in ca. 40% yields (Scheme 1).18 This reaction was later found to produce a 4:1 mixture of two isomers 2 and 3,19 which were very difficult to separate,20 and the Lewis acid-catalyzed condensation was not a practical preparation method either.21

Having developed an efficient one-pot preparation method of the Hagemann’s type esters by reaction of ethyl acetoacetate and various aldehydes under the t-BuOK/t-BuOH condition,12 we wanted to extend our approach to the preparation of 2,6,6-
Table 1. Representative Syntheses of ABA 1 in the Literature

| entry | ring structure | chain structure | stereoselectivity | reference |
|-------|----------------|-----------------|-------------------|-----------|
| 1     |                |                 | 60°               | 11a       |
| 2     |                |                 | 60°               | 11b       |
| 3     |                |                 | 78°               | 11c       |
| 4     |                |                 | 50°               | 12a,b     |
| 5     |                |                 | 33°               | 12c       |
| 6     |                |                 | 97°               | 14a       |
| 7     |                |                 | 97°               | 14b       |
| 8     |                |                 | N.A.              | 15        |
| 9     |                |                 | N.A.              | 16        |

“Diastereomeric excess (d.e.) in the generation of the quaternary (S)-OH group. Enantiomeric excess (e.e.) in the Sharpless asymmetric epoxidation of the allylic alcohol for the quaternary (S)-OH group. Not applicable.

Scheme 1. Exclusive Formation of Ethyl 2,6,6-Trimethyl-4-oxocyclohex-2-ene-1-carboxylate (2) under the t-BuOK/t-BuOH Condition

trimethyl-4-oxocyclohex-2-ene-1-carboxylate (2). The reaction of ethyl acetoacetate (2 equiv) and acetone (1 equiv), however, did not produce 2 under the t-BuOK/t-BuOH condition. On the other hand, the reaction of ethyl acetoacetate and ethyl isopropylideneacetoacetate 4,23 prepared by Lewis acid-mediated condensation between ethyl acetoacetate and acetone, exclusively produced the desired isophorone-4-carboxylic ester 2 in 86% yield upon refluxing in t-BuOK/t-BuOH for 2 days (Scheme 1). The reaction proceeded through the sequence of conjugate addition, aldol, and subsequent lactonization, followed by decarboxylation.22

No isomeric product 3 was obtained in this procedure through the symmetrical intermediate from the conjugate addition. We recently recognized with surprise that this procedure was suggested by Büchi about 70 years ago24 and that this reference was never utilized by others (no citation at all).

Equipped with an efficient and exclusive preparation method of ethyl 2,6,6-trimethyl-4-oxocyclohex-2-ene-1-carboxylate (2), we challenged the total synthesis of (+)-ABA 1 (Scheme 2). We adapted Sharpless asymmetric epoxidation of the corresponding allylic alcohol 5 for stereoselective introduction of the epoxy group. Vinylogous aldol condensation25 of the resulting chiral aldehyde 6 (obtained after Swern oxidation) with diester 7 and selective decarboxylation of diacid 8 would...
be a perfect fit to establish the required Z-configuration of conjugated dienic acid in (+)-ABA 1. Details of the syntheses are herein described.

■ RESULTS AND DISCUSSION

The total synthesis of ABA commenced from the conversion of ethyl 2,6,6-trimethyl-4-oxocyclohex-2-ene-1-carboxylate (2) into the corresponding allylic alcohol 5 for asymmetric Sharpless epoxidation. Protection of ketone in isophorone-4-carboxylic ester 2 was necessary because of strong acidity of the hydrogen at carbon number 4, which favorably induced a double-bond migration to give conjugated ester 9 (Scheme 3).19 Neopentyl glycol was used to secure acetal protection. Because of steric congestion by the ring substituents, the conversion was not complete (58% yield) and 33% of starting material 2 was recovered. Reduction of the ester group to allylic alcohol 5 (96% yield) required heating with LAH at 65 °C for 2.5 h because of the steric hindrance. The epoxidation of allylic alcohol 5 (83% yield) was first tested by using monoperphthalic acid, generated in situ by the reaction of urea–H2O2 and phthalic anhydride in MeCN. Swern oxidation (oxalyl chloride/DMSO, Et3N) of the racemic epoxy-alcohol (±)-10 provided the corresponding epoxy-aldehyde (±)-6 (94% yield).

Racemic intermediate 6 in hand, the feasibility of two downstream steps were checked: (1) introduction of the 4-hydroxyl group, and (2) appendage of the dienic acid moiety. Dimethyl 2-(propan-2-ylidene)malonate (7) was selected as the potential dienic acid moiety as Valla demonstrated it in the isotretinoin synthesis.26 Deprotection of the acetal function of epoxy-aldehyde (±)-6 by 1 M HCl simultaneously induced epoxide opening to give rise of the desired 4-hydroxycyclohex-11 (64% yield), which unfortunately did not undergo vinylogous diester condensation with 7. Instead, 2,6,6-trimethylcyclohexane-1,4-dione (12) was obtained in 48% yield by decarbonylation and tautomerization. It is because of the stability of the carbanion at C-4 from cyclohexenone 11 which does not allow condensation of the formyl group. On the other hand, condensation of diester 7 with protected epoxy-aldehyde (±)-6 proceeded very well under the condition using Triton B (benzyltrimethylammonium hydroxide) in THF. The condensation was accompanied by partial ester hydrolysis and followed by the hydrolysis of acetal to provide coupled monoacid (±)-13 (60% yield) and diacid (±)-8 (11% yield).

The feasibility tests were performed successfully; enantioselective total synthesis of ABA (+)-1 was demonstrated from chiral epoxy-aldehyde (−)-6 (Scheme 4), which was prepared from allylic alcohol 5 by Sharpless asymmetric epoxidation (Ti(Oi-Pr)4, (−)-diethyl tartrate, and t-butyl hydrogen peroxide, 88% yield), followed by Swern oxidation (94% yield). Enantioselectivity of the Sharpless epoxidation for allylic alcohol 5 was evaluated by the Eu(hfc)3 chiral shift reagent in the 1H NMR analysis of (S)-11, the hydrolysis product from (−)-6, in order to maximize the coordination effect (see the Supporting Information). It was not possible to observe the other stereoisomer for the Eu-coordinated (S)-11 even though significant chemical shifts were noticed especially for the vinylic and methylene protons. (S)-11 was considered enantiomerically pure within the detection limit of 1H NMR. On the other hand, racemic-11 which was prepared by hydrolysis of (±)-6 (Scheme 3) clearly showed two isomeric...
peaks for vinylc and one of the methylene protons. Accurate determination of the enantiomeric excess in the Sharpless epoxidation of allylic alcohol 5 was shifted to the final step of the ABA synthesis.

Appendage of the dienyl diacid moiety was performed directly by condensation with diester 7 in the presence of Triton B in THF, followed by hydrolysis (KOH, MeOH) at 70 °C for 5 h (64% overall yield). The resulting diacid (+)-8 was heated to reductine at 130 °C for 3 h to produce (+)-ABA 1 in 93% yield. Selective decarboxylation and exclusive formation of the Z-configured dienec acid can be rationalized by the formation of a lactone intermediate B by base-promoted intramolecular addition of the carboxylic in syn position in A. The free carboxylic acid in B underwent decarboxylation to give rise to the Z-dienic acid. Pyridine as the base also produced Z-dienic acid (+)-1 (63% yield) unlike the previous reports describing the formation of all-E-retinoic acid under similar conditions,27 which can be explained by steric congestion at the sp2-carbon near the ring junction. The enantiomeric purity of (+)-ABA 1 was then determined to be 94% e.e. by chiral HPLC analysis (see the Supporting Information), which reflected that of the Sharpless asymmetric epoxidation.

**CONCLUSIONS**

We demonstrated a concise de novo synthesis of (+)-ABA 1 from readily available acetonc, ethyl acetococete, and dimethyl maleonc, which was initiated from the practical synthesis of ethyl 2,6,6-trimethyl-4-oxocyclohex-2-enecarboxylate (2). Sharpless asymmetric epoxidation of allylic alcohol 5, vinylous diester condensation with isopropylidene dimethyl maleonc 7, and selective decarboxylation of the resulting diacid (+)-8 were highlighted for the efficient total synthesis of (+)-ABA 1 with 41% overall yield in seven steps from isophorone-4-carboxylic ester 2.

**EXPERIMENTAL SECTION**

**General Experimental Section.** 1H- and 13C NMR spectra were, respectively, recorded on a 400 MHz and 100 MHz NMR spectrometer in CDCl3 with tetramethylsilane as an internal reference unless noted otherwise. High-resolution mass spectroscopy was performed using the magnetic sector analyzer. The column chromatography was performed by the method of Still with silica gel 60, 70–230 mesh ASTM using a gradient mixture of EtOAc/hexanes. Reactions were performed in a well-dried flask under argon atmosphere unless noted otherwise.

**Ethyl 2,6,6-Trimethyl-4-oxocyclohex-2-enecarboxylate (2).** 19 To a stirred solution of ethyl acetocetate (7.88 g, 60.51 mmol) and 2-acetyl-3-methylbut-2-enocate (4) 23 (10.30 g, 60.51 mmol; CAS no. 35044-52-1) in t-BuOH (60 mL) was added t-BuOK (1.36 g, 12.10 mmol). The mixture was heated to reflux for 2 d under argon atmosphere and cooled to room temperature. Most of the solvent was removed under reduced pressure. The crude concentrate was diluted with Et2O, washed with NaHCO3 solution (50 mL), dried over anhydrous Na2SO4, filtered, and concentrated. The crude product (11.51 g) was purified by SiO2 flash column chromatography (eluent 20–35% EtOAc/hexane) to give ethyl 2,6,6-trimethyl-4-oxo-2-cyclohexene-1-carboxylate (2) (10.94 g, 52.03 mmol) in 86% yield as orange oil. Data for 2: Rf = 0.32 (1:4 EtOAc/hexene); 1H NMR: δ 1.08 (s, 3H), 1.09 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.95 (s, 3H), 2.07 (d, J = 16.4 Hz, 1H), 2.78 (d, J = 16.4 Hz, 1H), 2.97 (s, 1H), 4.15–4.27 (m, 2H), 6.98 (s, 1H) ppm; 13C NMR: δ 14.2, 23.4, 27.1, 28.2, 35.7, 47.0, 58.3, 61.1, 127.3, 154.8, 170.6, 198.9 ppm; HRMS (ESI): calcd for C17H28NaO4, 319.1880; found, 319.1881.

**Ethyl 3,3,8,10,10-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-carboxylate (9).** The mixture of ethyl 2,6,6-trimethyl-4-oxo-2-cyclohexene-1-carboxylate (2) (2.73 g, 12.97 mmol), neopentyl glycol (4.73 g, 45.39 mmol), and p-TsOH (123 mg, 0.65 mmol) in benzene (50 mL) was heated to reflux for 8 h in a reflux apparatus equipped with a Dean–Stark trap. The mixture was cooled to room temperature, quenched with 1 M NaOH (50 mL), extracted with Et2O, dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The crude product (4.70 g) was purified by SiO2 flash column chromatography (eluent 10–35% EtOAc/hexane) to give the corresponding acetal 9 (2.23 g, 7.52 mmol) in 58% yield and unconcerted starting enone 2 (901 mg, 4.28 mmol) in 33% yield as orange oils. Data for 9: Rf = 0.61 (1:4 EtOAc/hexane); 1H NMR: δ 0.86 (s, 3H), 1.09 (s, 3H), 1.18 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H), 1.70 (s, 3H), 1.89 (s, 2H), 2.36 (s, 2H), 3.40 (d, J = 12.0 Hz, 2H), 3.61 (d, J = 12.0 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H) ppm; 13C NMR: δ 14.3, 21.0, 22.3, 22.8, 28.8, 29.9, 35.5, 40.3, 42.2, 60.1, 70.3, 70.3, 97.0, 129.9, 134.0, 170.2 ppm; IR (KBr): ν = 2952, 2863, 1715, 1469, 1372, 1260, 1237, 1208, 1133, 1096, 1073, 1036, 984, 824, 865, 775, 678 cm-1; HRMS (ESI): calcd for C17H28NaO4, 319.1880; found, 319.1881.

**Ethyl 3,3,8,10,10-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-yl)methanol (5).** The mixture of ethyl 3,3,8,10-pentamethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-carboxylate (9) (2.20 g, 7.42 mmol) and LiAlH4 (563 mg, 14.84 mmol) in THF (30 mL) was heated at 65 °C for 2.5 h under argon atmosphere. The mixture was cooled to room temperature, quenched with 1 M NaOH (30 mL), extracted with EtOAc, dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The crude product 5 (1.81 g, 7.12 mmol, 96% yield, yellowish oil) was pure enough to be used without purification. Data for 5: Rf = 0.18 (1:4 EtOAc/hexane); 1H NMR: δ 0.84 (s, 3H), 1.11 (s, 3H), 1.13 (s, 6H), 1.80 (s, 3H), 1.90 (s, 2H), 2.35 (s, 2H), 3.38 (d, J = 11.6 Hz, 2H), 3.63 (d, J = 11.6 Hz, 2H), 4.16 (s, 2H) ppm; 13C NMR: δ 19.5, 22.3, 22.8, 28.7, 28.7, 30.0, 36.4, 40.2, 43.6, 58.2, 70.3, 70.3, 97.1, 129.6, 136.4 ppm; IR (KBr): ν = 3414, 2952, 2870, 1662, 1469, 1372, 1260, 1215, 1133, 1096, 977, 775, 753, 678 cm-1; HRMS (EI): calcd for C17H30O2, 254.1882; found, 254.1883.

**Ethyl 3,3,8,10,10-Pentamethyl-7-oxaspiro[4.1.0]heptane-3,2′-[1,3]dioxan-6-yl)methanol (4)-(10).** The mixture of urea–H2O2 (2.09 g, 22.26 mmol) and phthalic anhydride (1.65 g, 11.13 mmol) in MeCN (20 mL) was stirred vigorously at room temperature for 2 h under argon atmosphere to give a clear solution. Anhydrous K2CO3 (3.08 g, 22.26 mmol) and a solution of allylic alcohol 5 (1.79 g, 7.04 mmol) in CH2Cl2 (10 mL) were added to the above-mentioned solution. The resulting mixture was stirred at room temperature for 19 h and filtered through a filter paper. The filtrate was concentrated under reduced pressure, which was then dissolved in CHCl3. Undissolved solid was filtered, and the filtrate was concentrated under reduced pressure again. The crude product (1.79 g, yellow oil) was purified by SiO2 flash column chromatography (eluent 25–40% EtOAc/hexane) to
give the corresponding epoxy-aldehyde (±)-10 (1.59 g, 5.87 mmol) in 83% yield as clear oil. Data for (±)-10: R<sub>f</sub> = 0.43 (2:3 EtOAc/hexane); 1H NMR: δ 0.84 (s, 3H), 1.05 (s, 3H), 1.10 (s, 3H), 1.15 (s, 3H), 1.37 (d, J = 14.4 Hz, 1H), 1.42 (s, 3H), 1.89 (s, J = 4.8 Hz, 1H), 1.98 (dd, J = 14.4, 2.4 Hz, 1H), 2.15 (d, J = 15.6 Hz, 1H), 2.23 (dd, J = 15.6, 2.0 Hz, 1H), 3.31–3.38 (m, 2H), 3.50–3.58 (m, 2H), 3.69 (dd, J = 11.6, 4.8 Hz, 1H), 3.87 (dd, J = 11.6, 4.8 Hz) ppm; 13C NMR: δ 21.1, 22.3, 22.7, 23.6, 26.5, 29.8, 34.2, 37.3, 42.1, 57.9, 63.7, 68.4, 70.0, 70.1, 96.2 ppm; IR (KBr): 3459, 2952, 2870, 1655, 1469, 1372, 1208, 1126, 1096, 1036, 984, 907, 857, 753, 663 cm<sup>−1</sup>; HRMS (CI): calcld for C<sub>15</sub>H<sub>27</sub>O<sub>4</sub>Na<sub>2</sub>O, 271.1908; found, 271.1909.

1-Hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-ene-1-carbaldehyde (11).<sup>28</sup> To a stirred solution of aldehyde (±)-6 (439 mg, 1.63 mmol) in THF (15 mL) was added 1 M HCl (15 mL). The mixture was stirred at room temperature for 18 h, extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by SiO<sub>2</sub> flash column chromatography (eluent 20–40% EtOAc/hexane) to give 1-hydroxy-1-carbaldehyde 11 (191 mg, 1.05 mmol) in 64% yield as a white solid. Data for 11: R<sub>f</sub> = 0.15 (1:4 EtOAc/hexane); 1H NMR: δ 1.00 (s, 3H), 1.12 (s, 3H), 1.80 (d, J = 1.2 Hz, 3H), 2.45 (d = 17.6 Hz, 1H), 2.72 (d, J = 17.6 Hz, 1H), 3.93 (br s, 1H), 6.20 (br s, 1H), 9.72 (d, J = 1.6 Hz, 1H) ppm; 13C NMR: δ 18.8, 23.5, 24.1, 43.9, 85.3, 130.1, 157.1, 196.2, 198.5 ppm; CAS no. 130815-50-8.

(S)-1-Hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-ene-1-carbaldehyde (5)-11. According to the abovementioned procedure for 11 (racemic), aldehyde (−)-6 (244 mg, 0.91 mmol) in THF (10 mL) was hydrolyzed with 1 M HCl (10 mL) for 20 h to give (S)-11 (121 mg, 0.66 mmol) in 73% yield as a white solid.

Dimethyl (Propan-2-ylidene)malonate (7).<sup>29</sup> The mixture of dimethyl malonate (13.21 g, 0.100 mol), acetic anhydride (13.78 g, 0.135 mol), aceton (8.71 g, 0.150 mol), and ZnCl<sub>2</sub> (1.91 g, 0.014 mol) was heated to 65 °C for 3 d under argon atmosphere and cooled to room temperature. The mixture was diluted with Et<sub>2</sub>O, washed with 0.5 M HCl (0.10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by SiO<sub>2</sub> flash column chromatography (eluent 20–20% EtOAc/hexane) to give dimethyl 2-(propan-2-ylidene)-malonate (7) (10.09 g, 0.059 mol) in 59% yield as orange oil. Data for 7: R<sub>f</sub> = 0.48 (1:4 EtOAc/hexane); 1H NMR: δ 2.07 (s, 6H), 3.77 (s, 6H) ppm; 13C NMR: δ 23.2, 52.0, 124.0, 155.9, 166.1 ppm; CAS no. 22035-53-6.

2,2,6-Trimethylcyclohexane-1,4-dione (12).<sup>30</sup> To a stirred solution of dimethyl 2-(propan-2-ylidene)malonate (11) (112 mg, 0.65 mmol) and the 1-hydroxy-1-carbaldehyde 11 (99 mg, 0.54 mmol) in MeOH (20 mL) was added 40% methanolic solution of Triton B (544 mg, 1.30 mmol). The mixture was stirred at room temperature for 15 h under argon atmosphere, and most of the solvent was removed under reduced pressure. The crude product (153 mg, yellow brown oil) was purified by SiO<sub>2</sub> flash column chromatography (eluent 15–30% EtOAc/hexane) to give 1,4-dione 12 (40 mg, 0.26 mmol) in 48% yield as an off-white solid. Data for 12: R<sub>f</sub> = 0.23 (1:4 EtOAc/hexane); 1H NMR: δ 1.12 (s, 3H), 1.15 (d, J = 6.4 Hz, 3H), 1.22 (s, 3H), 2.34 (dd, J = 18.0, 13.2 Hz, 1H), 2.53 (d, J = 15.6 Hz, 1H), 2.76 (dd, J = 18.0, 6.4 Hz, 1H), 2.76 (d, J = 15.6 Hz, 1H), 3.01 (ddq, J<sub>1</sub> = 13.2, 6.4 Hz, J<sub>2</sub> = 6.4 Hz, 1H) ppm; CAS no. 205479-99-3.

(4E)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-en-1-yl)-2-(methoxy carbonyl)-3-methyl pentane-2,4-dienoic Acid (±)-13. To a stirred solution of dimethyl 2-(propan-2-ylidene)malonate (7) (320 mg, 1.86 mmol) and epoxy-aldehyde (±)-6 (500 mg, 1.86 mmol) in THF (40 mL)...
was added 40% methanolic solution of Triton B (1.71 g, 4.09 mmol). The mixture was stirred at room temperature for 1 d under argon atmosphere, and 2-(propan-2-ylidene)malonate (7) (320 mg, 1.86 mmol) and 40% methanolic solution of Triton B (1.71 g, 4.09 mmol) were added again. Stirring for one additional day, the mixture was quenched with H2O, and the organic layer was extracted with EtOAc (discarded). The orange-brown aqueous layer was acidified with 1 M HCl (40 mL), extracted with EtOAc, dried over anhydrous Na2SO4, and concentrated under reduced pressure to give a polar sticky oil (539 mg), which was purified by SiO2 flash column chromatography (eluent 15–30% EtOAc/hexane then MeOH) to give the coupled monocaid-esters (+)-13-major (264 mg, 0.82 mmol, 44% yield) and (+)-13-minor (98 mg, 0.30 mmol, 16% yield) as off-white solids, and the coupled diacid (±)-8 (64 mg, 0.21 mmol, 11% yield) as a light brick-colored solid. Data for the major isomer (+)-13: Rf = 0.31 (1:4 MeOH/CH2Cl2); 1H NMR (MeOH-d4): δ 0.99 (s, 3H), 1.03 (s, 3H), 1.89 (s, 3H), 2.10 (s, 3H), 2.17 (d, J = 16.8 Hz, 1H), 2.54 (d, J = 16.8 Hz, 1H), 3.70 (br s, 3H), 3.72 (s, 3H), 5.88 (br s, 1H), 6.24 (d, J = 16.0 Hz, 1H), 7.07 (d, J = 16.0 Hz, 1H) ppm; 13C NMR (MeOH-d4): δ 16.0, 19.6, 23.6, 24.7, 42.9, 50.6, 52.3, 80.6, 126.7, 131.4, 137.8, 143.9, 166.4, 166.8, 172.7, 201.0 ppm; UV (CH2Cl2, c = 1.02 × 10−3 M) (λ): 238 (7250), 275 (7760) nm; IR (KBr): 3422, 2960, 2922, 2855, 1715, 1655, 1439, 1330, 1215, 1044, 745, 663 cm−1; HRMS (EI): calcd for C15H20O4, 264.1362; found, 264.1364.

(S,E)-2-(4-(1-Hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-en-1-yl)but-3-en-2-ylidene)malonic Acid (+)-(8). To a stirred solution of dimethyl 2-(propan-2-ylidene)malonate (7) (201 mg, 1.17 mmol) and chiral epoxy-aldehyde (−)-6 (313 mg, 1.17 mmol) in THF (30 mL) was added 40% methanolic solution of Triton B (1.08 g, 2.57 mmol). The mixture was stirred at room temperature for 1 d under argon atmosphere, and 2-(propan-2-ylidene)malonate (7) (201 mg, 1.17 mmol) and 40% methanolic solution of Triton B (1.08 g, 2.57 mmol) were added again. Stirring for one additional day, the mixture was quenched with H2O and extracted with EtOAc (discarded). The orange-brown aqueous layer was acidified with 1 M HCl (30 mL), extracted with EtOAc, dried over anhydrous Na2SO4, and concentrated under reduced pressure to give the crude coupling product (478 mg) as light brown oil.

The abovementioned crude coupling product (478 mg) was dissolved in MeOH (20 mL) and aqueous solution (1 mL) of KOH (416 mg, 7.41 mmol) was added. The mixture was heated to 70 °C for 5 h and cooled to room temperature. Most of the solvent was removed under reduced pressure. The crude product was acidified with 1 M HCl (15 mL), extracted with EtOAc, dried over anhydrous Na2SO4, and concentrated under reduced pressure. The crude product was purified by SiO2 flash column chromatography (eluent 20–50% EtOAc/hexane then MeOH) to give diacid (+)-8 (231 mg, 0.75 mol) in 64% yield as a light brick-colored solid. Data for (+)-8: Rf = 0.41 (2:3 MeOH/CH2Cl2); [α]D25 +198.4 (c 0.28, MeOH); mp >250 °C; 1H NMR (MeOH-d4): δ 1.02 (s, 3H), 1.05 (s, 3H), 1.91 (s, 3H), 2.19 (s, 3H), 2.20 (d, J = 16.8 Hz, 1H), 2.56 (d, J = 16.8 Hz, 1H), 3.34 (s, 1H), 3.91 (s, 1H), 6.37 (d, J = 16.0 Hz, 1H), 7.16 (d, J = 16.0 Hz, 1H) ppm; 13C NMR (MeOH-d4): δ 16.6, 19.5, 23.6, 24.7, 42.9, 50.6, 80.5, 127.6, 128.5, 130.5, 139.3, 147.6, 166.1, 168.9, 169.2, 200.9 ppm; UV (EtOH, c = 1.85 × 10−3 M) (λ): 221 (8070) nm; IR (KBr): ε: 3422, 2960, 2922, 2855, 1715, 1655, 1439, 1372, 1252, 1133, 1088, 1029, 991, 768, 671 cm−1; HRMS (EI): calc: for C15H20O6 [M+ (C16H20O6) − CO2], 264.1362; found, 264.1364.

(2Z,4E)-5-(S)-1-Hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-en-2-yl)-3-methylpent-2,4-dienoic Acid: ABA (+)-(1). 2,6-Lutidine (40 mL) was added to diacid (+)-8 (86 mg, 0.28 mmol), and the mixture was heated to 130 °C for 3 h under argon atmosphere. Most of the solvent was removed by distillation under reduced pressure, and the crude product was acidified with 1 M HCl (40 mL), extracted with EtOAc, dried over anhydrous Na2SO4, and concentrated under reduced pressure. The crude product was purified by SiO2 flash column chromatography (eluent 100% CHCl3) to give ABA (+)-1 (68 mg, 0.26 mmol) in 93% yield as a light brick-colored solid. Specific rotation for (+)-1: [α]D25 +213.4° (c 0.83, MeOH) [literature1] [α]D25 +278.3° (c 0.21, MeOH); mp 168–171 °C (lit.12 mp 159–161 °C); UV (EtOH, c = 7.09 × 10−4 M) (λ): 258 (11,000) nm; HRMS (EI): calc for C15H20O6, 264.1362; found, 264.1364.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01332.

1H- and 13C NMR spectra, 1D N.O.E. spectra for (+)-1, 1H NMR spectra for (S)-11 and racemic-11 with chiral shift reagent Eu(hfc)3, and chiral HPLC analysis for (+)-1 (PDF)

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Notes

The authors declare no competing financial interest.

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