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An efficient route for the synthesis of methyl (−)-1,4a-dimethyl-5-oxodecahydronaphthalene-1-carboxylate by using baker's yeast-catalyzed asymmetric reduction

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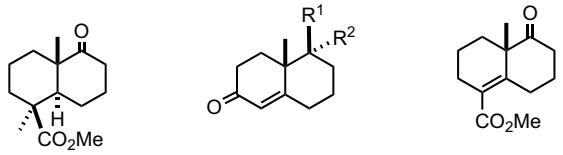
Abstract—Methyl (−)-1,4a-dimethyl-5-oxodecahydronaphthalene-1-carboxylate **1**, a key synthetic intermediate for the synthesis of terpenoids, was efficiently synthesized by using a baker's yeast-catalyzed asymmetric reduction of a σ-symmetrical 1,3-cyclohexanedione derivative.

1. Introduction

Methyl (−)-1,4a-dimethyl-5-oxo-*trans*-decaline-1-carboxylate **1** is a key intermediate in the synthesis of many biologically active terpenoids. For example, acanthoic acid and its derivatives were recently synthesized via (−)-**1** as anti-inflammatory agents.[1] Moreover, the isolation and structure elucidation of many bioactive diterpenes bearing (−)-**1** as a partial structure, such as globostearic acids[2] and 15-methoxyfasciculatins,[3] have been reported to date. Methyl ester (−)-**1** has often been synthesized from Wieland–Miescher ketone **2** that was prepared by a L-proline-catalyzed Robinson annelation;[4] however, the enantiomeric excess of **2** prepared in this method was not higher than 70% ee. Many methods to synthesize enantiomerically pure 4a-methyl-5-oxooctahydronaphthalene-1-carboxylate **3** were reported to date as a part of an alternative synthetic route (Fig. 1). For example, Theodorakis developed a novel Robinson annelation, which was initiated by the Michael addition of 3-oxopenten-5-amide having a chiral auxiliary on the amide group to afford two separable diastereomers, and the chiral auxiliary of each diastereomer was successively cleaved to afford enantiomerically pure **3**.[5] Tanaka et al. adopted an intramolecular Horner–Wadsworth–Emmons reaction, where (*S*)-BINAP formed a phosphonate ester as a spontaneously removable chiral auxiliary, in the formation of the double bond between C-1 and C-8a to afford (+)-**3**.[6]



(-)-1 — **2a**: $R^1 = R^2 = O$; **2b**: $R^1 = OH$, $R^2 = H$ — (+)-3

Figure 1. Structure of Wieland–Miescher ketone and related compounds.

Meanwhile, Sugai et al. established a new method to synthesize derivative **2b** of Wieland–Miescher ketone **2a** in good overall yield with excellent ee by using the microorganism-catalyzed asymmetric reduction of σ-symmetrical 1,3-cyclohexanedione.[7] Although **2a** and **2b** have been employed as good intermediates in the synthesis of steroids, methyl esters **3** and **1** were more direct intermediates in the synthesis of terpenoids as mentioned above. Moreover, asymmetric reductions of σ-symmetrical cyclic 1,3-diketones with baker's yeast have been developed to construct chiral building blocks for the synthesis of bioactive natural compounds.[8,9]

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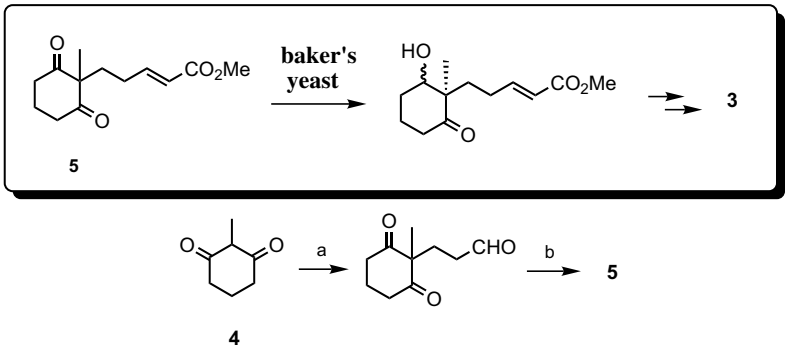
On the basis of our recently reported asymmetric reduction of σ-symmetrical cyclic-1,3-diketone using baker's yeast-catalyzed reaction as a practical method in organic synthesis,[10] we initiated a study on synthesis of enantiomerically pure (−)-**1** and (+)-**3** by using the biocatalyst. Herein, we would like to report our recent results obtained in this study.

2. Results and discussion

Our strategy for the synthesis of α,β-unsaturated methyl ester **3** was based on the asymmetric reduction of σ-symmetrical methyl 5-(2-methyl-1,3-dioxocyclohexyl)-2-pentenoate **5** with baker's yeast and successive annelation that should be attained between the α,β-unsaturated ester and ketone. In the beginning, the substrate **5** was synthesized by the Michael addition of the carbanion generated from 2-methyl-1,3-cyclohexanedione **4** to acrolein, followed by Wittig reaction (Scheme 1).

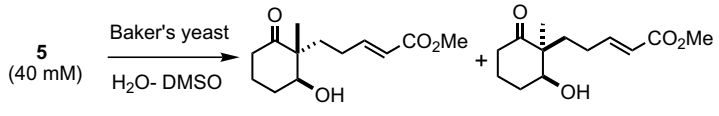
Next, three types of baker's yeast were tested and it was found that only the reaction with the yeast purchased as type II from Sigma gave the reduced products **6a** and **6b** albeit in low yield (27%) (Table 1, entry 3). Thus, an additional amount of yeast (Sigma type II) was added to the reaction medium to increase the chemical yield (Table 1, entries 4, 5, 8, and 9). After trying several reactions by changing the total amount of the yeast, we chose conditions where 3.0 g of the yeast per 1 mmol of the substrate was added twice with an interval of 24 h (Table 1, entry 5) in preference to that shown in entry 8 (Table 1) as the best conditions for further synthetic study because of the facility of the work-up procedure. In addition, the reaction with a lower substrate concentration (Table 1, entry 6) provided **6a** and **6b** in higher yield while adding sucrose into the reaction medium was more effective (Table 1, entry 7). As a conclusion up to this point, we succeed in establishing a practical method for the reduction of σ-symmetrical 1,3-cyclohexanedione **5** into hydroxyketone **6a** in good chemical yield (74–85%) with high diastereoselectivity (82–90% de) and high enantioselectivity (>99% ee) (Table 1, entries 7 and 8).

We derivatized the reduced product **6a** to spiroketal **7**, of which the two isomers among four possible ones were prepared by Brooks,[9] in order to determine the stereochemistry of two contiguous stereogenic centers. The transformation of **6a** started with the acetylation of the secondary hydroxyl group, followed by the acetalization of the carbonyl group with ethylene glycol in the presence of 2-ethyl-2-methyl-1,3-dioxolane and *p*-toleuenesulfonic



Scheme 1. Synthetic strategy for the synthesis of **3** and preparation of **5**. Reagents: (a) acrolein; (b) $Ph_3P{=}CHCO_2Me$.

Table 1. Baker's yeast-catalyzed asymmetric reduction of **5**



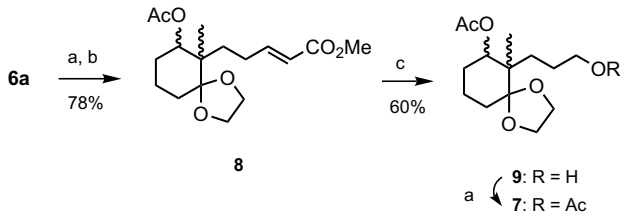
6a **6b**

Entry	Baker's yeast	Time (h)	Yield (%)	de (%)	ee of **6a** (%)
1	Oriental Co. Ltd (3.0 g/mmol)	24	3	—	—
2	Sigma type I (3.0 g/mmol)	72	0	—	—
3	Sigma type II (3.0 g/mmol)	48	27	80	>99
4	Sigma type II (5.0 g/mmol)	72	36	80	>99
5	Sigma type II (3.0 g/mmol × 2)	24 × 2	67	88	>99
6[a]	Sigma type II (3.0 g/mmol × 2)	24 × 2	72	86	>99
7[b]	Sigma type II (3.0 g/mmol × 2)	24 × 2	85	82	>99
8	Sigma type II (6.0 g/mmol × 2)	24 × 2	74	90	>99
9	Sigma type II (9.0 g/mmol × 2)	24 × 2	60	88	>99

[a] Substrate concentration was 8 mM.
[b] In the presence of sucrose.

acid to afford **8**. Acetal **8** was ozonolyzed and worked up with sodium borohydride to give primary alcohol **9**. The primary hydroxyl group of **9** was again acetylated by a conventional method to yield **7** (Scheme 2).

However, it was very difficult to determine the stereochemistry of **7** synthesized in this way on the basis of the ^{1}H and ^{13}C NMR spectroscopic data for (2*R*,3*S*)-**7** and (2*S*,3*S*)-**7** in the literature,[9] because both of our two diastereomers gave quite similar spectra, and unexpectedly, the coupling constants of the proton signals at δ 4.91 and 4.89 ppm in the reported spectra did not coincide with our data (Table 2). Therefore, the stereochemistry of product **6a** was independently determined to have (2*R*,3*S*)-configuration by means of X-ray crystallography after derivatizing to a *p*-bromobenzoate **10** (Fig. 2).

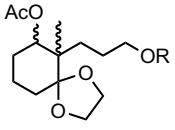
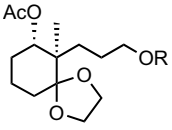
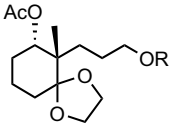


Scheme 2. Transformation to **6a** to the known derivative **7**. Reagents: (a) Ac_2O, py; (b) $HO(CH_2)_2OH$, 2-methyl-2-ethyl-1,3-dioxolane, *p*-TsOH; (c) O_3, then $NaBH_4$.

Since the major product **6a** of the baker's yeast-catalyzed asymmetric reduction had the desired configuration on the C-2 positions, the annelation reaction between the ketone and α,β-unsaturated ester groups was attempted after the protection of the hydroxyl group with a methoxymethyl group to derive **11**. The optimal reaction involved the Michael addition of the hydride to the α,β-unsaturated ester, followed by the addition of the resulting ester enolate to the ketone group on the cyclohexane ring. Although many cuprous hydrides prepared in diverse methods were reported for this type of reaction, only the reagents prepared from cuprous iodide, methyl lithium and DIBAL gave the annelated product as a mixture of *trans*- and *cis*-isomers **12a** and **12b**. While the dehydration of **12a** with thionyl chloride afforded **13a**, the same treatment of **12b** afforded **13b**. Unfortunately, migration of the double bond to transform **13b** into **13a** proceeded in only low yield by treatment with DBU in refluxing toluene. Deprotection of the methoxymethyl group of **13a** and oxidation of the alcohol **14** obtained gave (+)-**3** in good overall yield (overall 64% in two steps).

Meanwhile, in order to introduce a methyl group at the C-1 position of **13a**, the α,β-unsaturated ester on the A-ring was reduced under the conditions of a Birch reduction to generate the ester enolate, which was reacted further with methyl iodide to afford **15**. Finally, the methoxymethyl group of **15** was deprotected with 6 M hydrochloric acid to generate **16** and its hydroxyl group oxidized by Jones

Table 2. Comparison of spectral data of (2*R*,3*S*)-**7**, (2*S*,3*S*)-**7**, and our synthetic **7**

	 **synthesized-7**	 **(2*R*,3*S*)-7**	 **(2*S*,3*S*)-7**
$[\alpha]_D$	+23.7 ($CHCl_3$)	+27.9 ($CHCl_3$)	+18.5 ($CHCl_3$)
^{1}H NMR	1.06 (s, 3H)	1.05 (s, 3H)	0.92 (s, 3H)
	1.40–1.81 (m, 10H)	1.4–1.8 (m, 10H)	1.5–1.7 (m, 10H)
	2.03 (s, 3H),	2.03 (s, 6H)	2.04 (s, 6H)
	2.04 (s, 3H)		
	3.91–3.98 (m, 4H)	3.92 (m, 6H)	3.90 (m, 4H)
	3.96 (t, $J = 6.7$ Hz, 2H)		4.02 (t, $J = 7.0$ Hz, 2H)
	4.91 (dd, $J = 10.5$, 4.9 Hz, 1H)	4.89 (dd, $J = 5.0$, 3.0 Hz, 1H)	4.91 (dd, $J = 4.0$, 4.0 Hz, 1H)
^{13}C NMR	15.2	15.3	16.2
	19.0	19.0	19.1
	21.0	21.0	21.1
	21.3	21.3	21.3
	24.4	24.4	23.8
	26.2	26.3	25.9
	29.8	29.9	27.2
	30.0	30.0	29.7
	45.0	45.0	45.5
	64.3	64.3	64.6
	64.6	65.0	65.2
	65.6	66.7	65.7
	76.5	76.2	77.5
	113.1	113.1	112.6
	170.4	170.5	170.5
	171.2	171.2	171.2

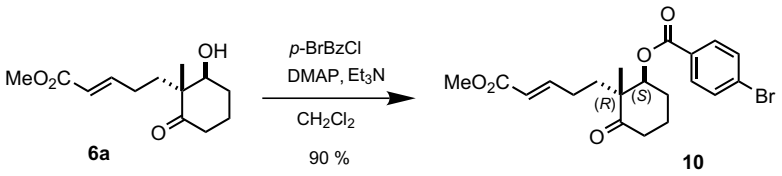
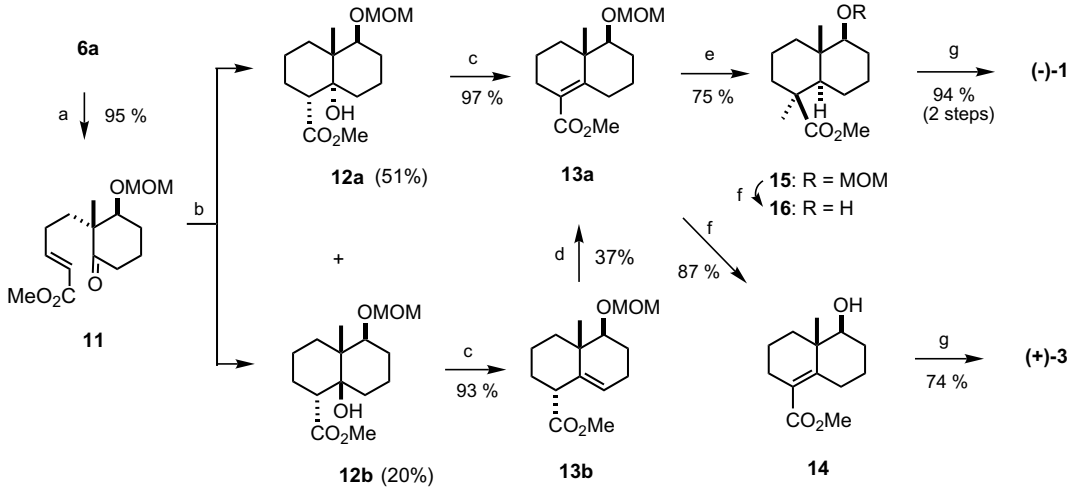


Figure 2. Determination of stereochemistry of **6a** by conversion to **10**.[11]



Scheme 3. Synthetic route of (−)-**1** and (+)-**3** from **6a**. Reagents: (a) MOMCl, *i*-Pr_2NEt, THF; (b) CuI, MeLi, DIBAL, THF–HMPA; (c) $SOCl_2$, py; (d) DBU; (e) Li, liq. NH_3, then MeI; (f) 6 M HCl; (g) Jones reagent.

oxidation to afford (−)-**1**. All the spectral and physical data of (−)-**1** obtained completely coincided with those in the literature[9] (Scheme 3).

3. Conclusion

In conclusion, we have established an effective synthetic route to (−)-**1** and (+)-**3**, which are key intermediates in the synthesis of bioactive terpenoids, by using a baker's yeast-catalyzed asymmetric reduction of a σ-symmetrical 1,3-cyclohexanedione. Our method required only eight and/or nine steps in order to synthesize (−)-**1** and (+)-**3** from commercially available 2-methylcyclohexa-1,3-dione **4**, with the overall yields proving satisfactory (30% and 27%, respectively). Moreover, since the key reaction, the baker's yeast-catalyzed reduction of **5**, was attained in an aqueous medium and at room temperature, it can be easily scaled up to afford large amounts of the enantiomerically pure intermediates for the synthesis of many bioactive natural products. The synthesis of bicyclic diterpenes, which showed potent anti-tumor activities, from (−)-**1** is currently in progress, and will be published elsewhere.[10]

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^1H NMR spectra were obtained on a JEOL JNM-AL300, or a Varian Unity INOVA-400 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a Varian Unity INOVA-400 or a Varian GEMINI 2000/200 spectrometer with $CDCl_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Chiral HPLC analyses were performed with a Shimadzu LC-10A Liquid Chromatograph series using a Daicel chiral column (CHIRALCEL OJ or CHIRALPAK AS). Their data were recorded on Shimadzu C-R6A Chromatopac. Wakogel C-200 (silica gel) (100–200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed by using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support of an immobile phase. Kieselgel 60 F-254 plates (0.25 mm, Merck) were used for thin layer chromatography (TLC). Unless purification with silica gel gave compounds pure enough, the compounds were treated further with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H). Diastereomeric mixtures were also separated by a recycle HPLC (JAI LC-908) on silica gel column (Kusano Si-10) after the purification mentioned above.

4.2. 3-(2-Methyl-1,3-dioxocyclohexyl)propionaldehyde 4

Acrolein (2.4 ml, 31.9 mmol) and distilled water (20 ml) were added to a suspension of 2-methyl-1,3-cyclohexanedione (2.01 g, 15.9 mmol) in tetrahydrofuran (20 ml), and

the mixture stirred for 21 h at room temperature. After the reaction, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 2:1) to afford **4** (2.69 g, 93%) as a colorless oil. Compound **4**; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.92–2.02 (m, 2H), 2.09–2.14 (m, 2H), 2.33–2.38 (m, 2H), 2.63–2.74 (m, 4H), 9.69 (t, $J = 1.1$ Hz, 1H); IR ($CHCl_3$): 3028, 2966, 2939, 2361, 1724, 1697, 1458 cm^{-1}; MS (70 eV) *m*/*z*: 182 (M^+, 28), 164 (4), 154 (17), 126 (78), 111 (37), 98 (59), 83 (21), 69 (59), 55 (100); HRMS calcd for $C_{10}H_{14}O_3$ (M^+): 182.0943, found: 182.0932.

4.3. Methyl (*E*)-5-(2-methyl-1,3-dioxocyclohexyl)-2-pentenoate 5

A solution of **4** in toluene (5 ml) was added to a suspension of methyl (triphenylphosphoranylidene)acetate (7.71 g, 23.0 mmol) in toluene (30 ml) at 0 °C, and the mixture stirred for 1 h while keeping the temperature same. After the reaction, the organic solvent was removed in vacuo and the residue purified by silica gel column chromatography (hexane–ethyl acetate = 1:1) to afford **5** (3.65 g, 80%) as a colorless oil. Compound **5**; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.90–2.07 (m, 6H), 2.58–2.75 (m, 4H), 3.72 (s, 3H), 5.80 (dt, $J = 15.5$ and 1.5 Hz, 1H), 6.86 (dt, $J = 15.5$ and 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 21.3, 27.5, 34.0, 37.9 (2), 51.5, 64.8, 121.5, 147.7, 166.8, 215.3 (2); IR ($CHCl_3$): 3020, 2955, 1693, 1659, 1458, 1439 cm^{-1}; MS (70 eV) *m*/*z*: 238 (M^+, 2), 207 (6), 139 (26), 126 (20), 113 (100), 98 (32), 81 (43), 69 (49), 55 (38); HRMS calcd for $C_{13}H_{18}O_4$ (M^+): 238.1205, found: 238.1200.

4.4. (−)-Methyl (*E*)-5-[(2*R*,3*S*)-3-hydroxy-2-methyl-1-oxocyclohexyl]-2-pentenoate 6a and methyl (*E*)-5-[(2*S*,3*S*)-3-hydroxy-2-methyl-1-oxocyclohexyl]-2-pentenoate 6b

4.4.1. Condition A. A solution of **5** (1.10 g, 4.62 mmol) in dimethyl sulfoxide (10 ml) was added to a suspension of baker's yeast (Sigma type II, 13.8 g) in distilled water (100 ml) and the mixture stirred for 24 h at 30 °C. Another baker's yeast (Sigma type II, 13.8 g) was then added to the reaction mixture, which was stirred for a further 24 h. The reaction mixture was filtered through Hyflo-Super-Cel®, which was washed with ethyl acetate (200 ml). The organic layer was washed with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 1:1) to afford a mixture of diastereomers **6a** and **6b** (651 mg, 67%, **6a**:**6b** = 94:6) as a colorless oil.

4.4.2. Condition B. A solution of **5** (100 mg, 0.42 mmol) in dimethyl sulfoxide (1 ml) was added to a suspension of baker's yeast (Sigma type II, 1.26 g) and sucrose (2.52 g) in distilled water (10 ml) and the mixture stirred for 24 h at 30 °C. Another baker's yeast (Sigma type II, 1.26 g) was then added to the reaction mixture, which was stirred for a further 24 h. The reaction mixture was filtered through Hyflo-Super-Cel®, which was washed with ethyl acetate (200 ml). The organic layer was washed with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 1:1) to afford a mixture of diastereomers **6a** and **6b** (86 mg, 85%, **6a**:**6b** = 91:9) as a colorless oil.

Compound **6a**; $[\alpha]_D^{20} = -19.2$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.64–2.44 (m, 11H), 3.72 (s, 3H), 3.84–3.88 (m, 1H), 5.83 (dt, $J = 15.4$ and 1.6 Hz, 1H), 6.95 (dt, $J = 15.4$ and 6.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.5, 20.5, 27.0, 28.7, 33.7, 37.7, 51.5, 54.2, 75.3, 121.0, 148.7, 166.9, 213.3; IR ($CHCl_3$): 2950, 1709, 1659, 1439, 1327, 1281, 1177, 1045, 961 cm^{-1}; MS (70 eV) *m*/*z*: 240 (M^+, 1), 222 (2), 208 (5), 191 (10), 141 (27), 128 (91), 100 (100), 87 (71), 68 (52), 55 (52); HRMS calcd for $C_{13}H_{20}O_4$ (M^+): 240.1361, found: 240.1355.

Compound **6b**; $[\alpha]_D^{25} = +58.2$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.60–1.69 (m, 2H), 1.74–2.06 (m, 6H), 2.13–2.23 (m, 1H), 2.32–2.42 (m, 2H), 3.72 (s, 3H), 3.72–3.76 (br m, 1H), 5.84 (dt, $J = 15.7$ and 1.6 Hz, 1H), 6.96 (dt, $J = 15.7$ and 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 20.6, 26.3, 28.8, 30.0, 37.5, 51.5, 54.1, 77.2, 121.1, 148.9, 167.0, 213.4; IR ($CHCl_3$): 3614, 3483, 2951, 1707, 1657, 1437, 1281, 1238, 1180, 1061, 1043 cm^{-1}; MS (20 eV) *m*/*z*: 240 (M^+, 1), 222 (1), 208 (5), 191 (8), 141 (45), 128 (100), 113 (37), 100 (63), 95 (38), 81 (18), 68 (9); HRMS calcd for $C_{13}H_{20}O_4$ (M^+): 240.1361, found: 240.1365.

4.5. (−)-(2*S*,3*S*)-3-Acetoxy-1,1-ethylenedioxy-2-methyl-2-(3-acetoxypropyl)cyclohexane 7

Acetic anhydride (3 ml) was added to a solution of **6a** (407 mg, 1.69 mmol) in pyridine (3 ml) and the mixture stirred for 2 h at room temperature. After the reaction, the mixture was quenched by adding methanol and then condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 3:1) to afford the acetate (474 mg, 99%). Next, 2-ethyl-2-methyl-1,3-dioxolane (4 ml) and *p*-toluenesulfonic acid (catalytic amount) were added to a solution of the acetate (450 mg, 1.59 mmol) in ethylene glycol (2 ml), and the reaction mixture then stirred for 12 h at room temperature. After the reaction, the reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 2:1) to afford **8** (411 mg, 79%) as a colorless oil. Ozone gas was then bubbled into a solution of **8** (66 mg, 0.203 mmol) in methanol (5 ml) at −78 °C for 30 min. After the excess ozone was excluded by bubbling nitrogen gas, sodium borohydride (27 mg, 0.609 mmol) was added and the reaction mixture stirred for 1 h at 0 °C. The organic solvent was removed in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium

chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by column chromatography (hexane–ethyl acetate = 3:2) to afford the primary alcohol **9** (34 mg, 62%). Next, acetic anhydride (1 ml) was added to a solution of **9** (30 mg, 0.11 mmol) in pyridine (1 ml) and the mixture stirred for 14 h at room temperature. The reaction was quenched by adding methanol, and the organic solvent removed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 3:2) to afford **7** (33 mg, 96%) as a colorless oil. Compound **7**; $[\alpha]_D^{25} = +23.7$ (*c* 1.48, $CHCl_3$); IR ($CHCl_3$): 2959, 2885, 1728, 1369, 1253, 1196, 1038 cm^{-1}; MS (FAB) *m*/*z*: 337 (M^++Na, 65); HRMS calcd for $C_{16}H_{26}O_6Na$ (M^++Na): 337.1627, found: 337.1631. ^1H and ^{13}C NMR are shown in Table 2.

4.6. (+)-Methyl (*E*)-5-[(2*R*,3*S*)-3-(4-bromobenzoyloxy)-2-methyl-1-oxocyclohexyl]-2-pentenoate 10

p-Bromobenzoyl chloride (1.1 g, 4.84 mmol), triethylamine (0.84 ml, 6.05 mmol), and 4-dimethylaminopyridine (60 mg, 0.48 mmol) were added to a solution of **6a** (291 mg, 1.21 mmol) in dichloromethane (5 ml) and the mixture refluxed for 4 days. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 5:1) to afford **10** (460 mg, 90%) as colorless plates. Compound **10**; mp 94–95 °C (ethyl acetate); $[\alpha]_D^{20} = +44.4$ (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.73–1.93 (m, 3H), 1.98–2.10 (m, 3H), 2.19–2.30 (m, 2H), 2.43–2.55 (m, 2H), 3.72 (s, 3H), 5.32 (dd, $J = 5.7$ and 2.5 Hz, 1H), 5.83 (dt, $J = 15.7$ and 1.5 Hz, 1H), 6.91 (dt, $J = 15.7$ and 6.8 Hz, 1H), 7.57–7.60 (m, 2H), 7.83–7.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 20.9, 25.5, 26.6, 34.2, 37.7, 51.5, 52.8, 78.4, 121.5, 128.5, 128.7, 131.1 (2), 131.9 (2), 147.9, 164.7, 166.8, 212.1; IR ($CHCl_3$): 1715, 1659, 1541, 1437, 1070 cm^{-1}; MS (70 eV) *m*/*z*: 424 (M^++2, 1), 422 (M^+, 1), 392 (8), 390 (8), 185 (53), 183 (58), 155 (13), 110 (100), 95 (11), 82 (19), 68 (15), 55 (20); HRMS calcd for $C_{20}H_{23}BrO_5$ (M^+): 422.0728, found: 422.0729. Anal. Calcd for $C_{20}H_{23}BrO_5$: C, 56.75; H, 5.48. Found: C, 56.68; H, 5.53.

4.7. (+)-Methyl (*E*)-5-[(2*R*,3*S*)-(3-methoxymethoxy-2-methyl-1-oxocyclohexyl)]-2-pentenoate 11

Di-*i*-propylethylamine (2.73 ml, 35.5 mmol) and methoxymethyl chloride (2.25 ml, 29.6 mmol) were added to a suspension of **6a** (1.42 g, 5.91 mmol) in tetrahydrofuran (20 ml) and the mixture refluxed for 12 h. After the reaction, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (50 ml) and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 3:1) to afford **11** (1.50 g, 90%) as a colorless oil. Compound **11**; $[\alpha]_D^{25} = +1.86$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.63–1.81 (m, 3H), 1.85–1.92 (m, 1H), 1.95–2.11 (m, 3H), 2.15–2.26 (m, 1H), 2.30–2.44 (m, 2H), 3.37 (s, 3H), 3.72 (dd, $J = 6.0$ and 3.5 Hz, 1H), 3.73 (s, 3H), 4.56 (ABd, $J_{AB} = 7.0$ Hz, 1H), 4.71 (ABd, $J_{AB} = 7.0$ Hz, 1H), 5.83 (dt, $J = 15.7$ and 1.6 Hz, 1H), 6.95 (dt, $J = 15.7$ and 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 20.4, 25.3, 26.8, 33.9, 37.8, 51.5, 53.8, 55.9, 80.7, 95.5, 121.1, 148.8, 167.0, 213.3; IR ($CHCl_3$): 3034, 3020, 2951, 1706, 1655, 1437, 1036 cm^{-1}; MS (20 eV) *m*/*z*: 284 (M^+, 3), 252 (4), 220 (8), 190 (21), 172 (21), 153 (33), 123 (28), 110 (100), 95 (16), 81 (23), 68 (12); HRMS calcd for $C_{15}H_{24}O_5$ (M^+): 284.1616, found: 286.1624.

4.8. (+)-Methyl (2*R*,4a*R*,5*S*,8a*S*)-8a-hydroxy-5-methoxymethoxy-4a-methyldecahydronaphthalene-1-carboxylate 12a and (−)-methyl (2*R*,4a*R*,5*S*,8a*R*)-8a-hydroxy-5-methoxymethoxy-4a-methyldecahydronaphthalene-1-carboxylate 12b

Methyllithium (1.07 M solution in Et_2O, 1.64 ml, 1.76 mmol) was added to a suspension of cuprous iodide (335 mg, 1.76 mmol) in tetrahydrofuran (2 ml) at −50 °C and the mixture was stirred for 30 min. HMPA (0.6 ml) and DIBAL-H (1.0 M solution in *n*-hexane, 1.76 mmol, 1.76 ml) were added to the mixture and the mixture was stirred for another 30 min. A solution of (+)-**11** (50 mg, 0.17 mmol) in THF (1 ml) was added dropwise to the reaction mixture, which was stirred for 2 h while keeping the temperature at −50 °C and for 48 h at room temperature. The reaction mixture was poured into 1 M hydrochloric acid and extracted with diethyl ether. The organic layer was successively washed with a saturated aqueous solution of sodium thiosulfate and that of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 5:1→3:1) to afford (+)-**12a** (26 mg, 51%) and (−)-**12b** (10 mg, 20%).

Compound **12a**: coloress oil; $[\alpha]_D^{25} = +75.6$ (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.19–1.38 (m, 2H), 1.46–2.02 (m, 10H), 2.90 (dd, $J = 14.2$ and 7.0 Hz, 1H), 3.37 (s, 3H), 3.69 (s, 3H), 3.76 (s, 1H, –O*H*), 3.81 (dd, $J = 11.5$ and 4.8 Hz, 1H), 4.55 (ABd, $J_{AB} = 7.0$ Hz, 1H), 4.72 (ABd, $J_{AB} = 7.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 19.9, 20.2, 26.0, 26.7, 29.4, 33.4, 42.9, 44.9, 52.0, 55.8, 73.3, 74.1, 95.5, 177.6; IR ($CHCl_3$): 3034, 2951, 2359, 2341, 1711, 1454, 1437 cm^{-1}; MS (20 eV) *m*/*z*: 286 (M^+, 2), 254 (12), 241 (30), 236 (37), 224 (48), 206 (66), 192 (100), 170 (54), 138 (94), 121 (47), 85 (59); HRMS calcd for $C_{15}H_{26}O_5$ (M^+): 286.1780, found: 286.1784.

Compound **12b**: colorless needles; mp 68 °C (hexane/ethyl acetate); $[\alpha]_D^{23} = -31.9$ (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.10–1.16 (m, 1H), 1.20 (s, 3H), 1.48–1.80 (m, 9H), 1.80–1.93 (m, 1H), 1.98 (dt, $J = 13.6$ and 4.2 Hz, 1H), 2.81–2.87 (m, 1H), 3.40 (s, 3H), 3.40 (m, 1H), 3.70 (s, 3H), 4.25 (s, 1H, –O*H*), 4.59 (ABd, $J_{AB} = 7.1$ Hz, 1H), 4.70 (ABd, $J_{AB} = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 17.7, 19.8, 24.4, 25.9, 28.3, 32.2, 41.6, 48.5, 51.6, 56.1, 74.8, 83.9, 95.7, 174.7; IR ($CHCl_3$): 3506, 3034, 2951, 1726, 1467, 1437, 1151, 1028 cm^{-1}.

4.9. (+)-Methyl (4a*R*,5*S*)-5-methoxymethoxy-4a-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-1-carboxylate 13a

Thionyl chloride (2.5 ml) was added to a solution of **12a** (1.02 g, 3.57 mmol) in pyridine (10 ml) and stirred for 1 h at room temperature. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 5:1) to afford **13a** (926 mg, 97%) as a colorless oil. Compound (+)-**13a**; $[\alpha]_D^{25} = +149$ (*c* 0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 3H), 1.18–1.32 (m, 2H), 1.42–1.72 (m, 4H), 1.74–1.86 (m, 2H), 1.86–2.04 (m, 2H), 2.14–2.30 (m, 2H), 2.68–2.76 (m, 1H), 3.26 (dd, $J = 11.5$ and 4.6 Hz, 1H), 3.38 (s, 3H), 3.71 (s, 3H), 4.56 (ABd, $J_{AB} = 6.8$ Hz, 1H), 4.69 (ABd, $J_{AB} = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 19.0, 23.9, 27.0, 27.6, 27.8, 35.6, 41.0, 51.4, 55.6, 84.0, 95.8, 125.9, 147.7, 171.0; IR ($CHCl_3$): 3032, 2947, 2866, 1709, 1448, 1435, 1238, 1138, 1099, 1036 cm^{-1}; MS (20 eV) *m*/*z*: 268 (M^+, 2), 236 (27), 206 (88), 192 (64), 174 (26), 164 (21), 147 (100), 131 (24), 105 (22), 91 (11); HRMS calcd for $C_{15}H_{22}O_4$ (M^+): 268.1674, found: 268.1666.

4.10. (−)-Methyl (2*R*,4a*R*,5*S*)-5-methoxymethoxy-4a-methyl-1,2,3,4,4a,5,6,7-octahydronaphthalene-1-carboxylate 13b

Thionyl chloride (0.5 ml) was added to a solution of **12b** (226 mg, 0.79 mmol) in pyridine (2 ml) and stirred for 1 h at room temperature. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 5:1) to afford **13b** (197 mg, 93%) as a colorless oil. Compound **13b**; $[\alpha]_D^{22} = -88.7$ (*c* 0.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.20–1.28 (m, 1H), 1.52–1.70 (m, 4H), 1.79–1.85 (m, 1H), 1.86–1.90 (m, 1H), 1.99–2.03 (m, 1H), 2.07–2.12 (m, 2H), 3.20–3.26 (m, 1H), 3.39 (s, 3H), 3.41 (dd, $J = 12.1$ and 3.5 Hz, 1H), 3.71 (s, 3H), 4.62 (ABd, $J_{AB} = 6.8$ Hz, 1H), 4.75 (ABd, $J_{AB} = 6.8$ Hz, 1H), 5.06 (dd, J =5.4 and 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 20.8, 23.6, 24.8, 30.6, 38.4, 40.0, 46.9, 51.7, 55.7, 83.9, 95.9, 119.2, 140.1, 175.3; IR ($CHCl_3$): 2947, 2889, 1730, 1460, 1437, 1375, 1319, 1147, 1045 cm^{-1}; MS (20 eV) *m*/*z*: 268 (M^+, 2), 236 (59), 218 (11), 208 (19), 191 (21), 180 (44); HRMS calcd for $C_{15}H_{22}O_4$ (M^+): 268.1674, found: 268.1679.

4.11. Isomerization from 13b to 13a

DBU (553 μl, 3.70 mmol) was added to a solution of **13b** (100 mg, 0.37 mmol) in toluene (5 ml) and the mixture refluxed for 24 h. After the reaction, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 5:1) to afford a mixture of **13a** and **13b** (98 mg, **13a**:**13b** = 62:38). The ratio was determined on the basis of the integral values of the olefinic protons.

4.12. (+)-Methyl (4a*R*,5*S*)-5-hydroxy-4a-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-1-carboxylate 14

Hydrochloric acid (6 M, 4 ml) was added to a solution of **13a** (33 mg, 0.123 mmol) in acetone (4 ml) and the mixture stirred for 10 h at room temperature. After the reaction, the reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 2:1) to afford **14** (24 mg, 87%) as colorless needles. Compound **14**; mp 82–84 °C, $[\alpha]_D^{25} = +162$ (*c* 0.44, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 3H), 1.22–1.38 (m, 1H), 1.22–1.74 (m, 5H), 1.74–1.84 (m, 3H), 1.93–2.05 (m, 1H), 2.17–2.31 (m, 2H), 2.70–2.78 (m, 1H), 3.39 (dd, $J = 11.6$ and 4.3 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 18.1, 24.0, 26.8, 27.8, 30.4, 35.4, 41.3, 51.5, 78.5, 126.1, 147.5, 170.9; IR ($CHCl_3$): 2943, 2866, 1709, 1603, 1435, 1274, 1238, 1097 cm^{-1}; MS (70 eV) *m*/*z*: 224 (M^+, 5), 206 (25), 192 (80), 180 (12); HRMS calcd for $C_{13}H_{20}O_3$ (M^+): 224.1412, found: 224.1408.

4.13. (+)-Methyl (4a*R*)-4a-methyl-5-oxo-2,3,4,4a,5,6,7,8-octahydronaphthalene-1-carboxylate (+)-3[6]

Jones' reagent (0.5 ml) was added to a solution of **14** (24 mg, 0.107 mmol) in acetone (5 ml) at 0 °C and the mixture stirred for 30 min while keeping the temperature constant. The reaction was then quenched by adding 2-propanol (1 ml) to the reaction mixture, which was stirred for another 10 min. The reaction mixture was filtered through Hyflo-Super-Cel®, which was washed with acetone. The filtrate was condensed in vacuo and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 5:1) to afford (+)-**3** (18 mg, 74%) as a colorless oil. Compound (+)-**3**; $[\alpha]_D^{25} = +189$ (*c* 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.56–1.70 (m, 4H), 1.89–1.96 (m, 1H), 1.99–2.07 (m, 1H), 2.17–2.31 (m, 2H), 2.35–2.45 (m, 2H), 2.59–2.69 (m, 1H), 3.06–3.14 (m, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 23.5, 25.8, 26.6, 27.4, 30.9, 37.7, 51.3, 51.6, 127.0, 146.4, 170.1, 213.5; IR ($CHCl_3$): 2951, 1707, 1630, 1456, 1435, 1275, 1238, 1086, 1011 cm^{-1}; MS (70 eV) *m*/*z*: 222 (M^+, 19), 204 (5), 191 (7), 163 (100), 135 (25), 121 (17); HRMS calcd for $C_{13}H_{18}O_3$ (M^+): 222.1256, found: 222.1252; HPLC analysis >99% ee [Daicel CHIRALPAK AS (25 × 0.46), eluent; hexane–isopropanol = 99:1, flow rate; 0.5 ml/min, temperature 25 °C, detector; 254 nm, (+)-**3**: 31 min, (−)-**3**: 51 min.

4.14. (+)-Methyl (2*S*,4a*R*,5*S*,8a*R*)-5-methoxymethoxy-1,4a-dimethyldecahydronaphthalene-1-carboxylate 15

Lithium metal (130 mg, 18.7 mmol) was added to liquid ammonia (70 ml) and the mixture stirred for 30 min at −78 °C, to which a solution of **13a** (715 mg, 2.67 mmol) in dimethoxyethane (5 ml) was added. The reaction mixture was stirred for 30 min at −33 °C and liquid ammonia was removed as gas. Methyl iodide (11.6 ml, 0.187 mol) was added and the mixture neutralized with 1 M hydrochloric acid followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 10:1) to afford **15** (568 mg, 75%) as a colorless oil. Compound **15**; $[\alpha]_D^{25} = +27.6$ (*c* 2.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (s, 3H), 0.99–1.09 (m, 3H), 1.12–1.23 (m, 4H), 1.36–1.51 (m, 2H), 1.56–1.97 (m, 6H), 2.14–2.20 (m, 1H), 3.02 (dd, $J = 11.7$ and 4.7 Hz, 1H), 3.36 (s, 3H), 3.65 (s, 3H), 4.56 (ABd, $J_{AB} = 6.8$ Hz, 1H), 4.69 (ABd, $J_{AB} = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 19.1, 22.8, 24.8, 27.5, 28.7, 38.19, 38.23, 39.8, 43.6, 51.2, 53.9, 55.5, 86.0, 95.7, 177.8; IR ($CHCl_3$): 2939, 1717, 1603, 1466, 1448, 1144, 1043, 1030 cm^{-1}; MS (20 eV) *m*/*z*: 284 (M^+, 2), 252 (24), 234 (10), 222 (25), 207 (13), 179 (38), 161 (100), 147 (20), 134 (22), 122 (33), 107 (43), 94 (28), 81 (25), 71 (24); HRMS calcd for $C_{16}H_{28}O_4$ (M^+): 284.1989, found: 284.1987.

4.15. (+)-Methyl (2*S*,4a*R*,5*S*,8a*R*)-5-hydroxy-1,4a-dimethyldecahydronaphthalene-1-carboxylate 16

Hydrochloric acid (6 M, 4 ml) was added to a solution of **15** (20 mg, 0.076 mmol) in acetone (4 ml) and the mixture stirred for 3 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by (hexane–ethyl acetate = 2:1) to afford **16** (17 mg, 99%) as a colorless oil. Compound **16**; $[\alpha]_D^{25} = +20.2$ (*c* 2.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (s, 3H), 1.00–1.14 (m, 3H), 1.18 (s, 3H), 1.19–1.28 (m, 1H), 1.34 (br s, 1H), 1.38–1.53 (m, 2H), 1.58–1.71 (m, 2H), 1.76–1.91 (m, 4H), 2.16–2.21 (m, 1H), 3.13–3.16 (m, 1H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 19.1, 22.8, 24.8, 28.7, 30.3, 37.9, 38.2, 39.9, 43.6, 51.2, 53.4, 80.6, 177.7; IR ($CHCl_3$): 3612, 2937, 2860, 1717, 1448, 1157, 1051 cm^{-1}; MS (70 eV) *m*/*z*: 240 (M^+, 1), 222 (4), 208 (2), 190 (2), 181 (24), 163 (15), 121 (9), 107 (13), 83 (100), 69 (18), 55 (31); HRMS calcd for $C_{14}H_{24}O_3$ (M^+): 240.1732, found: 240.1725.

4.16. (−)-Methyl (2*S*,4a*R*,8a*R*)-1,4a-dimethyl-5-oxodecahydronaphthalene-1-carboxylate (−)-1[9]

Jones' reagent (1 ml) was added to a solution of **16** (258 mg, 1.07 mmol) in acetone (20 ml) at 0 °C, and the mixture stirred for 30 min while keeping the temperature constant. The reaction was quenched by adding 2-propanol (3 ml) and stirred for 10 min, after which the reaction mixture was filtered through Hyflo-Super-Cel® which was washed with ethyl acetate. The organic layer of the filtrate was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 8:1) to afford (−)-**1** (237 mg, 97%) as colorless plates. Compound (−)-**1**; mp 82–84 °C (diethyl ether); $[\alpha]_D^{25} = -35.0$ (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 0.98–1.06 (m, 1H), 1.22 (s, 3H), 1.37–1.62 (m, 4H), 1.67–1.87 (m, 2H), 1.98–2.28 (m, 5H), 2.59 (dt, $J = 14.1$ and 6.4 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 19.0, 23.0, 26.7, 28.8, 33.4, 37.9, 38.2, 44.5, 49.6, 51.7, 54.8, 177.6, 215.7; IR ($CHCl_3$): 2951, 2868, 1719, 1701, 1460, 1450, 1250, 1153 cm^{-1}; MS (70 eV) *m*/*z*: 238 (M^+, 6), 210 (19), 179 (8), 163 (6), 151 (21), 135 (15), 123 (16), 109 (100), 95 (30), 81 (29), 67 (27), 55 (35); HRMS calcd for $C_{14}H_{22}O_3$ (M^+): 238.1569, found: 238.1567. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.70; H, 9.42.

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11. Crystal data for Figure 2 have been deposited with the Cambridge Crystallographic Data Centre (Deposition number 610 518).