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General Synthesis of *meso*-1,4-Dialdehydes and Their Application in Ir-Catalyzed Asymmetric Tishchenko Reactions

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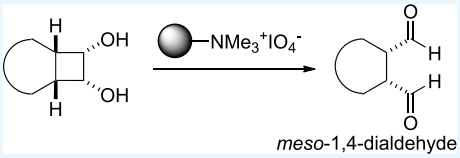
ABSTRACT: A practical synthesis of *meso*-1,4-dialdehydes based on the oxidative cleavage of cyclobutanediol derivatives using polymer-supported periodate was developed. The *meso*-1,4-dialdehydes were obtained in up to >99% yield and subsequently employed in Ir-catalyzed asymmetric Tishchenko reactions to give the corresponding chiral lactones, which are versatile synthetic intermediates, in good yield with moderate enantiomeric excess. The catalytically active species was identified by means of cold-spray ionization mass spectrometry and ^{1}H NMR spectroscopy.



1. INTRODUCTION

The desymmetrization of *meso* compounds has long been studied in asymmetric synthesis.[1−3] Especially, the desymmetrization of prochiral or *meso*-diols and the corresponding *meso*-diesters has been intensively investigated, including using enzymatic methods.[4,5] In contrast, research on the desymmetrization of prochiral or *meso*-dialdehydes is relatively scarce, mainly due to problems associated with the stability of the dialdehydes and the immaturity of the synthetic methodology.

In the last four decades, 1,5-prochiral,[6−9] 1,5-*meso*-,[10−17] 1,6-prochiral,[18−25] 1,6-*meso*-,[26−31] and 1,7-*meso*-dialdehydes[11,15,26,28−30,32] have been synthesized (Figure 1)[33] using

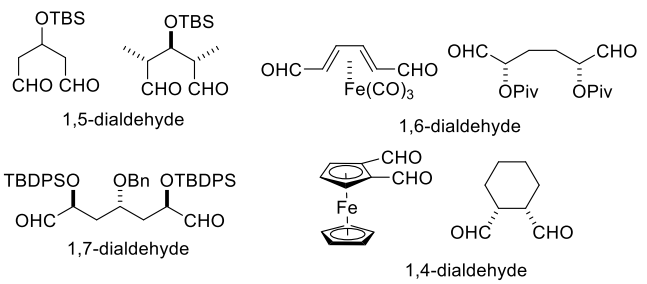


Figure 1. Selected Examples of Prochiral or *meso*-Dialdehydes.

various methods, including the Swern oxidation of the corresponding diols,[11−19,21,22,24] pyridinium-chlorochromate oxidation,[32] tetrapropylammonium-perruthenate oxidation,[32] oxidative cleavage of diols using H_5IO_6[15,26,27,30,31] or $NaIO_4$,[6] and ozonolysis of alkenes.[8,9,28,29] The purification of 1,7-*meso*-dialdehydes by column chromatography on silica gel has also been reported,[15] albeit that these dialdehydes are generally used without purification. In 1,5-dialdehydes, where the distance between the two formyl groups is shorter, cyclic hydrates are formed.[10] In some cases; such cyclic hydrates can be converted to the corresponding dialdehydes by refluxing in tetrahydrofuran (THF) in the presence of 4A molecular sieves.[6,9] To avoid hydrate formation in the synthesis of 1,5-dialdehydes, Rein's method based on Swern oxidation followed by workup under nonaqueous conditions is often used.[11]

Special 1,4-prochiral dialdehydes such as 1,2-diformylferrocene[34−36] can be prepared via oxidation of a dimethylamino group with MnO_2[34,35] or hydrolysis of acetal,[36] and these are sufficiently stable to withstand purification by column chromatography on silica gel.[35] However, the synthesis of aliphatic 1,4-*meso*-dialdehydes is not straightforward. For example, although the Pd-catalyzed ambient oxidation of primary alcohols is known to produce aldehydes, the application of these conditions to the reaction of *cis*-1,2-cyclohexanedimethanol fails to produce the corresponding 1,4-dialdehyde, furnishing instead a five-membered-ring lactone.[37] Similarly, the cerium-ammonium-nitrate oxidation of diols with a bicyclo skeleton also produces a five-membered-ring lactone instead of a 1,4-dialdehyde.[38] Jacobi has reported the Swern oxidation of 1,2-cyclohexanedimethanol for pyrrole synthesis; however, the stereochemistry of the 1,2-cyclohexanedicarboxaldehyde has not been mentioned.[39,40] Bosnich was the first to synthesize 1,2-cyclohexanedicarboxaldehyde from the corresponding amide, albeit that the yield was low (3%) and the aldehyde was obtained as a mixture with an amide-derived byproduct.[41]

Thus, the challenges associated with the synthesis of aliphatic 1,4-*meso*-dialdehydes can be summarized as follows:

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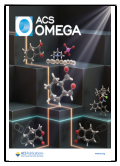
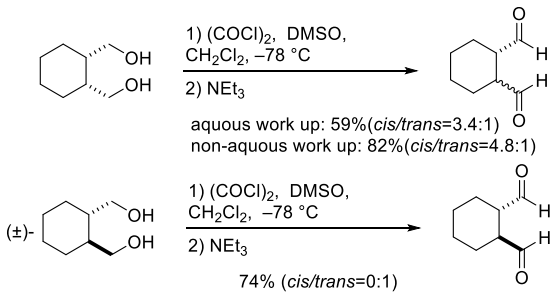


1) normal oxidation of *meso*-1,4-diols tends to give lactones; 2) 1,4-*meso*-dialdehydes are easily epimerized to racemic 1,4-*trans*-dialdehydes due to the high acidity of the alpha-position of the aldehydes; 3) 1,4-*meso*-dialdehydes easily form the corresponding cyclic hydrates. Here, we report the first practical method to prepare 1,4-*meso*-dialdehydes using anhydrous periodate as a heterogeneous oxidant and their application in asymmetric Tishchenko reactions.[42−44]

2. RESULTS AND DISCUSSION

First, we examined the synthesis of *meso*-cyclohexanedialdehyde from *cis*-1,2-cyclohexanedimethanol via Swern oxidation, according to Jacobi's report. Although the ^{1}H NMR spectrum of the product showed only one signal for the aldehydic protons, a careful comparison of the ^{1}H and ^{13}C NMR spectra of the products prepared from *cis*-1,2-cyclohexanedimethanol or *trans*-1,2-cyclohexanedimethanol revealed that the product from *cis*-1,2-cyclohexanedimethanol is a *cis*:*trans* = 3.4:1 mixture of 1,2-cyclohexanedicarboxaldehydes, which indicates that epimerization occurred under the basic conditions applied during the triethylamine workup (Scheme 1). It should also be noted that the Swern oxidation of *trans*-1,2-cyclohexanedimethanol affords the thermally stable *trans*-1,2-cyclohexanedicarboxaldehyde without epimerization.

Scheme 1. Swern Oxidation of 1,2-Cyclohexanedimethanols

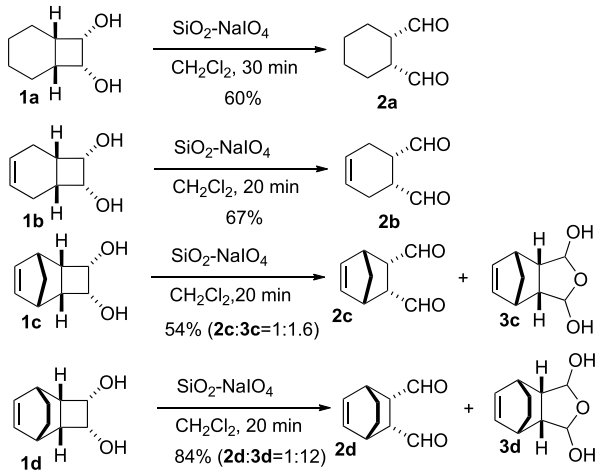


To overcome the epimerization of 1,4-dialdehydes, we attempted the oxidative cleavage of the corresponding 1,2-cyclobutanediols under neutral conditions. Thus, the oxidative cleavage of cyclobutanediols **1a** and **1b** using silica-gel-supported $NaIO_4$ (SiO_2−$NaIO_4$)[45] gave the desired *meso*-dialdehydes **2a** and **2b** in 60 and 76% yield, respectively, without epimerization (Scheme 2). However, in the case of bicyclic substrates **1c** and **1d**, the corresponding hydrates **3c** and **3d** were obtained preferentially, which can be attributed to the shorter distance between the two carbonyl carbons in the bicyclic systems compared to those in the monocyclic systems due to the cyclic strain.

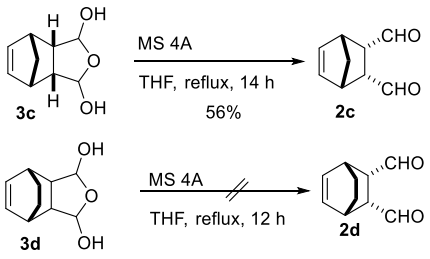
The regeneration of 1,4-dialdehydes **2c** and **2d** from the corresponding hydrates **3c** and **3d** was investigated by refluxing in THF in the presence of 4A molecular sieves. After 14 h, the dehydration of **3c** proceeded to some extent to give a mixture of dialdehyde **2c** (56%) and **3c** (44%), whereas the dehydration of **3d** did not give the desired product (**2d**) (Scheme 3).

Hodge has developed a polymer-supported periodate, which is prepared using the microporous anion-exchange resin Amberlite IRA 904, for the oxidative cleavage of 1,2-diols.[46] In contrast to SiO_2−$NaIO_4$, polymer-supported periodate can be used in the dried state; therefore, we envisioned that using the polymer-supported periodate could potentially help to

Scheme 2. Oxidative Cleavage Using SiO_2-Supported $NaIO_4$

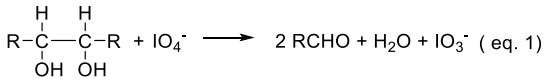


Scheme 3. Dehydration of Hydrates Using 4A Molecular Sieves



circumvent the hydrate formation, which would provide an effective approach for the synthesis of 1,4-dialdehydes (Table 1).

After screening the reaction conditions (for details, see the Supporting Information), we found that the reactions of **1a** and **1b** proceeded smoothly to give the desired 1,4-dialdehydes **2a** and **2b**, respectively, in excellent yield (Table 1, entries 1 and 2). Importantly, the reaction of **1c** gave **2c** without the formation of hydrate **3c** (Table 1, entry 3). The reaction of **1d** gave 1,4-dialdehyde **2d** in 83% yield, although hydrate **3d** was also obtained in 6% yield (Table 1, entry 4). During the oxidative cleavage of 1,2-diol with the polymer-supported periodate, a molecule of H_2O was produced (eq 1).[47]



Therefore, we attempted to obtain pure **2d** by adding desiccants such as 3A molecular sieves, $CaSO_4$, K_2CO_3, or $MgSO_4$ in the reaction of **1d**, albeit that no improvement was achieved.

With *meso*-1,4-dialdehydes **2** in hand, we next investigated asymmetric Tishchenko reactions using chiral Ir complexes as catalysts (Table 2). Screening of the chiral ligands and conditions revealed that the catalyst prepared from (1*S*,2*S*)-2-amino-1,2-diphenylethanol gave the best results (for details, see the Supporting Information). Treatment of **2a** with Ir catalyst **5a** (10 mol %) and ^{i}PrOH (20 mol %) in the presence of Cs_2CO_3 (40 mol %) at 25 °C for 3 h provided the desired lactone (**4a**) in 92% yield with 50% enantiomeric excess (ee) (Table 2, entry 1). The reaction of other 1,4-*meso*-dialdehydes proceeded with a good yield with moderate ee (Table 2,

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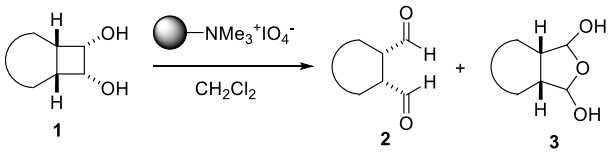
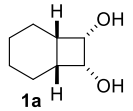
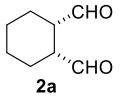
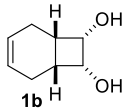
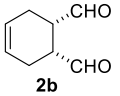
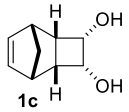
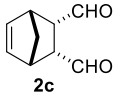
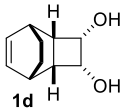
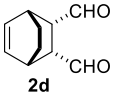
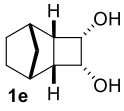
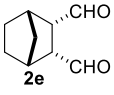
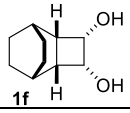
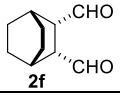
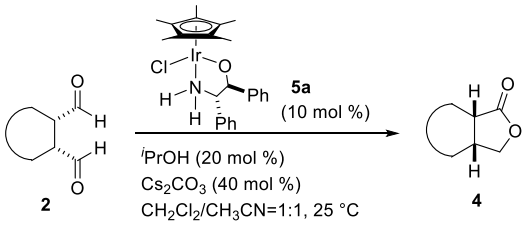
Table 1. Oxidative Cleavage of Cyclobutanediols[a]



Entry	Substrate	Product	Time (h)	% Yield 2	% Yield 3
1[b]	 1a	 2a	1	>99	0
2	 1b	 2b	1	99	0
3[c,d]	 1c	 2c	3	91	0
4[c,d]	 1d	 2d	3	83	6
5[d]	 1e	 2e	1	98	0
6[d]	 1f	 2f	1	94	0

[a]Unless otherwise noted, the reactions were carried out using 0.3−0.4 mmol of **1** with polymer-supported periodate (2 equiv) in CH_2Cl_2 at 25 °C. [b]1.2 mmol of **1a** at 30 °C. [c]Polymer-supported periodate (3 equiv). [d]Determined by ^{1}H NMR spectroscopy.

Table 2. Asymmetric Tishchenko Reaction of *meso*-1,4-Dialdehydes[a]



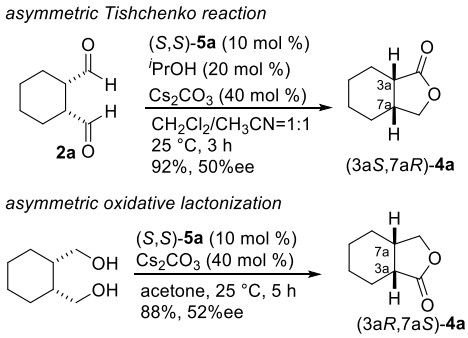
entry	substrate	time (h)	yield (%)[b]	ee (%)[c]
1	**2a**	3	92	50
2[d]	**2a**	17	94	55
3	**2b**	2	95	58
4	**2c**	3	90	61
5	**2c** + **3c**	10	64	67
6	**2d**	24	91	39
7	**2e**	3	89	10
8	**2f**	12	97	2

[a]Unless otherwise noted, the reactions were carried out using 0.25−0.31 mmol of **2** with **5a** (10 mol %), ^{i}PrOH (20 mol %), and Cs_2CO_3 (40 mol %) in CH_2Cl_2/CH_3CN = 1/1. [b]Determined by ^{1}H NMR spectroscopy. Isolated yield. [c]Determined by chiral GC. [d]1.0 mmol of **2a** with **5a** (1 mol %) and ^{i}PrOH (2 mol %).

entries 3−4, 6). The reaction of the mixture of 1,4-dialdehyde **2c** and hydrate **3c** also proceeded in 64% yield (67% ee) after 10 h, indicating the occurrence of an equilibrium between the 1,4-dialdehyde and the hydrate under the applied reaction conditions. However, the reaction did not reach completion, affording the corresponding lactol in 22% yield together with **3c** (14%) (Table 2, entry 5). The reaction of saturated bicyclic 1,4-dialdehydes **2e** and **2f** proceeded smoothly, albeit with low enantioselectivities (Table 2, entries 7 and 8). These results indicate the double bond might act as a directing group in the case of a conformationally more rigid bicyclic system (entry 4 vs 7, 6 vs 8). This result might be related to the fact that the CH−π interaction has a key role in the chiral recognition of the enantioselective transfer hydrogenation using the arene−metal complex.[48] The reaction of **2a** with 1 mol % catalyst also proceeded with a 94% yield with 55% ee in a 1 mmol-scale reaction (Table 2, entry 2).

As could be anticipated based on the results of one of our previous studies,[42] an enantiodivergent relationship between the asymmetric Tishchenko reaction of *meso*-1,4-dialdehydes and the asymmetric oxidative lactonization of *meso*-1,4-diols using the same chiral catalyst was observed. Thus, the asymmetric Tishchenko reaction of *meso*-1,4-dialdehydes using (*S*,*S*)-**5a** gave (3a*S*,7a*R*)-lactones, while the asymmetric oxidative lactonization of *meso*-1,4-diols gave (3a*R*,7a*S*)-lactones (Scheme 4).[49]

Scheme 4. Asymmetric Tishchenko Reaction and Asymmetric Oxidative Lactonization Catalyzed by an (*S*,*S*)-Catalyst



It should also be noted here that the obtained chiral lactones are versatile chiral building blocks. For example, chiral lactone **4a** is used for the synthesis of an NMDA antagonist[50] and an ACE inhibitor,[51] while **4b** serves as a starting material for brefeldin A,[52] mucosin,[53] compactin,[54] and aucantene.[55] Meanwhile, boschnialactone,[56] methyl jasmonate,[57] (−)-ngaione,[58] and (+)-quercus lactone[59] are synthesized from **4c**, while differolide[60] can be obtained from **4d** (Scheme 5).

A plausible catalytic cycle for the Ir-catalyzed asymmetric Tishchenko reaction of *meso*-1,4-dialdehydes is depicted in Scheme 6. Ir complex **5b**, which is obtained in situ from **5a**, reacts with 2-propanol to give Ir hydride complex **5c**. Then, *meso*-1,4-dialdehyde **2** is reduced by **5c** in an enantiotopos-selective manner to give hydroxy aldehyde A, which is in equilibrium with lactol B. Finally, lactol B is oxidized by **5b** to give the desired lactone **4**, accompanied by the regeneration of the catalyst 5c.

The structure of Ir amino alkoxide complexes **5** was examined by means of single-crystal X-ray diffraction analysis,

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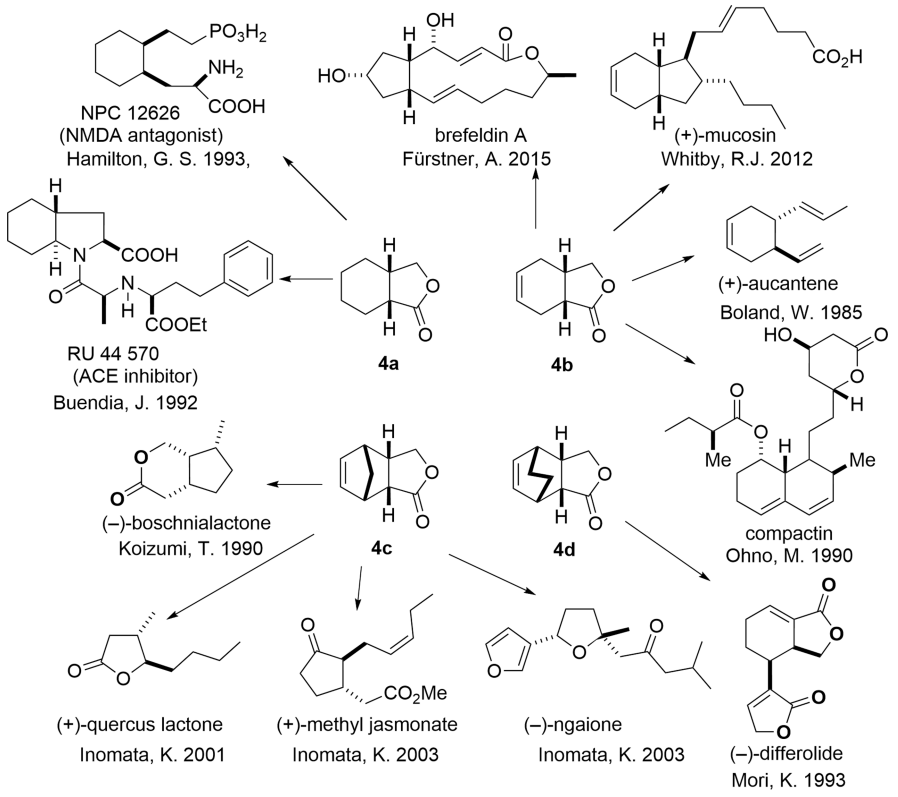
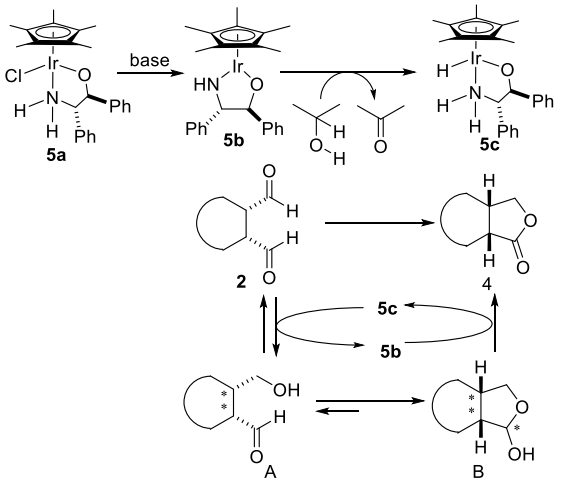
Scheme 5. Utility of Chiral Lactones



Scheme 6. Plausible Reaction Pathway for the Asymmetric Tishchenko Reaction of *meso*-1,4-Dialdehydes Catalyzed by a Chiral Ir Complex



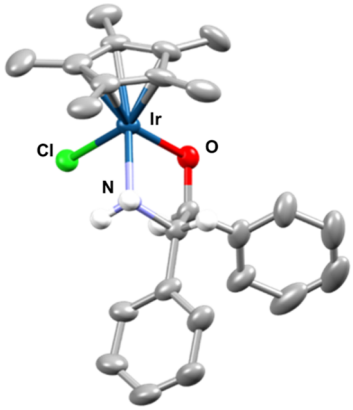


Figure 2. Molecular structure of **5a** in the single crystal with thermal ellipsoids at 30% probability; all hydrogen atoms, except for the proton of the aminoalcohol ligand and those at the carbon atoms in the chelate backbone, as well as one molecule of water and two molecules of chloroform, are omitted for clarity.

cold-spray ionization mass spectrometry (CSI-MS), and ^{1}H NMR spectroscopy. Figure 2 shows the solid-state structure of iridium complex **5a** in the single crystal, where **5a** adopts a pseudotetrahedral and three-legged piano stool geometry with Cp*, amino, alkoxide, and chloro ligands. The (*S*)-configuration around the Ir center stems arises from the chirality of the (*S*,*S*)-diphenyl aminoalcohol ligand, which forms a *δ*-configurated five-membered chelate. The CSI-MS spectra of **5a** show the chloride adduct of **5a** in negative mode (Figure 3, top). Treatment of **5a** with KOH in CH_2Cl_2 produced 16-electron complex **5b** as the chloride adduct (Figure 3, middle). Treatment of **5a** with Cs_2CO_3 in 2-propanol afforded a species with a 2-mass-unit increase, which supports the formation of an Ir hydride complex. All the obtained MS spectra matched the simulated Ir isotope pattern. ^{1}H NMR measurements were carried out to determine the structure of **5a** in solution. After treatment of **5a** with KOH, all signals shifted, and that corresponding to one of the NH protons disappeared, which supports the formation of 16-electron complex **5b**. Further addition of 2-propanol to the reaction mixture resulted in the appearance of a new peak at around −9 ppm, which was attributed to a hydride (for details, see the Supporting Information).

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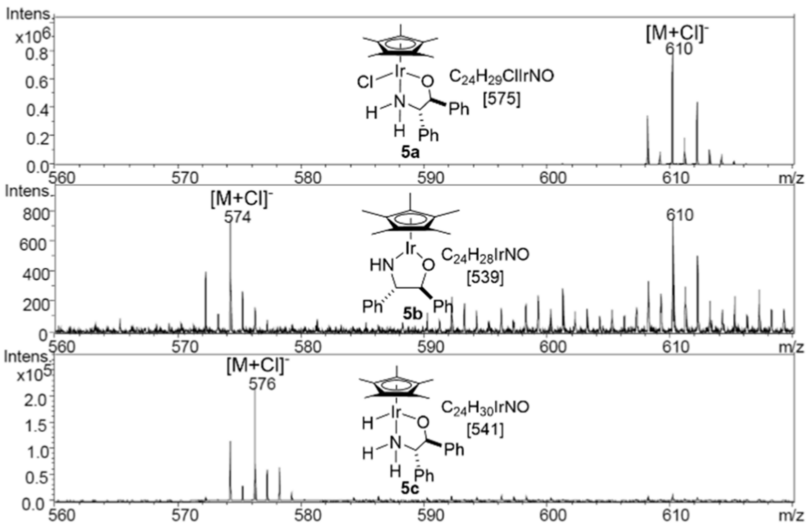

Figure 3. Negative CSI-MS spectra of iridium complexes: (top) **5a**; (middle) **5b**, obtained from treating **5a** with KOH in CH_2Cl_2; and (bottom) **5c**, obtained from treating **5a** with Cs_2CO_3 in 2-propanol.

3. CONCLUSIONS

In summary, we have developed the first practical method to prepare 1,4-*meso*-dialdehydes via heterogeneous oxidative cleavage of the corresponding cyclobutanediols using polymer-supported periodate and characterized 1,2-cyclohexanedicarboxaldehyde as one of the simplest 1,4-*meso*-dialdehydes for the first time. The obtained 1,4-*meso*-dialdehydes were subsequently employed in asymmetric Tishchenko reactions using a chiral Ir aminoalkoxide complex as the catalyst. This study can be expected to open new synthetic avenues for the desymmetrization of 1,4-*meso*-dialdehydes.

4. EXPERIMENTAL SECTION

4.1. General Information. The melting point was measured with the Rigaku TG-DTA Thermo Plus 8120. Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 spectrometer. ^{1}H NMR spectra were recorded on the JEOL JNM-ECS400 NMR, JEOL JNM-ECA600 NMR, or Bruker AVANCE III 700 NMR spectrometer. The chemical shifts are reported in ppm on the δ scale downfield from tetramethylsilane or relative to the residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 for $^{13}C\{^1H\}$ NMR, C_6D_6: 7.16 ppm for ^{1}H NMR and 128.06 for $^{13}C\{^1H\}$ NMR, $C_6D_5CD_3$: 2.08 ppm for ^{1}H NMR and 20.43 for $^{13}C\{^1H\}$ NMR, CD_2Cl_2: 5.32 ppm for ^{1}H NMR and 53.84 for $^{13}C\{^1H\}$ NMR, CD_3CN 1.94 ppm for ^{1}H NMR, CD_2Cl_2: 5.32 ppm for ^{1}H NMR and 53.84 for $^{13}C\{^1H\}$ NMR, and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad peak. $^{13}C\{^1H\}$ NMR spectra were measured on a JEOL JNM-ECA600 NMR spectrometer at 151 MHz, a Bruker AVANCE III 176 NMR spectrometer at 176 MHz, or a JEOL JNM-ECA400 NMR at 100 MHz. Electrospray ionization (ESI) mass spectra were recorded on a THERMO LTQ Orbitrap XL spectrometer. CSI-MS were recorded on a Bruker micrOTOF II spectrometer with a cryospray unit. X-ray crystallographic analysis was conducted on a Rigaku E-AXIS RAPID 191R diffractometer system equipped with a Rigaku FR-E^{+2} SuperBright (Cu) X-ray generator or a Rigaku XtaLAB PRO MM007 DW diffractometer system equipped with a MicroMax007HFM-DW(Cu/Mo) X-ray generator and a HyPix-6000HE detector. Optical rotations were measured with a JASCO P-2300 polarimeter. The *ee* of all the lactones was determined by the Shimazu GC system (GC-2014, AOC-20i autosampler, flame ionization detector): Column: Astec CHIRALDEX G-TA (0.25 mm × 30 m, DF = 0.12 μm). The GC condition: He as a carrier gas, split ratio = 100/1, purge/total flow = 3.0/103.0 mL/min, total pressure: 122.8 kPa, injector and detector temperature = 250 °C, column temperature = 170 °C.

Anhydrous solvents (THF, CH_2Cl_2, CH_3CN, hexane, and toluene from Kanto CHEMICAL Co., INC., Et_2O from FUJIFILM Wako Pure Chemical Corp.) were purified by a solvent purification system (GlassContour) equipped with columns of activated alumina prior to use. Other anhydrous solvents, dimethyl sulfoxide (DMSO), MeOH, and EtOH, were purchased from Kanto CHEMICAL Corp. and used without further purification. Amberlite IRA 904Cl (ORGANO.), KOH, Na, $NaBH_4$, Oxalyl chloride (Kishida Chemical), 5% Pd/C (N.E. CHEMCAT), and TMSCl (Tokyo Chemical Industry Co., Ltd. (TCI)), $NaIO_4$, Cs_2CO_3, 1,4-BTMSB-d_4 (FUJIFILM Wako Pure Chemical Corp.) were purchased and used without purification. Silica gel chromatography was performed using 40−50 μm Kanto (silica gel 60N, spherical, neutral). *Cis*- or *trans*-cyclohexanedimethanol,[61] (1*S*,2*S*)-2-amino-1,2-diphenylethan-1-ol[62] was prepared according to the literature.

4.1.1. (Scheme 1) Swern Oxidation of 1,2-Cyclohexanedimethanols. (aqueous workup using *cis*-diol)

Oxalyl chloride (0.156 mL, 1.80 mmol) was added dropwise to the DMSO (0.260 mL, 3.68 mmol) in CH_2Cl_2 solution (12 mL) at −78 °C and stirred for 1 h. *cis*-1,2-Cyclohexanedimethanol (100 mg, 0.693 mmol) in CH_2Cl_2 (4 mL) was added dropwise and stirred for 2 h. Triethylamine (0.967 mL, 6.93 mmol) was added at −78 °C, and then the reaction mixture was warmed up to an ambient temperature and stirred for 12 h. The reaction mixture was washed with 1 M aq HCl, sat. $NaHCO_3$, brine, dried over Mg_2SO_4, and filtrated. The filtrate was evaporated under reduced pressure. The crude mixture was purified with a silica gel column (ethyl acetate) to give the dialdehyde as a diastereo mixture (57.6 mg, 59%, *cis*/*trans* = 3.4:1).

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4.1.2. (Nonaqueous Workup Using cis-Diol). Oxalyl chloride (0.160 mL, 1.85 mmol) was added dropwise to the DMSO (0.260 mL, 3.68 mmol) in CH_2Cl_2 solution (30 mL) at −78 °C. *cis*-1,2-Cyclohexanedimethanol (102 mg, 0.707 mmol) in CH_2Cl_2 (4 mL) was added dropwise and stirred for 13 h. Triethylamine (1.00 mL, 7.17 mmol) was added at −78 °C, and then the reaction mixture was warmed up to an ambient temperature and stirred for 9 h. The reaction mixture was filtrated with a Celite pad and washed with hexane−toluene 1:1. The filtrate was evaporated under reduced pressure. The crude mixture was purified with a silica gel column (ethyl acetate) to give the dialdehyde as a diastereo mixture (81.2 mg, 82%, *cis*/*trans* = 4.8:1).

4.1.3. (Aqueous Workup Using trans-diol). Oxalyl chloride (0.156 mL, 1.80 mmol) was added dropwise to the DMSO (0.256 mL, 3.61 mmol) in CH_2Cl_2 solution (12 mL) at −78 °C and stirred for 20 min. *trans*-1,2-Cyclohexanedimethanol (100 mg, 0.693 mmol) in CH_2Cl_2 (4 mL) was added dropwise and stirred for 3 h. Triethylamine (0.967 mL, 6.93 mmol) was added at −78 °C, and then the reaction mixture was warmed up to an ambient temperature and stirred overnight. The reaction mixture was washed with brine, dried over Na_2SO_4, and filtrated. The filtrate was evaporated under reduced pressure. The crude mixture was purified with a silica gel column (ethyl acetate) to give the dialdehyde as a single diastereomer (72.2 mg, 74%, *cis*/*trans* = 0:1).

*4.1.4. trans-Cyclohexane-1,2-dicarbaldehyde (trans-**2a**)[63,64] Purple Color Oil (72.2 mg, 74%).* ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.71(s, 2H), 2.70−2.68(m, 2H), 2.08−2.05(m, 2H), 1.79−1.77(m, 2H), 1.37−1.25(m, 4H); $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$): 202.9(2C), 49.2(2C), 24.95(2C), 24.86(2C); ESI-HRMS: calcd for $C_8H_{12}O_2Na$, 163.0730(M + Na^+); found, 163.0729; IR(KBr): 2928, 1727 cm^{-1}

4.2. General Procedure for the Synthesis of Cyclobutandiols. The *cis*-cyclobutanediol derivatives were prepared by Hartmann's procedure.[64]

Starting from the corresponding methyl ester, the acyloin condensation (step 1) afforded cyclobutane acyloin in 83−95% yield. After sodium borohydride reduction (step 2), 1,2-cyclobutane diol is obtained in 35−75%.

4.2.1. (1R,6S*,7S*,8R*)-Bicyclo[4.2.0]octane-7,8-diol (**1a**)[65] (Step1:83%, Step2:51%).* ^{1}H NMR(600 MHz, $CDCl_3$): δ 4.31 (t, *J* = 4.1 Hz, 2H), 2.34−2.31 (m, 4H), 1.70−1.68 (m, 2H), 1.64−1.52 (m, 4H), 1.34−1.29 (m, 2H); $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$)δ: 71.3(2C), 34.7(2C), 22.8(2C), 21.3(2C); ESI-HRMS: calcd for $C_8H_{14}O_2Na$ (M + Na^+), 165.0886; found, 165.0884; IR(KBr): 3445, 3369, 2934 cm^{-1}; mp 70.1 °C.

4.2.2. (1R,6S*,7S*,8R*)-Bicyclo[4.2.0]oct-3-ene-7,8-diol (**1b**)[66] (Step1:81%, Step2:35%).* ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.98 (t, *J* = 1.2 Hz, 2H), 4.35 (s, 2H), 2.73−2.70 (m, 2H), 2.37 (s, 2H), 2.25−2.20 (m, 2H), 2.05−2.02 (m, 2H); $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$): 128.4(2C), 69.7(2C), 33.5(2C), 19.6(2C); ESI-HRMS: calcd for $C_8H_{12}O_2Na$ (M + Na^+), 163.0730; found, 163.0728; IR(KBr): 3367, 3040, 2940 cm^{-1}; mp 60.4 °C.

4.2.3. (1R,2S*,3S*,4R*,5R*,6S*)-Tricyclo[4.2.1.0^{2,5}]-7-nonene-3,4-diol (**1c**)[67] (Step1:82%, Step2:38%).* ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.32 (t, *J* = 1.7 Hz, 2H), 4.28 (d, *J* = 4.1 Hz, 2H), 2.97 (d, *J* = 1.4 Hz, 2H), 2.92−2.89 (m, 2H), 1.91 (br s, 2H), 1.39 (d, *J* = 8.2 Hz, 1H), 1.02 (d, *J* = 8.2 Hz, 1H); $^{13}C\{^1H\}$ NMR(150 MHz,$CDCl_3$):137.0(2C), 68.9(2C), 53.3, 45.8(2C), 44.8(2C); ESI-HRMS: calcd for $C_9H_{12}O_2Na$ (M + Na^+), 175.0730; found, 175.0727; IR(KBr): 3361, 3077 cm^{-1}; mp 106.5 °C.

4.2.4. (1R,2S*,3S*,4R*,5R*,6S*)-Tricyclo[4.2.2.0^{2,5}]-7-decene-3,4-diol (**1d**)[68] (Step1:95%, Step2:75%).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (dd, *J* = 4.6, 3.2 Hz, 2H), 4.38−4.34 (m, 2H), 2.72−2.69 (m, 4H), 2.16 (d, *J* = 8.2 Hz, 2H), 1.44−1.41 (m, 2H), 1.25−1.21 (m, 2H); $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$):135.3(2C), 70.1(2C), 45.8(2C), 29.4(2C), 24. 5(2C); ESI-HRMS: Calcd for $C_{10}H_{14}O_2Na$(M + Na^+), 189.0886; found, 189.0887; IR(KBr): 3505, 3367, 2950 cm^{-1}; mp 100.6 °C.

4.2.5. (1R,2R*,3R*,4S*,5S*,6S*)-Tricyclo[4.2.1.0^{2,5}]-]nonane-3,4-diol (**1e**).* Hydrogenation of **1c** (109 mg, 0.716 mmol) using 5% Pd/C (76.2 mg, 0.0716 mmol, 10 mol %) in EtOH (2.4 mL) under H_2 atmosphere (1 atm) at 25 °C for 2 h gave **1e** (108 mg, 98%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.54 (d, *J* = 5.2 Hz, 2H), 2.56−2.54 (m, 2H), 2.50−2.48 (m, 2H), 2.41−2.39 (m, 2H), 2.27 (br s, 2H), 1.45−1.43 (m, 2H), 1.27 (dt, *J* = 9.3, 1.4 Hz, 1H), 1.12−1.10 (m, 1H); $^{13}C\{^1H\}$ NMR(150 MHz, $CDCl_3$): δ 69.9(2C), 43.8(2C), 43.2, 40.9(2C), 25.1(2C); ESI-HRMS: calcd for $C_9H_{14}O_2Na$(M + Na^+), 177.0886; found, 177.0883; IR(KBr): 3380, 2924 cm^{-1}; mp 92.1 °C.

4.2.6. (2S,3S*,4R*,5R*)-Tricyclo[4.2.2.0^{2,5}]decane-3,4-diol (**1f**).* Hydrogenation of **1d** (101 mg, 0.606 mmol) using 5% Pd/C (64.5 mg, 0.030 mmol, 5 mol %) in EtOH (25 mL) under H_2 atmosphere (1 atm) at 30 °C for 12 h gave **1f** (91.8 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.63 (dd, *J* = 5.2, 4.1 Hz, 2H), 2.41−2.40 (m, 2H), 2.28−2.26 (m, 2H), 1.77−1.76 (m, 2H), 1.59−1.55 (m, 2H), 1.47 (dd, *J* = 11.9, 4.6 Hz, 2H), 1.39−1.35 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): 71.4(2C), 40.9(2C), 27.2(2C), 24.2(2C), 23.6(2C); ESI-HRMS: calcd for $C_{10}H_{16}O_2Na$(M + Na^+), 191.1043; found, 191.1040; IR(KBr): 3352, 2927 cm^{-1}; mp 89.5 °C.

4.3. (Scheme 2) General Procedure for Oxidative Cleavage by Silica Gel-Supported $NaIO_4$. To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent[45] (2 equiv) in a 10 mL test tube was added a solution of diol (0.9 mmol) in CH_2Cl_2 (0.1 M) at 30 °C. The reaction was monitored by TLC until the disappearance of the starting material (generally 10−30 min). The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with $CHCl_3$ (3 × 10 mL). Removal of solvents from the filtrate afforded aldehyde that was pure enough for most purposes. The chemical yield was estimated using 1,1,2,2-tetrachloroethane as an internal standard.

4.4. (Scheme 3) Dehydration of Hydrate by MS 4A. The hydrate **3c** (34.2 mg, 0.206 mmol) in THF (5 mL) was refluxed for 14 h using Dean−Stark with MS4A. After cooling the reaction mixture, the solution was evaporated under reduced pressure, and the crude material was subjected to NMR measurement.

4.5. Preparation of Resin-IO_4.[46] Amberlite IRA904-Cl (ORGANO corp., 25 g) was added into a 500 mL Erlenmeyer flask that contains fresh $NaIO_4$ aqueous solution (20.0 g, 93.5 mmol) in deionized water (200 mL) on the shaker (EYELA MRM-1000). After shaking (shaking speed: 100 rpm, tilt angle: 3°, mode: reciprocation and vibration) at room temperature for 6 h, the solution part was decanted off, and the solid part was again treated with a fresh $NaIO_4$ solution (20.0 g in 200 mL). After further shaking for 7 h, the resulting mixture was filtered and washed with water (100 mL), THF

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(100 mL), and Et_2O (100 mL) and dried in the vacuum at 40 °C overnight. The effective weight percentage of the resulting periodate resin was determined by iodometry using aq. 0.005 M aq. Na_2SO_3 solution. Normally, this procedure provides the resin product containing 0.10−0.24 mmol of periodate anion per gram.

4.6. General Procedure for Oxidative Cleavage by Resin-IO_4 Oxidative Cleavage. To a 0.075−0.09 M solution of diol **1** in CH_2Cl_2 was added resin periodate (2−3 equiv), and the reaction mixture was stirred at 25 °C. The reaction was monitored by TLC until the disappearance of the starting material. The mixture was filtered through a poly(tetrafluoroethylene) (PTFE) membrane, washed with CH_2Cl_2 (3 × 4 mL), and evaporated under reduced pressure to give the dialdehyde. In the case of *meso*-dialdehyde **2c**−**2f**, which is aerobically unstable, the chemical yield was determined using 1,4-BTMSB-d_4 as an internal standard. The filtered solution of **2c**−**2f** was concentrated to the suitable concentration and used as a solution for the following asymmetric Tishchenko reaction.

*4.6.1. cis-Cyclohexane-1,2-dicarbaldehyde (cis-**2a**).*[41] (Yellow oil: 98.8 mg, 99%: from 0.09 M of **1a** (0.713 mmol), 30 °C, 2 h) ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.70 (s, 2H), 2.71 (brm, 2H), 1.96 (brm, 2H), 1.89−1.82 (m, 2H), 1.49 (brm, 4H); ^{1}H NMR (700 MHz, C_6D_6): δ 9.29 (s, 2H), 1.91 (brm, 2H), 1.50 (ddd, 2H), 1.25 (brm, 2H), 1.02 (brm, 2H), 0.96−0.93 (m, 2H); $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$): 203.5(2C), 48.9(2C), 24.1(4C); $^{13}C\{^1H\}$ NMR(176 MHz, C_6D_6): 202.0(2C), 48.6(2C), 24.1(2C), 24.0(2C); ESI-HRMS: calcd for $C_8H_{12}O_2Na$ (M + Na^+), 163.0730(M + Na^+); found, 163.0729; IR(KBr): 2931, 1721 cm^{-1}.

*4.6.2. mmol Scale Reaction of Oxidative Cleavage by Resin-IO_4 of **1a**.* To a solution of diol **1a** (171 mg, 1.20 mmol) in CH_2Cl_2 (12 mL) in a 30 mL round-bottom flask was added 25% resin periodate (1.837 g, 2 equiv), and the reaction mixture was stirred at 30 °C for 1 h. The mixture was filtered through a PTFE membrane, washed with CH_2Cl_2 (3 × 5 mL), and evaporated under reduced pressure to give the dialdehyde (168 mg, >99%) as a yellow oil.

*4.6.3. cis-4-Cyclohexene-1,2-dicarbaldehyde (cis-**2b**).*[69] (Yellow liquid: 41.3 mg, 99%: from 0.075 M of **1b** (0.299 mmol) ^{1} H NMR(600 MHz, $CDCl_3$): δ 9.71 (s, 2H), 5.75 (t, *J* = 1.4 Hz, 2H), 2.92−2.90 (m, 2H), 2.52−2.49 (m, 2H), 2.43−2.40 (m, 2H); $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$): δ 202.9(2C), 125.8(2C), 45.8(2C), 23.7(2C); ESI-HRMS: calcd for $C_8H_{10}O_2Na$(M + Na^+), 161.0573; found, 161.0574; IR(KBr): 3023, 2910, 1722, 1660 cm^{-1}

4.6.4. (1R,2S*,3R*,4S*)-Bicyclo[2.2.1]-5-heptene-2,3-dicarbaldehyde (cis-**2c**).*[70] (91%, NMR yield: from 0.075 M of **1c** (0.302 mmol) ^{1}H NMR (600 MHz, $CDCl_3$): δ: 9.53 (s, 2H), 6.31 (t, *J* = 1.7 Hz, 2H), 3.33 (dq, *J* = 9.5, 2.4 Hz, 4H), 1.60 (dt, *J* = 8.7, 1.7 Hz, 1H), 1.45 (d, *J* = 8.9 Hz, 1H); $^{13}C\{^1H\}$ NMR: δ = 201.6, 135.6, 58.2, 49.4, 45.7.

ESI-HRMS: calcd for $C_9H_{10}O_2Na^+$(M + Na^+), 173.0573; found, 173.0572; IR(KBr): 2941, 1727 cm^{-1}

4.6.5. (1R,2S*,3R*,4S*)-Bicyclo[2.2.2]-5-octene-2,3-dicarbaldehyde (cis-**2d**).*[70] (83%, NMR yield: from 0.09 M of **1d** (0.367 mmol) ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.49 (s, 2H), 6.34 (dd, *J* = 4.6, 3.2 Hz, 2H), 3.03−2.98 (m, 4H), 1.69−1.62 (m, 2H), 1.40−1.36 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 201.4, 133.6, 56.4, 31.2, 24.8; ESI-HRMS: calcd for $C_{10}H_{12}O_2Na^+$(M + Na^+), 187.0730; found, 187.0730; IR-(KBr): 2943, 1720 cm^{-1}

*4.6.6. Bicyclo[2.2.2]octa-2,5-diene-2,3-dicarbaldehyde (**2d′**).*[71] (4%, determined by NMR using 1,4-BTMSB-d_4 as an internal standard)

^{1}H NMR (700 MHz, $CDCl_3$): δ 10.52 (s, 2H), 6.39 (dd, *J* = 4.4, 3.1 Hz, 2H), 4.44−4.43 (m, 2H), 1.48−1.47 (m, 2H), 1.34−1.33 (m, 2H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 185.8(2C), 154.6(2C), 133.8(2C), 34.8(2C), 24.4(2C); ESI-HRMS: calcd for $C_{10}H_{11}O_2$ (M + H^+), 163.0754; found, 163.0729; IR(KBr) 2943, 1716, 1665 cm^{-1}.

4.6.7. (1R,2S*,3R*,4S*)-Bicyclo[2.2.1]-5-heptane-2,3-dicarbaldehyde (cis-**2e**).*[70] (98%, NMR yield: from 0.0785 M of **1e** (0.314 mmol) ^{1}H NMR(600 MHz, $CDCl_3$): δ 9.83 (s, 2H), 2.98−2.97 (br m, 2H), 2.78−2.77 (m, 2H), 1.60−1.52 (m, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl3): δ: 202.0(2C), 55.2(2C), 40.0, 39.4(2C), 34.8(2C), 24.1(2C); ESI-HRMS: calcd for $C_9H_{12}O_2Na^+$(M + Na^+), 175.0730; found, 175.0728; IR(KBr): 2941, 1727 cm^{-1}.

4.6.8. (1R,2S*,3R*,4S*)-Bicyclo[2.2.2]-5-octane-2,3-dicarbaldehyde (cis-**2f**).*[70] (94%, NMR yield: from 0.075 M of **1f** (0.303 mmol) ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.80 (s, 2H), 2.85 (s, 2H), 2.23 (s, 2H), 1.68−1.55 (m, 8H); $^{13}C\{^1H\}$ NMR: δ 202.2(2C), 51.6(2C), 25.8(2C), 25.2(2C), 21.4(2C); IR(KBr): 2943, 1722 cm^{-1}; ESI-HRMS: calcd for $C_{10}H_{14}O_2Na^+$(M + Na^+), 189.0886; found, 189.0884.

4.6.9. (3aR,4S*,7R*,7aS*)-1,3,3a,4,7,7a-Hexahydro-4,7-methanoisobenzofuran-1,3-diol (**3c**).*[72] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (t, *J* = 1.8 Hz, 2H), 4.96−4.87 (m, 2H), 3.35 (br s, 1H), 3.03−2.99 (m, 4H), 1.67−1.65 (br s, 1H), 1.44 (d, *J* = 8.2 Hz, 1H), 1.32 (d, *J* = 8.2 Hz, 1H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 134.5 (2C), 102.4 (2C), 54.9 (2C), 51.5, 45.0 (2C).

4.6.10. (3aR,4S*,7R*,7aS*)-1,3,3a,4,7,7a-Hexahydro-4,7-ethanoisobenzofuran-1,3-diol (**3d**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (dd, *J* = 4.8, 3.4 Hz, 2H), 5.07 (s, 2H), 3.91 (br s, 2H), 2.75−2.73 (br m, 2H), 2.54 (s, 2H), 1.51−1.49 (m, 2H), 1.24−1.20 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ: 132.9(2C), 105.3(2C), 52.8(2C), 32.3(2C), 24.2(2C).

ESI-HRMS: calcd for $C_{10}H_{14}O_3Na^+$, 205.0835 (M + Na^+); found, 205.0835; IR(KBr): 3387, 3270, 2938 cm^{-1}; mp 100.8 °C.

4.7. General Procedure of the Asymmetric Tishchenko Reaction. The reactions were performed using an EYELA personal organic synthesizer, ChemiStation PPS-5511. To a 10 mL Schlenk tube, including Ir complex **5a** (10 mol %) and Cs_2CO_3 (40 mol %) was added a 0.1 M solution of 2-propanol in CH_3CN (20 mol %) and stirred for 10 min. Then CH_3CN and a solution of *meso*-**2** in CH_2Cl_2 were added and stirred at 25 °C. Without special mention, the reaction was performed with CH_3CN/CH_2Cl_2 = 1:1 as a solvent, 0.05 molar, based on the starting material. The mixture was passed through a short silica gel column (ethyl acetate) to remove the catalyst and concentrated under reduced pressure. Then, the crude mixture was analyzed by quantitative NMR using 1,4-bis(trimethylsilyl)benzene-d_4 (1,4-BTMSB-d_4) as an internal standard and purified by silica gel column chromatography (hexane/ethyl acetate = 90/10) to give lactone **4**. The ee of all the lactones was determined by a chiral GC analysis: Column: Astec CHIRALDEX G-TA (0.25 mm × 30 m, DF = 0.12 μm) Condition: He as a carrier gas, split ratio = 100/1, purge/total flow = 3.0/103.0 mL/min, total pressure: 122.8 kPa, injector and detector temperature = 250 °C, column temperature = 170 °C.

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4.8. Procedure of 1 mmol Scale Asymmetric Tishchenko Reaction of *cis*-2a with 1 mol % Catalyst-Loading. To a 10 mL Schlenk tube, including Ir complex **5a** (6.0 mg, 0.01 mmol, 1 mol %) and Cs_2CO_3 (135.5 mg, 0.416 mmol, 40 mol %) was added a 0.1 M solution of 2-propanol in CH_3CN 0.2 mL (0.02 mmol, 2 mol %) and stirred for 10 min. Then CH_3CN (5.0 mL) and a solution of *cis*-**2a** (145.7 mg, 1.039 mmol) in CH_2Cl_2 (5.2 mL) were added and stirred at 25 °C for 17 h. The mixture was passed through a short silica gel column (ethyl acetate) to remove the catalyst and concentrated under reduced pressure. Then, the crude mixture was analyzed by quantitative NMR using 1,4-BTMSB-d_4 as an internal standard (94% yield) and purified by silica gel column chromatography (hexane/ethyl acetate = 9/1) to give the lactone **4a** as a colorless oil (120.8 mg, 83%, 55% ee).

*4.8.1. (3aR, 7aS)-Hexahydroisobenzofuran-1(3H)-one (**4a**)*[73] *120.8 mg, Colorless Oil, 94%, 55 ee.* ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (dd, J = 8.8, 5.0 Hz, 1H), 3.96 (dd, J = 8.8, 1.3 Hz, 1H), 2.65 (td, J = 5.2, 2.8 Hz, 1H), 2.47−2.46 (m, 1H), 2.13−2.10 (m, 1H), 1.84−1.81 (m, 1H), 1.66−1.62 (m, 3H), 1.28−1.17 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 178.7, 71.9, 39.6, 35.5, 27.3, 23.6, 23.1, 22.6; $[\alpha]_D^{25}$ = +26.9° (c 0.5, $CHCl_3$, 55% ee). lit. $[\alpha]_D^{25}$ = +48.8° (c 0.5, $CHCl_3$, >99% ee);[61] Retention time: 8.5 min (3a*S*, 7a*R*), 8.8 min (3a*R*, 7a*S*).

*4.8.2. (3aR, 7aS)-3a,4,7,7a-Tetrahydroisobenzofuran-1(3H)-one (**4b**).*[74] White solid, 95%, 59% ee. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.75−5.75 (m, 2H), 4.32 (dd, J = 8.8, 5.2 Hz, 1H), 4.04 (dd, J = 8.8, 2.1 Hz, 1H), 2.79−2.78 (m, 1H), 2.66−2.61 (m, 1H), 2.53−2.50 (m, 1H), 2.42−2.36 (m, 1H), 2.29−2.27 (m, 1H), 1.95−1.89 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 179.2, 125.3124.9, 72.8, 37.4, 32.1, 24.8, 22.1; $[\alpha]_D^{25}$ = −27.1° (c 1.0, $CHCl_3$, 59% ee). lit. $[\alpha]_D^{rt}$ = +46.7° (c 1.0, $CHCl_3$, >99% ee).[75] Retention time: 9.3 min (3a*S*, 7a*R*), 9.7 min (3a*R*, 7a*S*).

*4.8.3. (3aR, 4S,7R,7aS)-3a,4,7,7a-Tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**4c**).*[74] White solid, 90%, 61% ee. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.31 (dd, J = 5.8, 2.9 Hz, 1H), 6.28 (dd, J = 5.8, 2.4 Hz, 1H), 4.29 (dd, J = 9.8, 8.5 Hz, 1H), 3.80 (dd, J = 9.8, 3.2 Hz, 1H), 3.36−3.34 (m, 1H), 3.26−3.25 (m, 1H), 3.11−3.10 (m, 2H), 1.65 (dt, J = 8.6, 1.5 Hz, 1H), 1.47 (d, J = 8.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 178.2, 137.1, 134.5, 70.4, 52.0, 47.7, 46.3, 45.9, 40.4; $[\alpha]_D^{25}$ = +88.9° (c 1.0, $CHCl_3$, 61% ee). lit. $[\alpha]_D^{20}$ = −147.8° (c 1.0, $CHCl_3$, >99% ee);[76] Retention time: 15.6 min (3a*R*, 4*S*, 7*R*, 7a*S*), 16.9 min (3a*S*, 4*R*, 7*S*, 7a*R*).

*4.8.4. (3aR, 4S, 7R, 7aS)-3a,4,7,7a-Tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**4d**).*[74] White solid, 91%, 39% ee. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.34 (t, J = 6.9 Hz, 1H), 6.28 (t, J = 7.2 Hz, 1H), 4.35 (t, J = 9.3 Hz, 1H), 3.85 (dd, J = 9.3, 3.8 Hz, 1H), 3.09−3.08 (m, 1H), 2.77 (dd, J = 10.3, 3.4 Hz, 1H), 2.72−2.71 (m, 2H), 1.59−1.57 (m, 1H), 1.51−1.49 (m, 1H), 1.37−1.27 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 179.5, 134.4, 132.8, 72.5, 44.9, 38.1, 33.5, 31.8, 23.6, 23.5; $[\alpha]_D^{25}$ = +30.4° (c 0.5, $CHCl_3$, 39%ee). lit. $[\alpha]_D^{25}$ = −86.8° (c 0.5, $CHCl_3$, >95% ee);[77] Retention time: 26.2 min (3a*R*, 4*S*, 7*R*, 7a*S*), 29.0 min (3a*S*, 4*R*, 7*S*, 7a*R*).

*4.8.5. (3aR,4R,7S,7aS)-Hexahydro-4,7-methanoisobenzofuran-1(3H)-one (**4e**).*[78] White solid, 89%, 10%ee. ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.30 (dd, J = 10.0, 8.4 Hz, 1H), 4.25 (dd, J = 10.1, 2.8 Hz, 1H), 2.98 (ddd, J = 11.4, 5.6, 1.5 Hz, 1H), 2.88−2.86 (m, 1H), 2.67−2.66 (m, 1H), 2.37−2.37 (brm, 1H), 1.61−1.48 (m, 6H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 179.0, 68.6, 46.9, 42.12, 42.0, 40.5, 40.0, 25.6, 21.7; $[\alpha]_D^{25}$ = +15.1 (c 0.84, $CHCl_3$). lit. $[\alpha]_D^{29}$ = −145.4°(c 1.0, $CHCl_3$, >95% ee) (3a*S*,4*S*,7*R*,7a*R*).[79]

*4.8.6. (3aR,7aS)-Hexahydro-4,7-ethanoisobenzofuran-1(3H)-one (**4f**).*[80] White solid, 97%, 2%ee. ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.46 (dd, J = 9.6, 8.9 Hz, 1H), 4.21 (dd, J = 9.6, 3.3 Hz, 1H), 2.71−2.63 (m, 2H), 2.07−2.07 (m, 1H), 1.73−1.41 (m, 9H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 180.2, 71.1, 41.9, 36.3, 27.2, 25.8, 25.0, 24.6, 21.7, 19.8.

*4.8.7. Preparation of Iridium Catalyst **5a**.* To a solution of $[Cp^*IrCl_2]_2$ (500 mg, 0.628 mmol), (1*S*, 2*S*)-2-amino-1,2-diphenylethan-1-ol[61] (268 mg, 1.26 mmol) in CH_2Cl_2 (12 mL) was added dropwise triethylamine (0.35 mL, 2.51 mmol) at 30 °C and stirred for 1 h. The resulting yellow solution was washed with H_2O (12 mL) twice, washed with brine, and dried with anhydrous Na_2SO_4. After filtration and evaporation, the reaction afforded 677 mg (93%) as a yellow solid.

*4.8.7.1. (1S,2S)-Cp*Ir[NH$_2$CHPhCHPhO]Cl-**5a**.*[81] ^{1}H NMR (700 MHz, CD_2Cl_2): δ 7.24−7.19 (m, 3H), 7.08−7.07 (m, 3H), 7.05−7.03 (m, 4H), 4.72 (d, J = 9.9 Hz, 1H), 4.49 (d, J = 6.2 Hz, 1H), 4.26 (t, J = 10.9 Hz, 1H), 3.18 (br s, 1H), 1.74 (s, 15H); $^{13}C\{^1H\}$ NMR (176 MHz, CD_2Cl_2): δ 144.0, 139.6, 128.9(2C), 128.3, 127.77(2C), 127.73(2C), 127.69(2C), 127.0, 85.2, 83.2(5C), 73.0, 9.0(5C); IR(KBr)3209, 2920, 1493, 1452, 1380, 1026, 700, 581 cm^{-1}; $[\alpha]_D^{25}$ = −73.0° (c 0.5, $CHCl_3$, >99% ee).

*4.8.7.2. (1S,2S)-Cp*Ir[NHCHPhCHPhO]-**5b**.* KOH (9.76 mg, 0.174 mmol, 10 equiv) was added to a solution of **5a** (10.0 mg, 0.0174 mmol) in degassed toluene-d8 (0.5 mL) on an NMR tube under an Ar stream and sonicated for 45 min before the NMR experiment. During the sonication, the color of the reaction mixture was changed from yellow to red.

^{1}H NMR (700 MHz, $C_6D_5CD_3$): δ 7.39 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.3 Hz, 2H), 7.12−7.11 (m, 3H), 7.08−7.03 (m, 3H), 5.31 (br s, 1H), 4.84 (d, J = 8.2 Hz, 1H), 4.36 (br s, 1H), 1.61 (s, 15H); $^{13}C\{^1H\}$ NMR (176 MHz, $C_6D_5CD_3$): δ 147.1, 146.1, 92.7, 83.2, 82.4(5C), 9.9(5C). (Other benzene ring carbons are overlapping with the NMR solvent.)

*4.8.7.3. (1S,2S)-Cp*Ir[NHCHPhCHPhO]-**5c**.* KOH (9.76 mg, 0.174 mmol, 10 equiv) was added to a solution of **5a** (10.0 mg, 0.0174 mmol) in degassed CD_3CN (0.5 mL) on an NMR tube under an Ar stream and sonicated for 45 min before the NMR experiment. During the sonication, the color of the reaction mixture was changed from yellow to red. After confirming the disappearance of **5a** by NMR measurement, 2-PrOH (0.1 mL, 1.30 mmol, 75 equiv) was added and mixed with a vortex mixer for 10 min before NMR measurement.

^{1}H NMR (600 MHz, CD_3CN): δ 7.06−7.01 (m, 10H), 4.78 (br s, 1H), 4.69 (br s, 1H), 4.00 (d, J = 9.6 Hz, 1H), 3.17−3.15 (brm, 1H), 1.84 (s, 15H),-9.26 (s, 1H).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09381.

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Experimental details, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Hoffmann, R. W. *meso* Compounds: Stepchildren or Favored Children of Stereoselective Synthesis? *Angew. Chem., Int. Ed.* **2003**, *42* (10), 1096−1109.

(2) Zeng, X. P.; Cao, Z. Y.; Wang, Y. H.; Zhou, F.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* **2016**, *116* (12), 7330−7396.

(3) Merad, J.; Candy, M.; Pons, J. M.; Bressy, C. Catalytic Enantioselective Desymmetrization of *Meso* Compounds in Total Synthesis of Natural Products: Towards an Economy of Chiral Reagents. *Synthesis* **2017**, *49* (09), 1938−1954.

(4) Suzuki, T. 5.21 Desymmetrization of *meso* Diols. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, 2012, pp 502−533..

(5) Suzuki, T. Recent Topics in the Desymmetrization of *meso*-Diols. *Tetrahedron Lett.* **2017**, *58* (51), 4731−4739.

(6) Buckley, S. L. J.; Drew, M. G. B.; Harwood, L. M.; Macías-Sánchez, A. J. Desymmetrisation of Dialdehydes: (+)-(*S*) and (−)-(*R*) *nor*-Methyl Mevaldate as Versatile Synthetic Intermediates. *Tetrahedron Lett.* **2002**, *43* (19), 3593−3596.

(7) Buckley, S. L. J.; Harwood, L. M.; Macías-Sánchez, A. J. Synthesis of (±)-Mevalonic Acid Lactone via a *meso*-Dialdehyde: a Model for Desymmetrization. *Arkivoc* **2002**, *2002* (8), 46−56.

(8) Botubol-Ares, J. M.; Durán-Peña, M. J.; Hernández-Galán, R.; Collado, I. G.; Harwood, L. M.; Macías-Sánchez, A. J. Diastereoselective and Enantioselective Preparation of *nor*-Mevaldic Acid Surrogates through Desymmetrisation Methodology. Enantioselective Synthesis of (+) and (−) *nor*-Mevalonic Lactones. *Tetrahedron* **2015**, *71* (40), 7531−7538.

(9) Botubol-Ares, J. M.; Durán-Peña, M. J.; Hernández-Galán, R.; Collado, I. G.; Harwood, L. M.; Macías-Sánchez, A. J. *nor*-Mevaldic Acid Surrogates as Selective Antifungal Agent Leads against Botrytis Cinerea. Enantioselective Preparation of 4-Hydroxy-6-(1-phenylethoxy)tetrahydro-2*H*-pyran-2-one. *Bioorg. Med. Chem.* **2015**, *23* (13), 3379−3387.

(10) Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. A Highly Convergent Asymmetric Synthesis of the C(19)-C(27) Segment of Rifamycin S: an Application of Enantiodifferentiating Acetalization with Menthone. *J. Org. Chem.* **1992**, *57* (6), 1637−1639.

(11) Kann, N.; Rein, T. Asymmetric Horner-Wadsworth-Emmons Reactions Using *meso* Dialdehydes as Substrates. *J. Org. Chem.* **1993**, *58* (15), 3802−3804. 10.1021/jo00067a010

(12) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardinelli, G. Asymmetric Synthesis of (−)-Denticulatins A and B via Group-selective Aldolization of a *meso* Dialdehyde with a Chiral *N*-Propionylsultam. *Tetrahedron Lett.* **1995**, *36* (25), 4413−4416. 10.1016/0040−4039(95)00787-D

(13) De Brabander, J.; Oppolzer, W. Enantioselective Total Synthesis of (−)-Denticulatins A and B Using a Novel Group-selective Aldolization of a *meso* Dialdehyde as a Key Step. *Tetrahedron* **1997**, *53* (27), 9169−9202.

(14) Oppolzer, W.; Walther, E.; Balado, C. P.; Brabander, J. D. Enantioselective Synthesis of the Prelog-Djerassi Lactonic acid via Group-selective Aldolization/Desymmetrization of a *meso* Dialdehyde with a Chiral *N*-Propionylsultam. *Tetrahedron Lett.* **1997**, *38* (5), 809−812.

(15) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. Reagent Control of Geometric Selectivity and Enantiotopic Group Preference in Asymmetric Horner-Wadsworth-Emmons Reactions with *meso*-Dialdehydes. *J. Org. Chem.* **1998**, *63* (23), 8284−8294. 10.1021/JO981102Z

(16) BouzBouz, S.; Popkin, M. E.; Cossy, J. Desymmetrization of *meso*-Dialdehydes with Optically Active Cyclopentadienyldialkoxyallyltitanium Complexes. *Org. Lett.* **2000**, *2* (22), 3449−3451.

(17) BouzBouz, S.; Cossy, J. Stereoselective Synthesis of the C15-C24 Fragment of Discodermolide by Desymmetrization of a *meso* Dialdehyde. *Synlett* **2004**, *2004* (11), 2034−2036. 10.1055/s-2004−830882

(18) Roush, W. R.; Jae, C. P. Asymmetric Allylborations of Diene Aldehyde $Fe(CO)_3$ Derivatives: Efficient Kinetic Resolution of Racemic Complexes and the Highly Enantiotopic Group and Face Selective Allylboration of a *meso* Substrate. *Tetrahedron Lett.* **1990**, *31* (33), 4707−4710.

(19) Roush, W. R.; Wada, C. K. Application of η^4-Diene Iron Tricarbonyl Complexes in Acyclic Stereocontrol: Asymmetric Synthesis of the as-Indacene Unit of Ikarugamycin (A Formal Total Synthesis). *J. Am. Chem. Soc.* **1994**, *116* (5), 2151−2152.

(20) Casiraghi, G.; Zanardi, F.; Rassu, G. Asymmetric Synthesis of (−)-Denticulatins A and B via Group-selective Aldolization of a *meso* Dialdehyde with Chiral *N*-Propionylsultam. *Chemtracts: Org. Chem.* **1996**, *9* (2), 134−139.

(21) Iwata, C.; Takemoto, Y. [Fe(diene)$(CO)_3$] Complexes as a Guide in Stereocontrol. Applications to the Asymmetric Synthesis of Natural Products. *Chem. Commun.* **1996**, No. 22, 2497−2504. 10.1039/CC9960002497

(22) Takemoto, Y.; Baba, Y.; Noguchi, I.; Iwata, C. Asymmetric Synthesis of (diene)$Fe(CO)_3$ Complexes via Catalytic Enantioselec-

tive Alkylation with Dialkylzinc. *Tetrahedron Lett.* **1996**, *37* (19), 3345−3346.
(23) Takemoto, Y.; Ibuka, T.; Takemoto, Y.; Baba, Y.; Yoshikawa, N.; Iwata, C.; Tanaka, T. Utility of a Diene-tricarbonyliron Complex as Mobile Chiral Auxiliary: Iterative Use for Constructing Contiguous Chiral Centers. *Chem. Commun.* **1998**, No. 17, 1911−1912. 10.1039/A805171B
(24) Takemoto, Y.; Yoshikawa, N.; Baba, Y.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H. Utility of a Diene-Tricarbonyliron Complex as a Mobile Chiral Auxiliary: Regio- and Stereocontrolled Functionalization of Acyclic Diene Ligands. *J. Am. Chem. Soc.* **1999**, *121* (39), 9143−9154.
(25) Takemoto, Y.; Baba, Y.; Honda, A.; Nakao, S.; Noguchi, I.; Iwata, C.; Tanaka, T.; Ibuka, T. Asymmetric Synthesis of (diene)-$Fe(CO)_3$ Complexes by a Catalytic Enantioselective Alkylation Using Dialkylzincs. *Tetrahedron* **1998**, *54* (51), 15567−15580.
(26) Vares, L.; Rein, T. A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives via Sequential Asymmetric Horner-Wadsworth-Emmons and Palladium-catalyzed Ring Closure Reactions. *Org. Lett.* **2000**, *2* (17), 2611−2614.
(27) Vares, L.; Rein, T. A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives by Use of Sequential Asymmetric Horner-Wadsworth-Emmons and Ring-Closure Reactions. *J. Org. Chem.* **2002**, *67* (21), 7226−7237. 10.1021/jo0259111
(28) Kurteva, V. B.; Afonso, C. A. M. A Study on the Intramolecular Catalytic Aldol Cyclodehydration of 3,4-Disubstituted 1,6-Dialdehydes. *J. Mol. Catal. A: Chem.* **2005**, *234* (1−2), 159−167. 10.1016/j.molcata.2005.02.028
(29) Kurteva, V. B.; Afonso, C. A. M. A Direct Intramolecular Asymmetric Catalytic Aldol Cyclodehydration of *meso*-3,4-Disubstituted-1,6-dialdehydes. *Tetrahedron* **2005**, *61* (1), 267−273.
(30) Strand, D.; Rein, T. Total Synthesis of Pyranicin. *Org. Lett.* **2005**, *7* (2), 199−202. 10.1021/ol0479242
(31) Strand, D.; Norrby, P.-O.; Rein, T. Divergence en Route to Nonclassical Annonaceous Acetogenins. Synthesis of Pyranicin and Pyragonicin. *J. Org. Chem.* **2006**, *71* (5), 1879−1891. 10.1021/jo052233k
(32) Mans, D. M.; Pearson, W. H. Total Synthesis of (+)-Cocaine via Desymmetrization of a *meso*-Dialdehyde. *Org. Lett.* **2004**, *6* (19), 3305−3308. 10.1021/ol048777a
(33) The numbering of dialdehydes has been inconsistently performed in the literature. In this paper, the compounds are named by including the aldehyde carbons.
(34) Malfait, S.; Pelinski, L.; Maciejewski, L.; Brocard, J. A Convenient Synthesis of 1,2-Diformylferrocene and 2-Acyl-1-formylferrocenes. *Synlett* **1997**, *1997* (7), 830−832. 10.1055/s-1997−5765
(35) Bastin, S.; Agbossou-Niedercorn, F.; Brocard, J.; Pelinski, L. Enantioselective Alkylation of Benzaldehyde with Diethylzinc Catalyzed by 1,1'- and 1,2-Disubstituted Ferrocenyl Amino Alcohols. *Tetrahedron: Asymmetry* **2001**, *12* (17), 2399−2408. 10.1016/S0957−4166(01)00415−3
(36) Steffen, W.; Laskoski, M.; Collins, G.; Bunz, U. H. F. Triformylferrocenes, Novel Modules for Organometallic Scaffolds. *J. Organomet. Chem.* **2001**, *630* (1), 132−138. 10.1016/S0022−328X(01)00893−2
(37) Schultz, M. J.; Park, C. C.; Sigman, M. S. A convenient palladium-catalyzed aerobic oxidation of alcohols at room temperature. *Chem. Commun.* **2002**, No. 24, 3034−3035.
(38) Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. Cerium or Ruthenium Catalyzed Oxidation of Alcohols to Carbonyl Compounds by Means of Sodium Bromate. *Bull. Chem. Soc. Jpn.* **1986**, *59* (1), 105−108.
(39) Jacobi, P. A.; Buddhu, S. C.; Fry, D.; Rajeswari, S. Studies on the Synthesis of Phytochrome and Related Tetrapyrroles. Dihydropyrromethenones by Photochemical Rearrangement of *N*-Pyrrolo Enamides. *J. Org. Chem.* **1997**, *62* (9), 2894−2906.
(40) Piscitelli, F.; Ligresti, A.; La Regina, G.; Gatti, V.; Brizzi, A.; Pasquini, S.; Allarà, M.; Carai, M. A. M.; Novellino, E.; Colombo, G.; et al. 1-Aryl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-3-carboxamide: An Effective Scaffold for the Design of Either CB_1 or CB_2 Receptor Ligands. *Eur. J. Med. Chem.* **2011**, *46* (11), 5641−5653.
(41) Bergens, S. H.; Fairlie, D. P.; Bosnich, B. Homogeneous catalysis: catalytic intramolecular conversion of 1,4-dialdehydes to γ–lactones. *Organometallics* **1990**, *9* (3), 566−571.
(42) Ismiyarto; Kishi, N.; Adachi, Y.; Jiang, R.; Doi, T.; Zhou, D.-Y.; Asano, K.; Obora, Y.; Suzuki, T.; Sasai, H.; Suzuki, T. Catalytic Enantioselective Intramolecular Tishchenko Reaction of *meso*-Dialdehyde: Synthesis of (*S*)-Cedarmycins. *RSC Adv.* **2021**, *11* (19), 11606−11609. 10.1039/D1RA00915J
(43) Jiang, R.; Ismiyarto; Abe, T.; Zhou, D.-Y.; Asano, K.; Suzuki, T.; Sasai, H.; Suzuki, T. Using α- and β-Epimerizations of *cis*-2,3-Bis(hydroxymethyl)-γ-butyrolactone for the Synthesis of Both Enantiomers of Enterolactone. *J. Org. Chem.* **2022**, *87* (8), 5051−5056. 10.1021/acs.joc.1c02801
(44) Jiang, R.; Zhou, D. Y.; Asano, K.; Suzuki, T.; Suzuki, T. Catalytic Asymmetric Synthesis of (−)-Arctigenin Using a Chiral Ir Complex. *Tetrahedron* **2023**, *133*, 133287. ARTN 133287 10.1016/j.tet.2023.133287
(45) Zhong, Y.-L.; Shing, T. K. M. Efficient and Facile Glycol Cleavage Oxidation Using Improved Silica Gel-Supported Sodium Metaperiodate. *J. Org. Chem.* **1997**, *62* (8), 2622−2624.
(46) Harrison, C. R.; Hodge, P. Polymer-supported Periodate and Iodate as Oxidizing Agents. *J. Chem. Soc.,Perkin Trans. 1* **1982**, No. 2, 509−511. 10.1039/P19820000509
(47) Carey, F. A.; Sundberg, R. J., Oxidations. In *Part B: Reactions and Synthesis*, 4th ed. ed.; Carey, F. A.; Sundberg, R. J., Eds. Springer Berlin Heidelberg: Berlin, Heidelberg, 2001; pp 790−794.
(48) Yamakawa, M.; Yamada, I.; Noyori, R. CH/π Attraction: The Origin of Enantioselectivity in Transfer Hydrogenation of Aromatic Carbonyl Compounds Catalyzed by Chiral η6-Arene-Ruthenium(II) Complexes. *Angew. Chem., Int. Ed.* **2001**, *40* (15), 2818−2821.
(49) Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. Catalytic Asymmetric Oxidative Lactonizations of *meso*-Diols Using a Chiral Iridium Complex. *Tetrahedron Lett.* **2003**, *44* (10), 2003−2006.
(50) Hamilton, G. S.; Huang, Z.; Yang, X. J.; Patch, R. J.; Narayanan, B. A.; Ferkany, J. W. Asymmetric Synthesis of a Potent and Selective Competitive NMDA Antagonist. *J. Org. Chem.* **1993**, *58* (25), 7263−7270.
(51) Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J. M.; Buendia, J. Stereoselective Synthesis of a *trans*-Octahydroindole Derivative, Precursor of Trandolapril (RU 44 570), an Inhibitor of Angiotensin Converting Enzyme. *Tetrahedron Lett.* **1992**, *33* (34), 4889−4892.
(52) Fuchs, M.; Fürstner, A. *trans*-Hydrogenation: Application to a Concise and Scalable Synthesis of Brefeldin A. *Angew. Chem., Int. Ed.* **2015**, *54* (13), 3978−3982.
(53) Henderson, A. R.; Stec, J.; Owen, D. R.; Whitby, R. J. The First Total Synthesis of (+)-Mucosin. *Chem. Commun.* **2012**, *48* (28), 3409−3411. 10.1039/C2CC17915F
(54) Kobayashi, S.; Eguchi, Y.; Shimada, M.; Ohno, M. Enantioselective synthesis of cyclohexenone derivatives by a chemicoenzymatic approach: Stereo- and regioselective route to potential intermediates of compactin (ML 236B) and mevinolin. *Chem. Pharm. Bull.* **1990**, *38* (6), 1479−1484.
(55) Boland, W.; Niedermeyer, U.; Jaenicke, L.; Görisch, H. Enantioselective Syntheses and Absolute Configurations of Viridiene and Aucantene, Two Constitutents of Algae Pheromone Bouquets. *Helv. Chim. Acta* **1985**, *68* (7), 2062−2073.
(56) Arai, Y.; Kawanami, S.; Koizumi, T. Enantioselective Synthesis of (−)-Boschnialactone. *Chem. Lett.* **1990**, *19* (9), 1585−1586.
(57) Suzuki, K.; Inomata, K.; Endo, Y. Enantiocontrolled Synthesis of Jasmonates via Tandem Retro-Diels-Alder-Ene Reaction Activated by a Silyl Substituent. *Org. Lett.* **2004**, *6* (3), 409−411.
(58) Suzuki, K.; Inomata, K.; Endo, Y. New Chiral Synthesis of Methyl and Allyl Disubstituted Butyro Lactone: A Formal Synthesis of (−)-Ngaione. *Heterocycles* **2003**, *60* (12), 2743−2748.

https://doi.org/10.1021/acsomega.3c09381
ACS Omega 2024, 9, 17945−17955

(59) Suzuki, K.; Shoji, M.; Kobayashi, E.; Inomata, K. Concise Enantiodivergent Synthesis of (+)- and (−)-*trans*-Quercus Lactones. *Tetrahedron: Asymmetry* **2001**, *12* (20), 2789−2792.
(60) Mori, K.; Tomioka, H.; Fukuyo, E.; Yanagi, K. Synthetic Microbial Chemistry, XXV. Synthesis of the Enantiomers of Differolide [4-(2′,5′-Dihydro-2′-oxo-3′-furanyl)-3a,4,5,6-tetrahydro-1(3*H*)-isobenzofuranone], a Microbial Bioregulator for the Formation of Aerial Mycelium and Spores of *Streptomyces glaucescens*. *Liebigs Ann. Chem.* **1993**, *1993* (6), 671−681.
(61) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. Enzymes in Organic Synthesis. 24. Preparations of Enantiomerically Pure Chiral Lactones via Stereospecific Horse Liver Alcohol Dehydrogenase Catalyzed Oxidations of Monocyclic *meso* Diols. *J. Am. Chem. Soc.* **1982**, *104* (17), 4659−4665.
(62) Morales, M. R.; Mellem, K. T.; Myers, A. G. Pseudoephenamine: A Practical Chiral Auxiliary for Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51* (19), 4568−4571.
(63) Weinig, H.-G.; Krauss, R.; Seydack, M.; Bendig, J.; Koert, U. Molecular Signal Transduction by Conformational Transmission: Use of Tetrasubstituted Perhydroanthracenes as Transducers. *Chem.—Eur. J.* **2001**, *7* (10), 2075−2088.
(64) Aso, C.; Kunikake, T.; Sasaki, M.; Koyama, K. Studies on the Polymerization of Bifunctional Monomers. *Kobunshi Kagaku* **1970**, *27* (300), 260−264.
(65) Hartmann, W.; Heine, H. G.; Fischler, H. M.; Wendisch, D. Die Stereoisomeren Bicyclo[4.2.0]octan-*cis*-Diole-(7,8). *Tetrahedron* **1973**, *29* (15), 2333−2336.
(66) Casadevall, E.; Pouet, Y. Contraction de Cycle a Partir de la Tosyloxy-8 bicyclo[4.2.0]octanone-7 cis. *Tetrahedron* **1975**, *31* (7), 757−763.
(67) Vedejs, E.; Wu, E. S. C. Synthesis of Olefins from Thionocarbonates by an Alkylation-Reduction Sequence. *J. Org. Chem.* **1974**, *39* (25), 3641−3645.
(68) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Rastelli, A. Role of Steric, Electrostatic and Hydrogen Bonding Effects as Face Selectivity Controlling Factors in Nitrone Cycloadditions. *Tetrahedron Lett.* **1987**, *28* (11), 1225−1228.
(69) Hufford, D. L.; Tarbell, D. S.; Koszalka, T. R. Maleic and Fumaric Dialdehydes, Δ4-Tetrahydrophthalaldehyde and Related Compounds1. *J. Am. Chem. Soc.* **1952**, *74* (12), 3014−3018.
(70) Alder, K.; Betzing, H.; Heimbach, K. Neue Verbindungen vom Tropinontyp *cis*- und *trans*-2.5-Dimethoxy-2.5-dihydro-furan. *Liebigs Ann. Chem.* **1960**, *638* (1), 187−198.
(71) Gorgues, A.; Simon, A.; Le Coq, A.; Hercouet, A.; Corre, F. Versatilite de Reactivite de L̀acetylene Dicarbaldehyde et des Aldehydes α-Acetyleniques a L'egard des Dienes Conjugues Cycliques et Heterocycliques en Milieu Acide. *Tetrahedron* **1986**, *42* (1), 351−370.
(72) Lin, H.-C.; Wu, C.-Y.; Wu, H.-J. Synthesis of 3,11-Dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecanes and 3,5,7-Trioxapentacyclo-[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecane. *J. Chin. Chem. Soc.* **1997**, *44* (6), 609−616.
(73) Olejniczak, T.; Boratyński, F.; Białońska, A. Fungistatic Activity of Bicyclo[4.3.0]-γ-lactones. *J. Agric. Food Chem.* **2011**, *59* (11), 6071−6081.
(74) Boratyński, F.; Pannek, J.; Walczak, P.; Janik-Polanowicz, A.; Huszcza, E.; Szczepańska, E.; Martinez-Rojas, E.; Olejniczak, T. Microbial Alcohol Dehydrogenase Screening for Enantiopure Lactone Synthesis: Down-stream Process from Microtiter Plate to Bench Bioreactor. *Process Biochem.* **2014**, *49* (10), 1637−1646.
(75) Ramón, D. J.; Guillena, G.; Seebach, D. Nonreductive Enantioselective Ring Opening of *N*-(Methylsulfonyl)dicarboximides with Diisopropoxytitanium α,α,α′,α′-Tetraaryl-1,3-dioxolane-4,5-dimethanolate. *Helv. Chim. Acta* **1996**, *79* (3), 875−894.
(76) Suzuki, K.; Inomata, K. A New Chiral Route to Optically Pure (+)- and (−)-*cis*-endo-4-Oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one. *Synthesis* **2002**, *2002* (13), 1819−1822.
(77) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. Enantioselective Reduction of *meso*-Cyclic-1, 2-dicarboxylic Anhydrides and 1, 2-Dicarboximides: Asymmetric Synthesis of Bicyclic Lactones and Hydroxylactams. *Chem. Pharm. Bull.* **1994**, *42* (1), 9−18.
(78) Morita, S.; Ren, Z.; Gorla, L.; Tong, Z.; Edouarzin, E.; Averkiev, B.; Day, V. W.; Hua, D. H. Indication of Pd-C or Cu-C Intermediates in Bimetallic Nanoclusters During Pd/Au-PVP- or Cu/Au-PVP-Catalyzed Oxidations of *endo*-4-Oxatricyclo[5.2.1.0^{2,6}]-8-decene and Tetrahydro-γ-carbolines. *Synthesis* **2023**, *55* (08), 1227−1240.
(79) Taniguchi, T.; Goto, Y.; Ogasawara, K. Preparation of a Promising Cyclobutanone Chiral Building Block: Its Stereochemistry and Utilization. *Synlett* **1997**, *1997* (6), 707−709.
(80) Liu, T.-L.; Li, W.; Geng, H.; Wang, C.-J.; Zhang, X. Catalytic Enantioselective Desymmetrization of *Meso* Cyclic Anhydrides via Iridium-Catalyzed Hydrogenation. *Org. Lett.* **2013**, *15* (7), 1740−1743.
(81) Park, Y.; Chang, S. Asymmetric Formation of γ-lactams via C-H Amidation Enabled by Chiral Hydrogen-Bond-Donor Catalysts. *Nat. Catal.* **2019**, *2* (3), 219−227.

https://doi.org/10.1021/acsomega.3c09381
ACS Omega 2024, 9, 17945−17955