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Parallel kinetic resolution of propargyl ketols: formal synthesis of (+)-bakkenolide A

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Abstract

We describe an intriguing new example of a parallel kinetic resolution; an asymmetric cyclization–carbonylation of propargyl ketols catalyzed by palladium(II) with chiral bisoxazoline (box) ligands. The 2*S*,3*S* enantiomer of (±)-**6** was preferentially converted to **13** (45–49% yields, 37–46% ee), and the 2*R*,3*R* enantiomer of (±)-**6** was preferentially converted to **14** (21–23% yields, 92–97% ee). As an application of this reaction, formal synthesis of (+)-bakkenolide A was achieved.

Keywords: Palladium; Bisoxazoline; Parallel kinetic resolution; Carbonylation; Hydrindane

1. Introduction

Palladium(II)-catalyzed reactions are of fundamental importance in the area of organic transformations.[1] In contrast to the impressive development of Pd(II)-catalyzed oxidative asymmetric reactions of alkenes,[2] those of alkynes have received scant attention.[3] We previously reported the first examples of asymmetric cyclization–carbonylation of *meso*-2-alkyl-2-propargylcyclohexane-1,3-diols[3a,b] and 2-alkyl-2-propargylcyclohexane-1,3-diones[3c,d] catalyzed by palladium(II) with chiral bisoxazoline (box) ligands. During the course of our study,[4] we became interested in comparing the reactivity of hydroxyl groups and carbonyl groups in the Pd(II)-catalyzed cyclization–carbonylation reaction. First, we investigated chemoselectivity in the Pd(II)-catalyzed cyclization–carbonylation reactions of propargyl ketols **3**–**6a**. Based on these results, we investigated a new example of a parallel kinetic resolution;[5] an asymmetric cyclization–carbonylation of propargyl ketols (±)-**6** catalyzed by palladium(II) with box ligands.

2. Results and discussion

2.1. Preparation of substrates

Substrates **3** and **4** were synthesized from the known β-keto ester **1** (Scheme 1).[6] Acetalization of **1** followed by reduction of the ester group and subsequent acid hydrolysis gave ketol **3** in 56% yield (three steps). Treatment of **2** with MeLi followed by acid hydrolysis gave ketol **4** in 74% yield (three steps). Substrates **5** and **6** were prepared from the corresponding 2-methylcyclohexane-1,3-dione.[7]

2.2. Comparison of the reactivity of hydroxyl group and carbonyl group (chemoselectivity)

As shown in Scheme 2, cyclization–methoxycarbonylation of acyclic ketol **3** in the presence of $(CH_3CN)_2PdCl_2$ (5 mol %) and *p*-benzoquinone (1.1 equiv) in methanol at −20 °C under a carbon monoxide atmosphere (balloon) afforded alcohol **7** (1:1 mixture of diastereomers, 37% yield) together with ketone **8** (1:1 mixture of diastereomers, 32% yield). Acyclic ketol **4** containing a tertiary alcohol group also produced a ca. 1:1 mixture of alcohol **9a** (3.8:1 mixture of diastereomers, 28% yield)

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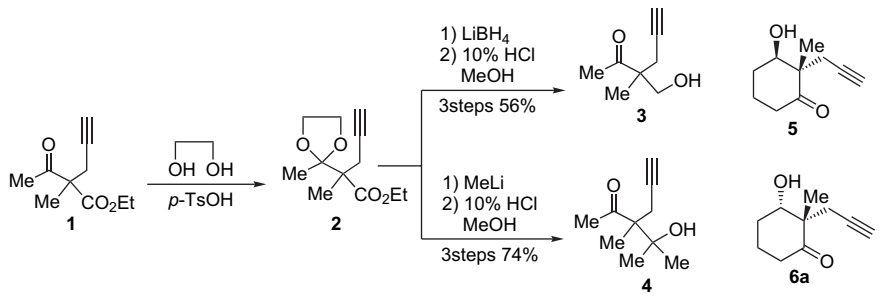
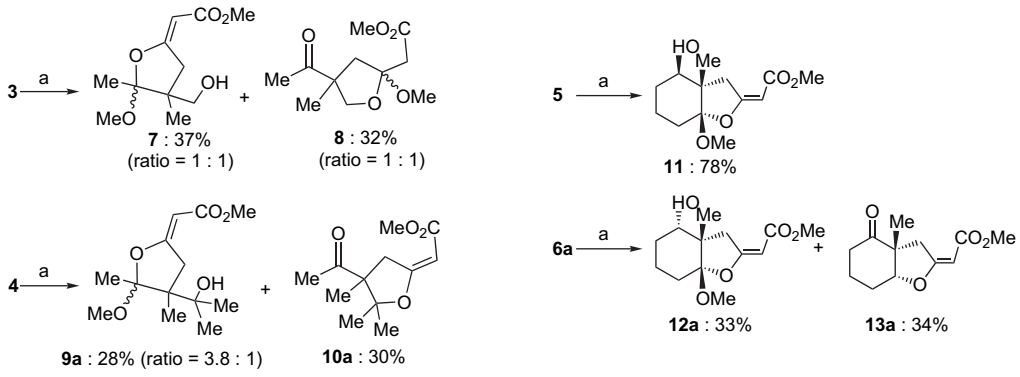
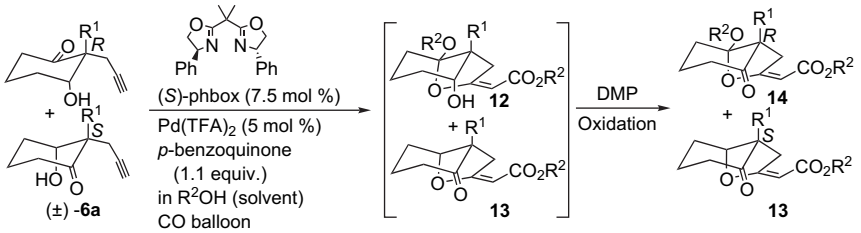


Scheme 1.



Scheme 2.



Scheme 3.

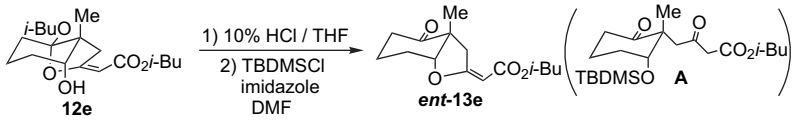
and ketone **10a** (30% yield). The reactivity of the carbonyl oxygen (ketone) was unexpectedly high, almost the same as that of the hydroxyl group. Next, we examined the six-membered ring substrates **5** and **6**. We previously reported that the hydroxyl group bearing a cis-relationship to the propargyl group was more reactive than the trans-hydroxyl group.[3a] The reaction of *trans*-ketol **5** afforded secondary alcohol **11**; a ketone was not obtained. However, *cis*-ketol **6a** gave a ca. 1:1 mixture of alcohol **12a** and ketone **13a**. Thus, *cis*-ketol **6a** was selected as a suitable substrate for subsequent parallel kinetic resolution.

2.3. Parallel kinetic resolution of (±)-6a

Cyclization–methoxycarbonylation of (±)-**6a** in the presence of $Pd(TFA)_2$ (5 mol %), (*S*)-phbox (7.5 mol %), and *p*-benzoquinone (1.1 equiv) in methanol at −20 °C under a carbon monoxide atmosphere (balloon) afforded a mixture of alcohol **12a** and ketone **13a**. The crude product was oxidized with DMP reagent to give two types of optically active products, **13a** (43% ee) and **14a** (31% ee), in 45% and 34% yield, respectively (Scheme 3, entry 1, Table 1).[8] The

Table 1
Parallel kinetic resolution of **6a** (R^1=Me) (Scheme 3)

Entry	Solvent (R^2OH)	Conditions	Product: **13**; yield % (ee %)	Product: **14**; yield % (ee %)
1	MeOH	−20 °C, 20h	**13a**; 45 (43)	**14a**; 34 (31)
2	EtOH	−50 °C, 132 h	**13b**; 51 (45)	**14b**; 25 (43)
3	*n*-PrOH	−50 to −30 °C, 67 h	**13c**; 52 (49)	**14c**; 29 (71)
4	*n*-BuOH	−50 to −30 °C, 67 h	**13d**; 49 (42)	**14d**; 24 (82)
5	*i*-BuOH	−20 °C, 20 h	**13e**; 41 (35)	**14e**; 23 (91)
6	Isopentanol	−20 °C, 20 h	**13f**; 52 (53)	**14f**; 25 (91)
7	*i*-PrOH	−20 °C, 11 days	**13g**; 52 (23)	**14g**; 14 (92)



Scheme 4.

bulkiness of the alcohol used in the reaction strongly affected the enantioselectivity of the products **14**, as shown in entries 1–6. When the reaction was performed using bulky alcohols, the enantiomeric excesses of the products were increased (MeOH 31% ee<EtOH 43% ee<*n*-PrOH 71% ee<*n*-BuOH 82% ee<*i*-BuOH 91% ee=isopentanol 91% ee). The use of a secondary alcohol (*i*-PrOH) as solvent resulted in a higher ee, but the yield was reduced (entry 7).

The absolute configuration of **14e** was determined by correlation of the optical rotation with an authentic sample.[3d] The absolute configuration of **13e** was determined by conversion of **12e** to *ent*-**13e** (Scheme 4). A barely separable mixture of **12e** and **13e** was purified twice by preparative TLC to give a small amount of **12e** in pure form. In an attempt to prepare β-keto ester **A**, **12e** was treated with 10% HCl and subsequently with TBDMSCl/imidazole in DMF, accidentally affording *ent*-**13e** (78%). This result indicated that the absolute configurations of **12** and **13** (or **14** and **13**) are reversed with respect to each other.

2.4. Parallel kinetic resolution of (±)-6: ligand screening

In order to increase the enantioselectivity of the reaction, ligand screening was performed with various box ligands (Table 2, Fig. 1). First, we selected 3,4-dimethoxyphenyl box ligand **15**, which was effective in the asymmetric cyclization–carbonylation of 2-alkyl-2-propargylcyclohexane-1,3-diones.[3d]

Table 2
Parallel kinetic resolution of **6**: ligand screening (Scheme 3)

Entry	R[1]	Ligand	Conditions[a]	Product: **13**; yield % (ee %)	Product: **14**; yield % (ee %)
1	Me	**15**	−35 °C, 24 h	**13e**; 40 (18)	**14e**; 13 (88)
2	Me	**16**	0 °C, 24 h	**13e**; 37 (34)	**14e**; 17 (87)
3	Me	**17**	−30 °C, 63 h	**13e**; 46 (47)	**14e**; 23 (93)
4	Me	**18**	−30 °C, 63 h	**13e**; 50 (41)	**14e**; 22 (94)
5	Me	**18**	−20 °C, 49 h	**13f**; 45 (42)	**14f**; 22 (95)
6	Allyl	**18**	−20 °C, 40 h	**13h**; 49 (37)	**14h**; 23 (92)
7	Propyl	**18**	−20 °C, 70 h	**13i**; 48 (46)	**14i**; 21 (97)

[a] Solvent: entries 1–4, *i*-BuOH; entries 5–7, isopentanol.

Unfortunately, the yield and ee of both **13e** and **14e** were reduced (entry 1, Table 2). Next, three further types of box ligands were examined (entries 2–4). Among these, the 4,5-*cis*-di-2-naphthyl ligand **18** was the most effective, giving **14e** in 94% ee (22% yield) together with **13e** (50%, 41% ee) (entry 4). The use of isopentanol as a solvent resulted in a slight increase in the ee of both products (entry 5). Replacement of the methyl group of substrate **6a** with an allyl group resulted in a slight decrease in selectivity to 92% ee (entry 6), while replacement with a propyl group resulted in an increase to 97% ee (entry 7).

In the case of acyclic substrate (±)-**4**, the reaction becomes complex. The products were obtained in a barely separable mixture of four compounds, and a small amount of each compounds could be obtained in pure form (Scheme 5). The reaction of acyclic substrate (±)-**4** under the conditions in Table 2 (entries 5–7) afforded **9b** (10% yield, 17% ee), **9b′** (7% yield, 11% ee), **10b** (20% yield, 4% ee), and **B** (25% yield, 80% ee). The absolute configuration of the products was not determined.

2.5. Formal synthesis of (+)-bakkenolide A: synthesis of optically active bicyclic ketone 21

As an approach toward developing a synthetic application for the present reaction, product **14f** was converted to optically active bicyclic ketone **21**,[9] a precursor of bakkenolides (Scheme 6).[10] Wittig reaction of **14f** followed by acid hydrolysis afforded the corresponding β-keto ester, which was subjected to Knoevenagel condensation to afford hydrindane **19** in 68% yield (three steps).[3d] *i*-Pentyl ester **19** was converted to methyl ester **20**, which was then subjected to hydrogenation followed by decarboxylation to afford **21** in 54% yield (three steps).

2.6. Plausible mechanism

A possible mechanism for the present reaction is shown in Scheme 7. Two types of reactions may proceed simultaneously with kinetic resolution. The 2*R*,3*R* enantiomer of (±)-**6** was preferentially converted to alcohol **12** by reaction of the carbonyl oxygen, and the 2*S*,3*S* enantiomer of (±)-**6** was

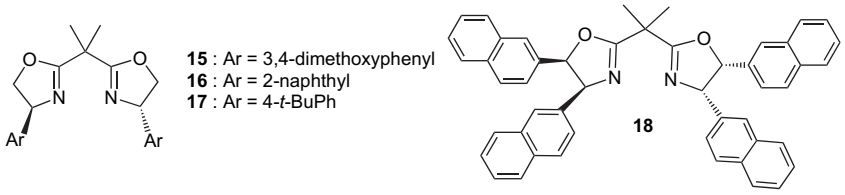
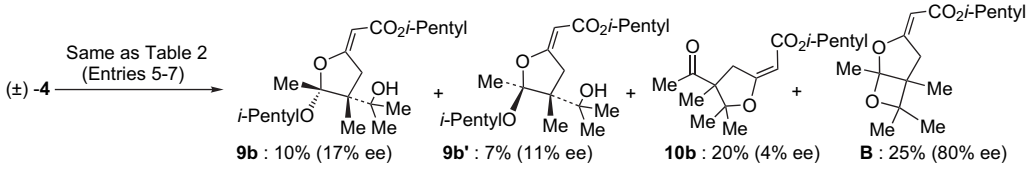
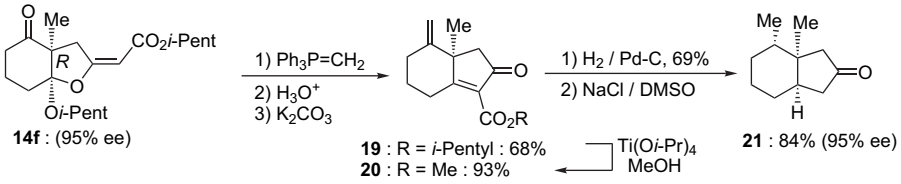


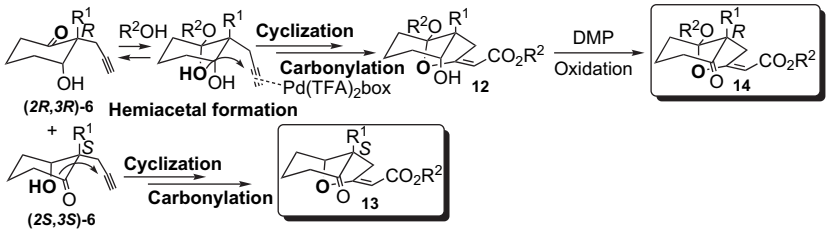
Figure 1. Screening of ligands.



Scheme 5.



Scheme 6.



Scheme 7.

preferentially converted to ketone **13** by reaction of the secondary hydroxyl group. In the former reaction, the bulkiness of the alcohol strongly affected enantioselectivity toward **12** or **14**, as shown in Table 1 (entries 1–7), which suggests that the alcohol is incorporated into the substrate as a hemiacetal before cyclization.[3d] At first, two types of hemiacetal intermediate, with hydroxyl groups that are either trans or cis with respect to the propargyl group, are produced. In general, the hydroxyl group with a cis-relationship to the propargyl group was more reactive than the trans-hydroxyl group.[3d] Coordination of the alkyne to Pd(II) may be induced by an attack by the cis-hydroxyl group, producing a vinyl palladium intermediate, followed by CO insertion and subsequent reaction with R^2OH to provide **12** as a single diastereomer. This was then converted to **14** using DMP reagent. In the reaction of the secondary alcohol, the hydroxyl group cyclized with the Pd(II)-coordinated alkyne with subsequent alkoxy–carbonylation to provide **13**.

Although the precise mechanism of the enantiomer discrimination is still an open question, possible transition states (T_1–T_4) are shown in Figure 2 based on the assigned absolute stereochemistry described above. The reaction might proceed via T_3 and T_4 to avoid steric and/or electronic repulsion between the phenyl ring and hydroxyl group (T_1) or carbonyl group (T_2). In the case of T_1, additional steric and/or electronic repulsion between the bulky alkoxy group and another phenyl ring might be considered.

3. Conclusion

We investigated chemoselectivity in the Pd(II)-catalyzed cyclization–carbonylation reaction of propargyl ketols. The reactivity of the carbonyl oxygen (ketone) was unexpectedly high, almost the same as that of the hydroxyl group. Based

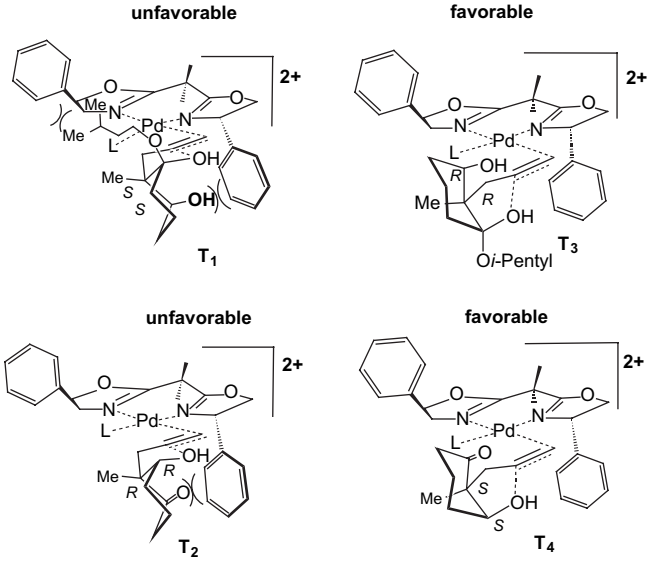


Figure 2. Tentative mechanism of enantiomer discrimination.

on these results, we investigated a new example of parallel kinetic resolution in the oxidative cyclization–carbonylation of racemic propargyl ketol **6**. The 2*S*,3*S* enantiomer of (±)-**6** was preferentially converted to **13** (45–49% yield, 37–46% ee), and the 2*R*,3*R* enantiomer of (±)-**6** was preferentially converted to **14** (21–23% yield, 92–97% ee). The formal synthesis of (+)-bakkenolide A was achieved.

4. Experimental section

4.1. General experimental methods

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 400 and JEOL Lambda 500 spectrometer in $CDCl_3$ with Me_4Si as an internal reference. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FABMS) were obtained with a JEOL GC mate II, a JMS-SX102 and a JEOL JMS 600H spectrometers. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica-gel (Kieselgel 60) was employed. The substrates **5** and **6** were known compounds.[7]

4.2. Preparation of substrates *3* and *4*

4.2.1. Preparation of ethyleneacetal *2*

To a solution of ethylene glycol (7.8 g, 125.6 mmol) and ethyl 2-acetyl-2-methyl-4-pentynoate[2] (11.4 g, 62.6 mmol) in benzene (100 mL) was added *p*-TsOH (754 mg, 4.4 mmol), and the mixture was refluxed with azeotropic removal of water for 12 h. The mixture was quenched with $NaHCO_3$ (1 g), and diluted with EtOAc (50 mL) and satd $NaHCO_3$ aq (100 mL). The layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Crude **2** (14.2 g, quant.) was obtained as a colorless oil, and it was used for the preparation of **3** and **4** without purification.

4.2.2. Preparation of 3-hydroxymethyl-3-methylhex-5-yn-2-one (*3*)

To a solution of **2** (2.0 g, 8.8 mmol) in dry THF (50 mL) was added $LiBH_4$ (585 mg, 26.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc (50 mL) and water (50 mL), and stirred for 12 h. The layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in MeOH (30 mL) was added 10% HCl aq (4 mL), and the mixture was stirred for 4 h. The mixture was diluted with EtOAc (50 mL) and satd $NaHCO_3$aq (80 mL). The layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (15/1) afforded **3** (695 mg, 56%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, s), 2.05 (1H, t, J=2.8 Hz), 2.24 (3H, s), 2.46 (1H, dd, J=2.8, 17.2 Hz), 2.54 (1H, dd, J=2.8, 17.2 Hz), 3.69 (1H, d, J=11.2 Hz), 3.81 (1H, d, J=11.2 Hz); ^{13}C NMR ($CDCl_3$) δ 19.1, 24.1, 26.2, 52.0, 67.0, 71.3, 80.3, 212.4; IR (neat)=3425, 3291, 2926, 1698 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_8H_{12}O_2$ 140.0837; found 140.0833.

4.2.3. Preparation of 3-(1-hydroxy-1-methylethyl)-3-methylhex-5-yn-2-one (*4*)

To a solution of **2** (1.0 g, 4.4 mmol) in dry Et_2O (30 mL) was added MeLi (2 M in ether, 6.6 mL, 13.2 mmol) at −78 °C under an argon atmosphere, and the mixture was stirred at −40 °C for 48 h. The mixture was diluted with satd NH_4Cl aq (40 mL) and EtOAc (50 mL). The layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in MeOH (20 mL) was added 10% HCl aq (4 mL), and the mixture was stirred for 1 h. The mixture was diluted with EtOAc (40 mL) and satd $NaHCO_3$ aq (80 mL). The layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (10/1) afforded **4** (550 mg, 74%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, s), 1.16 (3H, s), 1.38 (3H, s), 1.97 (1H, t, J=2.8 Hz), 2.25 (1H, dd, J=2.8, 14.0 Hz), 2.30 (3H, s), 2.92 (1H, dd, J=2.8, 14.0 Hz), 3.33 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.8, 24.3, 25.0, 26.6, 30.7, 56.4, 70.9, 74.2, 81.6, 217.0; IR (neat)=3469, 3292, 1688 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{10}H_{16}O_2$ 168.1150; found 168.1148.

4.3. General procedure for the cyclization–carbonylation of *3–5* and *6a*

A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $(CH_3CN)_2PdCl_2$ (0.03 mmol), *p*-benzoquinone (0.66 mmol), and MeOH (4 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. The substrate (0.6 mmol) was added dropwise using MeOH (1 mL×3) to the stirred mixture via a syringe at −40 °C. After being stirred at −20 °C for 2.5–12 h, the mixture was diluted with CH_2Cl_2 (30 mL) and 5% NaOH aq (40 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (30/1–10/1) afforded **7**, **8**, **9a**, **10a**, **11**, **12a**, and **13a**.

4.3.1. Methyl (2E)-(4-hydroxymethyl-5-methoxy-4,5-dimethyldihydrofuran-2-ylidene)acetate (*7*)

Less polar diastereomer, colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, s), 1.42 (3H, s), 1,93 (1H, br s), 2.84 (1H, dd, J=2.2, 18.2 Hz), 3.28 (3H, s), 3.33 (1H, dd, J=1.3, 18.2 Hz),

3.45 (2H, br s), 3.66 (3H, s), 5.30 (1H, dd, J=1.3, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.6, 16.1, 39.8, 48.7, 49.2, 50.8, 67.2, 91.1, 111.8, 169.0, 174.1; IR (neat)=3462, 2949, 1695, 1643 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{11}H_{18}O_5$ 230.1154; found 230.1149.

More polar diastereomer, colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, s), 1.45 (3H, s), 2.69 (1H, dd, J=3.2, 8.8 Hz), 2.96 (1H, dd, J=1.4, 18.1 Hz), 3.29 (1H, dd, J=2.3, 18.1 Hz), 3.33 (3H, s), 3.57 (1H, dd, J=8.8, 11.5 Hz), 3.65–3.69 (1H, m), 3.68 (3H, s), 5.36 (1H, dd, J=1.4, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 15.5, 20.8, 39.0, 48.0, 49.7, 50.8, 65.3, 92.2, 113.7, 168.7, 173.7; IR (neat)=3470, 2950, 1706, 1643 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{11}H_{18}O_5$ 230.1154; found 230.1153.

*4.3.2. Methyl (4-acetyl-2-methoxy-4-methyltetrahydrofuran-2-yl)acetate (**8**)*

Inseparable mixture of diastereomers (1:1), colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.23 (3/2H, s), 1.33 (3/2H, s), 1.93 (1/2H, d, J=13.6 Hz), 2.10 (1/2H, d, J=13.6 Hz), 2.15 (3/2H, s), 2.17 (3/2H, s), 2.60 (1/2H, d, J=14.2 Hz), 2.61 (1H, d, J=14.2 Hz), 2.70 (1/2H, d, J=13.6 Hz), 2.89 (1/2H, d, J=14.2 Hz), 2.92 (1/2H, d, J=14.2 Hz), 3.10 (3/2H, s), 3.21 (3/2H, s), 3.50 (1/2H, d, J=9.4 Hz), 3.52 (1/2H, d, J=8.8 Hz), 3.65 (3/2H, s), 3.66 (3/2H, s), 4.23 (1/2H, d, J=9.4 Hz), 4.37 (1/2H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.5, 23.1, 25.0, 25.6, 39.4, 39.4, 46.7, 47.3, 48.0, 48.4, 51.8, 51.8, 55.2, 55.5, 73.9, 74.2, 106.8, 107.6, 169.6, 169.7, 209.3, 209.5; IR (neat)=2952, 1704, 1647 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{11}H_{18}O_5$ 230.1154; found 230.1152.

*4.3.3. Methyl (2E)-[4-(1-hydroxy-1-methylethyl)-5-methoxy-4,5-dimethyldihydrofuran-2-ylidene]acetate (**9a**)*

Inseparable mixture of diastereomers (3.8:1), analytical sample of major diastereomer was obtained by recrystalization, major diastereomer, colorless needles, mp 84–85 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.12 (3H, s), 1.26 (3H, s), 1.29 (3H, s), 1.31 (1H, s), 1.61 (3H, s), 3.00 (1H, dd, J=1.8, 18.0 Hz), 3.36 (3H, s), 3.38 (1H, dd, J=1.8, 18.0 Hz), 3.66 (3H, s), 5.25 (1H, t, J=1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.9, 26.7, 28.6, 39.8, 50.2, 50.6, 54.0, 73.3, 90.1, 113.8, 169.2, 173.8; IR (CCl_4)=3500, 2992, 2950, 1690, 1636 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{13}H_{22}O_5$ 258.1467; found 258.1484.

Minor diastereomer; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, s), 1.17 (3H, s), 1.33 (3H, s), 1.56 (3H, s), 3.03 (1H, d, J=18.5 Hz), 3.37 (3H, s), 3.68 (3H, s), 3.73 (1H, dd, J=2.2, 18.5 Hz), 4.16 (1H, s), 5.35 (1H, dd, J=1.4, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 17.0, 21.8, 26.0, 27.3, 38.7, 49.6, 50.8, 53.6, 72.5, 92.1, 114.7, 168.7, 173.9.

*4.3.4. Methyl (2E)-(4-acetyl-4,5,5-trimethyltetrahydrofuran-2-ylidene)acetate (**10a**)*

Colorless oil, ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, s), 1.19 (3H, s), 1.40 (3H, s), 2.18 (3H, s), 3.18 (1H, dd, J=1.4, 18.4 Hz), 3.57 (1H, dd, J=2.2, 18.4 Hz), 3.63 (3H, s), 5.24 (1H, dd, J=1.4, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.1, 23.1, 24.1, 27.8, 40.8, 50.7, 57.8, 88.2, 90.5, 168.9, 172.7, 208.3; IR (neat)=2984, 1701, 1637, 1119, 1080 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{12}H_{18}O_4$ 226.1205; found 226.1230.

*4.3.5. Methyl (2E)-[(3aSR,4RS,7aRS)-hexahydro-4-hydroxy-7a-methoxy-3a-methyl-2(3H)-benzofuranylidene]acetate (**11**)*

Colorless oil, ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, s), 1.31–1.48 (3H, m), 1.59–1.73 (3H, m), 2.29 (1H, br d, J=11.6 Hz), 2.78 (1H, dd, J=2.4, 17.7 Hz), 3.25 (3H, s), 3.27–3.30 (1H, m), 3.46 (1H, d, J=17.7 Hz), 3.67 (3H, s), 5.39 (1H, dd, J=0.8, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.8, 19.1, 26.1, 29.5, 41.1, 49.1, 50.8, 50.8, 73.2, 93.1, 111.6, 168.6, 174.2; IR (neat)=3444, 2946, 1694, 1642, 1043 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{13}H_{20}O_5$ 256.1311; found 256.1316.

*4.3.6. Methyl (2E)-[(3aSR,4SR,7aRS)-hexahydro-4-hydroxy-7a-methoxy-3a-methyl-2(3H)-benzofuranylidene]-acetate (**12a**)*

Colorless oil, ^{1}H NMR (CD_3COCD_3) δ 1.09 (3H, s), 1.36–1.43 (1H, m), 1.56–1.63 (1H, m), 1.66–1.79 (3H, m), 2.08 (1H, br s), 2.73 (1H, dd, J=2.0, 17.8 Hz), 3.25 (3H, s), 3.32 (1H, dd, J=1.6, 17.8 Hz), 3.56 (3H, s), 3.61–3.65 (1H, m), 3.81 (1H, d, J=5.6 Hz), 5.10 (1H, dd, J=1.6, 2.0 Hz); ^{13}C NMR (CD_3COCD_3) δ 17.3, 19.4, 27.7, 29.8, 41.4, 48.2, 49.3, 50.5, 73.9, 90.1, 112.3, 168.9, 176.8; IR (neat)=3471, 2945, 1692, 1637 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{13}H_{20}O_5$ 256.1311; found 256.1315.

*4.3.7. Methyl (2E)-[(3aSR,7aRS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13a**)*

Colorless oil, ^{1}H NMR (CD_3COCD_3) δ 1.32 (3H, s), 1.76–1.94 (2H, m), 2.07–2.21 (2H, m), 2.24–2.31 (1H, m), 2.55 (1H, dd, J=2.2, 17.9 Hz), 2.57–2.65 (1H, m), 3.58 (3H, s), 4.02 (1H, dd, J=1.3, 17.9 Hz), 4.52–4.53 (1H, m), 5.14 (1H, dd, J=1.3, 2.2 Hz); ^{13}C NMR (CD_3COCD_3) δ 20.2, 21.2, 25.8, 38.4, 40.9, 50.7, 53.9, 89.5, 90.6, 168.5, 175.2, 211.2; IR (neat)=2950, 1703, 1638, 1107 cm^{-1}; HRMS-EI *m/z*: [M$^+$] calcd for $C_{12}H_{16}O_4$ 224.1049; found 224.1045.

*4.4. General procedure for the asymmetric cyclization–carbonylation of (±)-**6***

A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $Pd(TFA)_2$ (0.015 mmol), ligand (0.0225 mmol), *p*-benzoquinone (0.33 mmol), and ROH (3–4 mL), was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. (In some cases, the mixture of $Pd(TFA)_2$ and ligand was sonicated for 5 min before adding *p*-benzoquinone.) The apparatus was purged with carbon monoxide by pumping-filling via the three-way stopcock. The substrate (0.3 mmol) was added dropwise using ROH (1 mL×3) to the stirred mixture via a syringe. After being stirred for the period of time at appropriate temperature, the mixture was diluted with CH_2Cl_2 (30 mL) and 5% NaOH aq (40 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in CH_2Cl_2

(6 mL) was added Dess–Martin reagent (382 mg, 0.90 mmol). After being stirred at room temperature for 1 h, the reaction mixture was diluted with satd $NaHCO_3$ aq (20 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (30/1 to 50/1) afforded **13** (less polar) and **14** (more polar). Enantiomeric excess was determined by HPLC analysis.

*4.4.1. Methyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13a**)*

Colorless oil, $[\alpha]_D^{25}$ −87.5 (*c* 0.31, $CHCl_3$), 43% ee (Chiralpak AS, hexane/EtOH=50/1, 1.0 mL/min, t_R=14.4 min, 17.0 min). Spectral data were identical with those of (±)-**13a**.

*4.4.2. Methyl (2E)-[(3aR,7aS)-hexahydro-7a-methoxy-3a-methyl-4-oxo-2(3H)-benzofuranylidene] acetate (**14a**)*[3d]

Colorless oil, $[\alpha]_D^{24}$ −49.8 (*c* 0.40, $CHCl_3$), 31% ee (Chiralcel OD, hexane/EtOH=30/1, 1.0 mL/min, t_R=10.1 min, 12.0 min).

*4.4.3. Ethyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13b**)*

Colorless oil, $[\alpha]_D^{26}$ −79.3 (*c* 0.45, $CHCl_3$), 45% ee (Chiralpak AS, hexane/EtOH=50/1, 1.0 mL/min, t_R=13.5 min, 17.5 min). ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, *J*=7.2 Hz), 1.31 (3H, s), 1.83–2.07 (3H, m), 2.13–2.19 (1H, m), 2.36–2.52 (2H, m), 2.61 (1H, dd, *J*=2.2, 18.3 Hz), 4.04 (1H, dd, *J*=1.3, 18.3 Hz), 4.10–4.16 (2H, m), 4.38–4.40 (1H, m), 5.27 (1H, dd, *J*=1.3, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 20.1, 20.4, 25.6, 37.9, 40.5, 53.0, 59.3, 88.3, 91.3, 168.0, 173.2, 210.7; IR (neat)=2939, 1693, 1635, 1108 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{13}H_{18}O_4$ 238.1205; found 238.1209.

*4.4.4. Ethyl (2E)-[(3aR,7aS)-7a-ethoxyhexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**14b**)*

Colorless oil, $[\alpha]_D^{27}$ −73.5 (*c* 0.19, $CHCl_3$), 43% ee (Chiralcel OD, hexane/EtOH=50/1, 0.5 mL/min, t_R=15.6 min, 17.5 min). ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, t, *J*=7.2 Hz), 1.27 (3H, s), 1.27 (3H, t, *J*=7.2 Hz), 1.54–1.66 (1H, m), 1.82–1.96 (2H, m), 2.34–2.40 (1H, m), 2.45–2,55 (2H, m), 2.73 (1H, dd, *J*=2.3, 17.6 Hz), 3.57–3.63 (2H, m), 4.07 (1H, d, *J*=17.6 Hz), 4.14 (2H, q, *J*=7.2 Hz), 5.27 (1H, dd, *J*=1.4, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 15.4, 17.9, 19.2, 27.2, 37.3, 37.6, 57.6, 58.2, 59.4, 92.8, 111.5, 167.8, 172.5, 209.6; IR (neat)=2977, 1705, 1649, 1126 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{15}H_{22}O_5$ 282.1467; found 282.1472.

*4.4.5. Propyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13c**)*

Colorless oil, $[\alpha]_D^{28}$ −78.9 (*c* 0.28, $CHCl_3$), 49% ee (Chiralpak AS, hexane/EtOH=80/1, 0.5 mL/min, t_R=28.6 min, 36.0 min). ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, *J*=7.6 Hz), 1.31 (3H, s), 1.61–1.72 (2H, m), 1.82–2.07 (3H, m), 2.13–2.19 (1H, m), 2.36–2.52 (2H, m), 2.61 (1H, dd, *J*=2.4, 18.2 Hz), 4.02–4.06 (3H, m), 4.39 (1H, t, *J*=4.0 Hz), 5.28 (1H, dd, *J*=1.2, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.5, 20.2, 20.5, 22.2, 25.7, 37.9, 40.6, 53.1, 65.1, 88.4, 91.4, 168.1, 173.2, 210.8; IR (CCl_4)=2966, 1705, 1645 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{14}H_{20}O_4$ 252.1362; found 252.1359.

*4.4.6. Propyl (2E)-[(3aR,7aS)-hexahydro-3a-methyl-7a-propoxy-4-oxo-2(3H)-benzofuranylidene] acetate (**14c**)*

Colorless oil, $[\alpha]_D^{28}$ −77.9 (*c* 0.48, $CHCl_3$), 71% ee (Chiralcel OD, hexane/EtOH=250/1, 0.5 mL/min, t_R=29.6 min, 35.3 min). ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, *J*=7.1 Hz), 0.95 (3H, t, *J*=7.1 Hz), 1.28 (3H, s), 1.49–1.71 (5H, m), 1.82–1.96 (2H, m), 2.34–2.39 (1H, m), 2.45–2.55 (2H, m), 2.73 (1H, dd, *J*=2.4, 17.6 Hz), 3.46–3.54 (2H, m), 4.05 (2H, t, *J*=7.1 Hz), 4.08 (1H, d, *J*=17.6 Hz), 5.28 (1H, dd, *J*=1.2, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.5, 10.6, 17.9, 19.2, 22.1, 23.1, 27.2, 37.3, 37.7, 58.3, 63.5, 65.1, 92.9, 111.4, 167.9, 172.4, 209.6; IR (neat)=2965, 1708, 1650 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{17}H_{26}O_5$ 310.1780; found 310.1773.

*4.4.7. Butyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13d**)*

Colorless oil, $[\alpha]_D^{29}$ −61.4 (*c* 0.52, $CHCl_3$), 42% ee (Chiralpak AS, hexane/EtOH=80/1, 0.5 mL/min, t_R=26.0 min, 30.6 min). ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, *J*=7.6 Hz), 1.31 (3H, s), 1.34–1.44 (2H, m), 1.58–1.65 (2H, m), 1.82–2.19 (4H, m), 2.36–2.53 (2H, m), 2.60 (1H, dd, *J*=2.4, 18.0 Hz), 4.04 (1H, dd, *J*=1.2, 18.2 Hz), 4.08 (2H, t, *J*=6.8 Hz), 4.38–4.40 (1H, m), 5.27 (1H, dd, *J*=1.2, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.1, 20.1, 20.4, 25.6, 30.8, 37.9, 40.5, 53.0, 63.3, 88.3, 91.3, 168.1, 173.1, 210.7; IR (CCl_4)=2959, 2875, 1704, 1645 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{15}H_{22}O_4$ 266.1518; found 266.1523.

*4.4.8. Butyl (2E)-[(3aR,7aS)-7a-butoxyhexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene] acetate (**14d**)*[3d]

Colorless oil, $[\alpha]_D^{30}$ −78.7 (*c* 0.31, $CHCl_3$), 82% ee (Chiralcel OD, hexane/EtOH=250/1, 0.5 mL/min, t_R=27.0 min, 33.1 min).

*4.4.9. 2-Methylpropyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13e**)*

Colorless oil, $[\alpha]_D^{25}$ −74.9 (*c* 0.30, $CHCl_3$), 35% ee (Chiralpak AS, hexane/EtOH=80/1, 0.5 mL/min, t_R=21.6 min, 24.9 min). ^{1}H NMR ($CDCl_3$) δ 0.94 (6H, d, *J*=6.8 Hz), 1.31 (3H, s), 1.84–2.06 (4H, m), 2.14–2.19 (1H, m), 2.36–2.51 (2H, m), 2.60 (1H, dd, *J*=2.0, 18.2 Hz), 3.86 (2H, d, *J*=6.8 Hz), 4.04 (1H, dd, *J*=1.2, 18.2 Hz), 4.40–4.38 (1H, m), 5.29 (1H, dd, *J*=1.2, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 19.2 (2C), 20.1, 20.5, 25.6, 27.8, 37.9, 40.5, 53.1, 69.7, 88.4, 91.4, 168.1, 173.1, 210.7; IR (neat)=2959, 1699, 1641, 1105 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{15}H_{22}O_4$ 266.1518; found 266.1527.

*4.4.10. 2-Methylpropyl (2E)-[(3aR,7aS)-hexahydro-3a-methyl-7a-(2-methylpropoxy)-4-oxo-2(3H)-benzofuranylidene]-acetate (**14e**)*[3d]

Colorless oil, $[\alpha]_D^{24}$ −69.1 (*c* 0.31, $CHCl_3$); 91% ee (Chiralcel OD-H, hexane/EtOH=200/1, 0.4 mL/min, t_R=29 min, 35 min).

*4.4.11. 3-Methylbutyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13f**)*

Colorless oil, $[\alpha]_D^{23}$ −83.3 (*c* 0.40, $CHCl_3$), 53% ee (Chiralpak AS, hexane/*i*-PrOH=100/1, 0.5 mL/min, t_R=42.6 min, 52.9 min). ^{1}H NMR ($CDCl_3$) *δ* 0.92 (6H, d, *J*=6.4 Hz), 1.31 (3H, s), 1.53 (2H, q, *J*=6.8 Hz), 1.65−1.77 (1H, m), 1.83−2.06 (3H, m), 2.13−2.18 (1H, m), 2.36−2.51 (2H, m), 2.60 (1H, dd, *J*=2.0, 18.1 Hz), 4.03 (1H, dd, *J*=1.4, 18.1 Hz), 4.10 (2H, t, *J*=6.8 Hz), 4.38−4.44 (1H, m), 5.27 (1H, dd, *J*=1.4, 2.0 Hz); ^{13}C NMR ($CDCl_3$) *δ* 20.2, 20.5, 22.5, 22.5, 25.1, 25.7, 37.6, 37.9, 40.6, 53.1, 62.2, 88.4, 91.4, 168.1, 173.2, 210.7; IR (neat)=2954, 1706, 1646, 1110 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{24}O_4$ 280.1675; found 280.1675.

*4.4.12. 3-Methylbutyl (2E)-[(3aR,7aS)-hexahydro-3a-methyl-7a-(3-methylbutoxy)-4-oxo-2(3H)-benzofuranylidene]-acetate (**14f**)*

Colorless oil, $[\alpha]_D^{26}$ −80.6 (*c* 0.33, $CHCl_3$), 95% ee (Chiralcel OD, hexane/EtOH=250/1, 0.5 mL/min, t_R=28.8 min, 35.4 min). ^{1}H NMR ($CDCl_3$) *δ* 0.88 (3H, d, *J*=7.2 Hz), 0.86 (3H, d, *J*=6.8 Hz), 0.93 (6H, d, *J*=6.8 Hz), 1.27 (3H, s), 1.33−1.47 (2H, m), 1.53 (2H, q, *J*=6.9 Hz), 1.59−1.75 (3H, m), 1.81−1.95 (2H, m), 2.35−2.38 (1H, m), 2.44−2.56 (2H, m), 2.71 (1H, dd, *J*=2.3, 17.6 Hz), 3.57 (2H, t, *J*=6.4 Hz), 4.08 (1H, d, *J*=17.6 Hz), 4.12 (2H, t, *J*=6.9 Hz), 5.27 (1H, dd, *J*=1.4, 2.3 Hz); ^{13}C NMR ($CDCl_3$) *δ* 18.0, 19.2, 22.3, 22.5, 22.5, 22.7, 24.9, 25.2, 27.2, 37.3, 37.6, 37.7, 38.6, 58.3, 60.2, 62.2, 92.9, 111.5, 167.9, 172.5, 209.6; IR (neat)=2955, 1711, 1654, 1125 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{21}H_{34}O_5$ 366.2406; found 366.2405.

*4.4.13. 1-Methylethyl (2E)-[(3aS,7aS)-hexahydro-3a-methyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13g**)*

Colorless oil, $[\alpha]_D^{27}$ −46.7 (*c* 0.33, $CHCl_3$), 23% ee (Chiralpak AS, hexane/EtOH=80/1, 0.5 mL/min, t_R=22.6 min, 31.2 min). ^{1}H NMR ($CDCl_3$) *δ* 1.23 (3H, d, *J*=2.4 Hz), 1.25 (3H, d, *J*=2.0 Hz), 1.31 (3H, s), 1.82−2.06 (3H, m), 2.13−2.18 (1H, m), 2.36−2.51 (2H, m), 2.61 (1H, dd, *J*=2.0, 20.0 Hz), 4.03 (1H, dd, *J*=1.2, 20.0 Hz), 4.37−4.39 (1H, m), 4.97−5.06 (1H, m), 5.24 (1H, dd, *J*=1.2, 2.0 Hz); ^{13}C NMR ($CDCl_3$) *δ* 20.1, 20.6, 22.1 (2C), 25.7, 38.0, 40.6, 53.1, 66.5, 88.3, 91.9, 167.6, 173.0, 210.8; IR (CCl_4)=2977, 2934, 1698, 1643 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{14}H_{20}O_4$ 252.1362; found 252.1359.

*4.4.14. 1-Methylethyl (2E)-[(3aR,7aS)-hexahydro-3a-methyl-7a-(1-methylethoxy)-4-oxo-2(3H)-benzofuranylidene]-acetate (**14g**)*[3d]

Colorless oil, $[\alpha]_D^{26}$ −104.8 (*c* 0.31, $CHCl_3$), 92% ee (Chiralcel OD, hexane/EtOH=250/1, 0.5 mL/min, t_R=19.9 min, 22.5 min).

*4.4.15. 3-Methylbutyl (2E)-[(3aS,7aS)-hexahydro-3a-(2-propenyl)-4-oxo-2(3H)-benzofuranylidene] acetate (**13h**)*

Colorless oil, $[\alpha]_D^{27}$ −51.2 (*c* 0.43, $CHCl_3$, 37% ee) (Chiralpak AS, hexane/EtOH=250/1, 0.5 mL/min, t_R=31.0 min, 41.0 min). ^{1}H NMR ($CDCl_3$) *δ* 0.92 (6H, d, *J*=6.4 Hz), 1.52 (2H, q, *J*=6.9 Hz), 1.66−1.73 (1H, m), 1.82−2.06 (3H, m), 2.11−2.17 (1H, m), 2.37−2.48 (4H, m), 2.70 (1H, dd, *J*=2.0, 18.4 Hz), 3.94 (1H, dd, *J*=1.2, 18.4 Hz), 4.10 (2H, t, *J*=6.9 Hz), 4.49−4.51 (1H, m), 5.07−5.14 (2H, m), 5.27 (1H, dd, *J*=1.2, 2.0 Hz), 5.59−5.70 (1H, m); ^{13}C NMR ($CDCl_3$) *δ* 20.0, 22.5, 22.5, 25.1, 26.0, 37.6, 38.6, 38.7, 38.8, 56.8, 62.2, 86.5, 91.4, 119.4, 132.1, 168.1, 173.1, 209.7; IR (neat)=3077, 2954, 1705, 1646, 1116 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{18}H_{26}O_4$ 306.1831; found 306.1819.

*4.4.16. 3-Methylbutyl (2E)-[(3aR,7aS)-hexahydro-7a-(3-methylbutoxy)-3a-(2-propenyl)-4-oxo-2(3H)-benzofuran-ylidene]acetate (**14h**)*

Colorless oil, $[\alpha]_D^{26}$ −104.9 (*c* 0.27, $CHCl_3$, 92% ee) (Chiralcel OD, hexane/EtOH=300/1, 0.5 mL/min, t_R=28.2 min, 40.6 min). ^{1}H NMR ($CDCl_3$) *δ* 0.87 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=7.2 Hz), 0.93 (6H, d, *J*=6.4 Hz), 1.35−1.46 (2H, m), 1.50−1.76 (5H, m), 1.84−1.96 (2H, m), 2.38−2.48 (3H, m), 2.53−2.61 (2H, m), 2.72 (1H, dd, *J*=2.4, 17.8 Hz), 3.58 (2H, t, *J*=6.4 Hz), 4.07 (1H, d, *J*=17.8 Hz), 4.12 (2H, t, *J*=6.8 Hz), 5.04 (2H, dd, *J*=2.0, 13.6 Hz), 5.27 (1H, dd, *J*=1.6, 2.4 Hz), 5.55−5.65 (1H, m); ^{13}C NMR ($CDCl_3$) *δ* 19.4, 22.3, 22.5, 22.5, 22.6, 24.9, 25.1, 27.6, 36.5, 37.0, 37.6, 38.5, 38.6, 60.2, 62.2, 93.0, 111.5, 118.3, 133.0, 167.9, 172.4, 208.1; IR (neat)=2955, 1711, 1653, 1120 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{23}H_{36}O_5$ 392.2563; found 392.2559.

*4.4.17. 3-Methylbutyl (2E)-[(3aS,7aS)-hexahydro-3a-propyl-4-oxo-2(3H)-benzofuranylidene]acetate (**13i**)*

Colorless oil, $[\alpha]_D^{30}$ −89.3 (*c* 0.58, $CHCl_3$, 46% ee) (Chiralpak AS, hexane/EtOH=250/1, 0.5 mL/min, t_R=22.1 min, 26.6 min). ^{1}H NMR ($CDCl_3$) *δ* 0.91 (3H, t, *J*=7.4 Hz), 0.92 (6H, d, *J*=6.4 Hz), 1.12−1.36 (2H, m), 1.50−1.58 (3H, m), 1.65−1.79 (2H, m), 1.88−2.06 (3H, m), 2.16−2.22 (1H, m), 2.34−2.50 (2H, m), 2.51 (1H, dd, *J*=2.4, 18.0 Hz), 4.10 (2H, t, *J*=6.8 Hz), 4.12 (1H, dd, *J*=1.6, 18.0 Hz), 4.41−4.43 (1H, m), 5.25 (1H, dd, *J*=1.6, 2.4 Hz); ^{13}C NMR ($CDCl_3$) *δ* 14.4, 18.7, 20.8, 22.5, 22.5, 25.1, 25.6, 36.7, 37.6, 38.6, 38.6, 57.5, 62.1, 87.9, 91.3, 168.2, 173.6, 210.2; IR (neat)=2956, 1702, 1644, 1099 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{18}H_{28}O_4$ 308.1988; found 308.1987.

*4.4.18. 3-Methylbutyl (2E)-[(3aR,7aS)-hexahydro-7a-(3-methylbutoxy)-3a-propyl-4-oxo-2(3H)-benzofuranylidene]-acetate (**14i**)*

Colorless oil, $[\alpha]_D^{30}$ −99.3 (*c* 0.15, $CHCl_3$, 97% ee) (Chiralpak AD, hexane/EtOH=300/1, 1.0 mL/min, t_R=20.2 min, 27.3 min). ^{1}H NMR ($CDCl_3$) *δ* 0.85−0.91 (9H, m), 0.93 (6H, d, *J*=6.4 Hz), 0.98−1.09 (1H, m), 1.15−1.23 (1H, m), 1.32−1.47 (2H, m), 1.51−1.74 (6H, m), 1.78−1.97 (3H, m), 2.33−2.38 (1H, m), 2.41−2.55 (2H, m), 2.64 (1H, dd, *J*=2.4, 17.2 Hz), 3.55 (2H, t, *J*=6.6 Hz), 4.08−4.13 (3H, m), 5.27 (1H, dd, *J*=1.6, 2.4 Hz); ^{13}C NMR ($CDCl_3$) *δ* 14.5, 18.6, 19.7, 22.3, 22.5, 22.7, 24.9, 25.1, 27.3, 34.0, 35.9, 37.6, 38.0, 38.6, 60.2, 62.2, 62.6, 93.0, 112.0, 168.0, 172.9, 208.7; IR (neat)=2956, 1709, 1649, 1076 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{23}H_{38}O_5$ 394.2719; found 394.2720.

4.5. Asymmetric cyclization–carbonylation of (±)-**4**

Asymmetric cyclization–carbonylation of (±)-**4** was performed according to the general procedure (Section 4.4). The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (20/1 to 10/1) afforded the mixture of **9b** (less polar) and compound **B** (more polar). The fraction eluted with hexane/ethyl acetate (10/1) afforded the mixture of **10b** (less polar) and **9b′** (more polar). The barely separable mixtures were purified twice by preparative TLC to give a small amount of each compound in pure form. Enantiomeric excess was determined by HPLC analysis, but absolute configuration of these compounds (**9b**, **B**, **10b**, **9b′**) could not be determined. The relative configuration of **9b** and **9b′** was determined by NOE experiments.

4.5.1. 3-Methylbutyl (2E)-[4-(1-hydroxy-1-methylethyl)-5-(3-methylbutoxy)-4,5-dimethyldihydrofuran-2-ylidene]-acetate (**9b**)

Colorless oil. $[\alpha]_D^{23}$ −0.24 (*c* 0.41, $CHCl_3$, 17% ee) (Chiralpak OD-H, hexane/EtOH=20/1, 0.5 mL/min, t_R=6.2 min, 12.5 min). ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, d, *J*=6.4 Hz), 0.88 (3H, d, *J*=6.4 Hz), 0.93 (6H, d, *J*=6.7 Hz), 1.01 (3H, s), 1.16 (3H, s), 1.29–1.46 (2H, m), 1.33 (3H, s), 1.51–1.74 (4H, m), 1.57 (3H, s), 3.05 (1H, d, *J*=18.2 Hz), 3.60–3.69 (2H, m), 3.73 (1H, d, *J*=18.2 Hz), 4.07–4.16 (2H, m), 4.37 (1H, br s), 5.32 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.8, 21.6, 22.2, 22.5, 22.5 (2C), 24.9, 25.2, 26.1, 27.3, 37.6, 38.5, 38.8, 53.5, 60.6, 62.2, 72.5, 92.3, 114.5, 168.4, 173.7; IR (neat)=3519, 2956, 1707, 1649, 1065 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{21}H_{38}O_5$ 370.2719; found 370.2709.

4.5.2. Compund ***B***

Colorless oil, $[\alpha]_D^{19}$ +36.8 (*c* 0.4, $CHCl_3$, 80% ee) (Chiralpak OD-H, hexane/EtOH=20/1, 0.5 mL/min, t_R=8.8 min, 11.8 min). ^{1}H NMR ($CDCl_3$) δ 0.93 (6H, d, *J*=6.6 Hz), 1.29 (3H, s), 1.30 (3H, s), 1.37 (3H, s), 1.52–1.56 (2H, m), 1.53 (3H, s), 1.65–1.75 (1H, m), 2.65 (1H, dd, *J*=2.4, 19.2 Hz), 3.81 (1H, d, *J*=19.2 Hz), 4.06–4.18 (2H, m), 5.39 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 16.6, 20.4, 22.5, 22.5, 25.2, 25.5, 26.0, 37.6, 40.8, 48.6, 62.2, 82.8, 91.7, 116.5, 168.4, 174.2; IR (neat)=2957, 1702, 1644, 1064 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{26}O_4$ 282.1831; found 282.1826.

4.5.3. 3-Methylbutyl (2E)-(4-acetyl-4,5,5-trimethyltetrahydrofuran-2-ylidene)acetate (***10b***)

Colorless oil, $[\alpha]_D^{23}$ −4.0 (*c* 0.35, $CHCl_3$, 4% ee) (Chiralpak OD-H, hexane/EtOH=20/1, 0.5 mL/min, t_R=14.1 min, 16.6 min). ^{1}H NMR ($CDCl_3$) δ 0.93 (6H, d, *J*=6.8 Hz), 1.21 (3H, s), 1.23 (3H, s), 1.43 (3H, s), 1.53 (2H, q, *J*=6.8 Hz), 1.65–1.76 (1H, m), 2.22 (3H, s), 3.22 (1H, dd, *J*=1.6, 18.4 Hz), 3.60 (1H, dd, *J*=2.0, 18.4 Hz), 4.06–4.16 (2H, m), 5.28 (1H, dd, *J*=1.6, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 22.5 (2C), 23.2, 24.2, 25.2, 27.9, 37.6, 40.8, 57.8, 62.1, 88.2, 91.0, 168.7, 172.5, 208.5; IR (neat)=2956, 1700, 1637, 1638, 1079 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{26}O_4$ 282.1831; found 282.1836.

4.5.4. 3-Methylbutyl (2E)-[4-(1-hydroxy-1-methylethyl)-5-(3-methylbutoxy)-4,5-dimethyldihydrofuran-2-ylidene]-acetate (***9b′***)

Colorless oil. $[\alpha]_D^{22}$ −5.0 (*c* 0.48, $CHCl_3$, 17% ee) (Chiralpak OD-H, hexane/EtOH=30/1, 0.5 mL/min, t_R=8.1 min, 10.1 min). ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, d, *J*=6.6 Hz), 0.92 (6H, d, *J*=6.6 Hz), 1.11 (3H, s), 1.26 (3H, s), 1.29 (3H, s), 1.39–1.44 (3H, m), 1.50–1.55 (2H, m), 1.61 (3H, s), 1.64–1.75 (2H, m), 3.01 (1H, dd, *J*=18.0, 1.2 Hz), 3.36 (1H, dd, *J*=18.0, 1.2 Hz), 3.59–3.63 (2H, m), 4.09 (2H, t, *J*=6.1 Hz), 5.22 (1H, t, *J*=1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 18.2, 19.8, 22.4, 22.5 (2C), 22.6, 24.9, 25.2, 26.6, 28.7, 37.6, 38.7, 39.7, 54.0, 60.8, 62.0, 73.3, 90.3, 113.6, 169.0, 173.7; IR (neat)=3491, 2955, 1686, 1634 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{21}H_{38}O_5$ 370.2719; found 370.2719.

4.6. Conversion of ***12e*** to ent-***13e***

To a solution of **12e** (41.5 mg, 0.12 mmol) in MeOH (4 mL) was added 10% HCl aq (8 mL) and H_2O (4 mL), and the mixture was stirred for 1.5 h. The mixture was diluted with H_2O (40 mL) and EtOAc (20 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in DMF (2 mL) was added TBDMSCl (73 mg, 0.48 mmol) and imidazole (41 mg, 0.60 mmol), and the mixture was heated at 80 °C for 8 h. The mixture was diluted with H_2O (40 mL) and EtOAc (20 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by preparative TLC (hexane/ethyl acetate=2/1), afforded *ent*-**13e** (22 mg, 67%) as a colorless oil.

4.6.1. ent-***13e***

$[\alpha]_D^{30}$ +140.3 (*c* 0.38, $CHCl_3$, 91% ee).

4.7. 3-Methylbutyl (7aS)-2,4,5,6,7,7a-hexahydro-7a-methyl-7-methylene-2-oxo-1H-indene-3-carboxylate (***19***)

Compound **14f** was converted to **19** according to the reported procedure.[3d]

Colorless oil, $[\alpha]_D^{25}$ +23.4 (*c* 0.33, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.94 (6H, d, *J*=6.8 Hz), 1.44 (3H, s), 1.53–1.63 (3H, m), 1.69–1.79 (1H, m), 2.06–2.13 (1H, m), 2.34–2.57 (3H, m), 2.42 (1H, d, *J*=18.0 Hz), 2.91 (1H, d, *J*=18.0 Hz), 3.41–3.47 (1H, m), 4.26 (2H, t, *J*=7.0 Hz), 4.78 (1H, br s), 4.85 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 22.5 (2C), 25.1, 26.4, 27.5, 28.8, 31.6, 37.3, 48.5, 48.7, 63.6, 109.0, 128.3, 152.1, 163.4, 190.5, 201.0; IR (neat)=2956, 1742, 1712, 1627 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{17}H_{24}O_3$ 276.1726; found 276.1726.

4.8. Methyl (7aR)-2,4,5,6,7,7a-hexahydro-7a-methyl-7-methylene-2-oxo-1H-indene-3-carboxylate (***20***)[3d]

To a solution of **19** (94 mg, 0.34 mmol) in MeOH (10 mL) was added Ti(*i*-PrO)$_4$ (9.7 mg, 0.034 mmol), and the mixture

was refluxed for 6 h. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (10/1) afforded **20** (69.7 mg, 93%) as colorless needles.

$[\alpha]_D^{25}$ +31.0 (*c* 0.31, $CHCl_3$).

*4.9. Hydrogenation of **20***

To a solution of **20** (500 mg, 2.27 mmol) in ethyl acetate (25 mL) was added 10% Pd–C (87 mg). The apparatus was purged with hydrogen. After being stirred for 2 h, the mixture was filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (20/1 to 10/1) afforded the corresponding β-keto ester (351.2 mg, 69%) as a colorless oil.

$[\alpha]_D^{22}$ −46.3 (*c* 0.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, d, *J*=6.4 Hz), 1.09 (3H, s), 1.18–1.26 (2H, m), 1.37–1.50 (2H, m), 1.59–1.64 (2H, m), 1.70–1.80 (1H, m), 2.12 (1H, d, *J*=18.4 Hz), 2.51 (1H, d, *J*=18.4 Hz), 2.56 (1H, ddd, *J*=2.0, 5.0, 12.8 Hz), 3.41 (1H, d, *J*=12.8 Hz), 3.75 (3H, s); ^{13}C NMR ($CDCl_3$) δ 16.4, 18.6, 20.5, 22.4, 29.8, 34.4, 39.4, 47.3, 52.4, 52.5, 55.8, 169.9, 211.2; IR (neat)=2932, 2883, 1753, 1723, 1435 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{13}H_{20}O_3$ 224.1413; found 224.1412.

*4.10. (−)-(1R,2S,6R)-1,2-Dimethylbicyclo[4.3.0]-nonan-8-one (**21**)*

To a solution of the above β-keto ester (119.6 mg, 0.53 mmol) in DMSO (10 mL) was added NaCl (155.7 mg, 2.67 mmol) and H_2O (48 mg, 2.67 mmol), and the mixture was heated at 130 °C for 7 h. After cooling, the mixture was diluted with H_2O (40 mL) and EtOAc (20 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane/ethyl acetate (50/1) afforded **21** (74.3 mg, 84%) as a colorless oil.

Colorless oil, $[\alpha]_D^{28}$ −110.9 (*c* 0.27, CH_3OH). ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, d, *J*=6.4 Hz), 1.04 (3H, s), 1.17–1.26 (1H, m), 1.30–1.37 (1H, m), 1.42–1.50 (2H, m), 1.54–1.60 (2H, m), 1.68–1.77 (1H, m), 1.94 (1H, d, *J*=17.8 Hz), 2.13–2.20 (2H, m), 2.33–2.40 (1H, m), 2.40 (1H, d, *J*=17.8 Hz); ^{13}C NMR ($CDCl_3$) δ 16.4, 19.1, 20.5, 23.5, 30.1, 33.5, 40.3, 41.1, 43.1, 53.2, 219.5; IR (neat)=2958, 2924, 2858, 1740 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{11}H_{18}O$ 116.1358; found 116.1356.

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