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A Unified Stereodivergent Strategy for Prostaglandin and Isoprostanoid Synthesis

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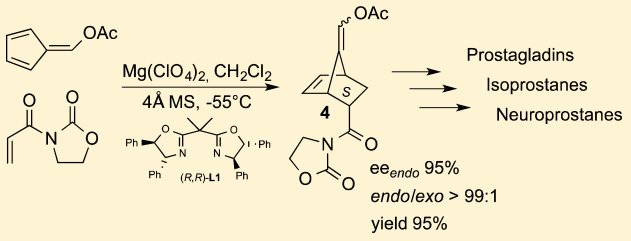
Supporting Information

ABSTRACT: Acetoxyfulvene surrended to asymmetric Diels–Alder cycloaddition, paving the way to the development of a unified strategy for the stereodivergent synthesis of both prostaglandins and isoprostanoids. In fact, the cycloadduct was subsequently converted to a common intermediate, which through two different stereoselective pathways afforded the two lactones **1** and **2**, which are key building blocks in the synthesis of prostaglandins and isoprostanoids, respectively.



1. INTRODUCTION

Prostaglandins (PGs) and isoprostanoids, such as isoprostaglandins (IsoPGs) and neuroprostanes (NeuroPs), are naturally occurring metabolites derived from oxidation of polyunsaturated fatty acids (PUFA).[1] Mother Nature efficiently produces both prostaglandins and series-2 isoprostaglandins from the same precursor, i.e., arachidonic acid (AA), via two different pathways: prostaglandins are formed through an enzymatic cyclooxygenase (COX) controlled reaction cascade, while a non-enzymatic free radical peroxidation of membrane-bound AA, triggered by reactive oxygen species (ROS), leads to the corresponding isoprostanes. As a consequence of these two different pathways, the different relative stereochemistry of the two side chains, i.e., *trans* vs *cis*, and the enantioselectivity of the enzymatic vs the non-enzymatic transformations stand as characteristic features of the two types of compounds (Figure 1).

Thus, enzymatic transformation of AA affords only one *enantiopure* stereomeric series of prostaglandins; instead, non-enzymatic AA oxidation affords all possible stereoisomeric isoprostanes in racemic form. A similar non-enzymatic radical mechanism leads to the formation of neuroprostanes by peroxidation of docosahexaenoic acids (DHA).[1]

The potent pharmacological and biological activities of prostaglandins and isoprostanes, respectively, have stimulated the development of new methods of synthesis for a long time.[1,2]

Modern synthetic approaches to prostaglandins are based upon the monumental work of E. J. Corey, which is centered on the Corey aldehyde-lactone **1** as a common building block. This compound was prepared in an enantioselective fashion via an atom-economical asymmetric Diels–Alder reaction.[2]

On the other hand, different avenues have been developed for the total syntheses of isoprostanoids;[1] however, none of them resembles the Corey general atom economy strategy, namely, the Diels–Alder approach.[3]

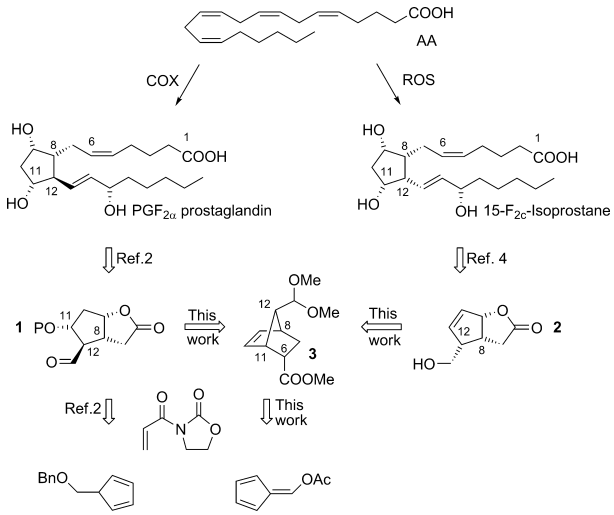


Figure 1. Comparison between Nature and modern synthetic chemistry for prostaglandin and isoprostanoid synthesis.

Moreover, the inversion of the configuration at C-12 of lactone **1** to provide the all-*cis* stereochemistry of isoprostanoids is not a trivial task, since it is a counter-thermodynamic transformation. In fact, the prostaglandin *trans* orientation of the two side chains is more stable than the *cis* stereochemistry typical of isoprostanoids.[1]

In this communication we describe a unified strategy for the synthesis of prostaglandins and isoprostanoids, which is based on the common key building block **3**. This is, indeed, a key issue for a practicable divergent synthetic approach to the two isomeric families, since we envisioned two efficient routes to convert **3** into either Corey lactone **1** or lactone **2**. The latter compound was shown by us to be a versatile starting material

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for the construction of several isoprostanes and neuroprostanes.[4]

The bicyclo[2.2.1]heptane backbone of compound **3** was ultimately assembled via an unprecedented asymmetric Diels–Alder reaction between 6-acetoxyfulvene and 3-acryloyloxazolidin-2-one, promoted by a catalytic amount of a chiral bisoxazoline-Mg complex (Figure 1). Moreover, the following conversion of **3** into lactones **1** and **2** was realized through a careful control of the configuration at C-12 of the bicyclic system to achieve either the prostaglandin or the isoprostanoid stereochemistry.

2. RESULTS AND DISCUSSION

The first example of 6-acetoxyfulvene [$4\pi + 2\pi$] cycloaddition, using 2-chloroacrylonitrile as a dienophile, was reported by ICI Ltd. chemists in their alternative route to the Corey aldehyde;[5] however, the beauty of this approach was plagued in the original work by a troublesome resolution of diastereomeric salts, in order to achieve enantiopure compounds.[6]

Despite some advantages of this strategy,[7] no asymmetric variant of this useful transformation nor examples of enantioselective fulvene cycloaddition have been reported to date.[2b,8] In this context, our first attempt to use copper(II) as a Lewis acid catalyst for the cycloaddition of 6-acetoxyfulvene to 2-chloroacrylonitrile[9] proved to be unsuccessful. Actually, we observed extensive decomposition of the diene, even at −30 °C, while no reaction was observed by reducing the reaction temperature to −78 °C.

We reasoned that the Lewis acid preferentially coordinated to the diene rather than to the dienophile, thus decreasing the $HOMO_{diene}$ energy and consequently reducing the overall Diels–Alder rate. A dienophile with greater aptitude for Lewis acid coordination was then identified in the bidentate 3-acryloyloxazolidin-2-one, which is known to form highly organized complexes with an ample class of Lewis acids.[10] In the event, a few representative Lewis acids of moderate strength were found to induce a significant acceleration of the reaction compared to the thermal uncatalyzed version. After some trials, $Mg(ClO)_4$ and $Cu(OTf)_2$ (Tf = CF_3SO_2) were selected for further enantioselective experiments (Table 1).

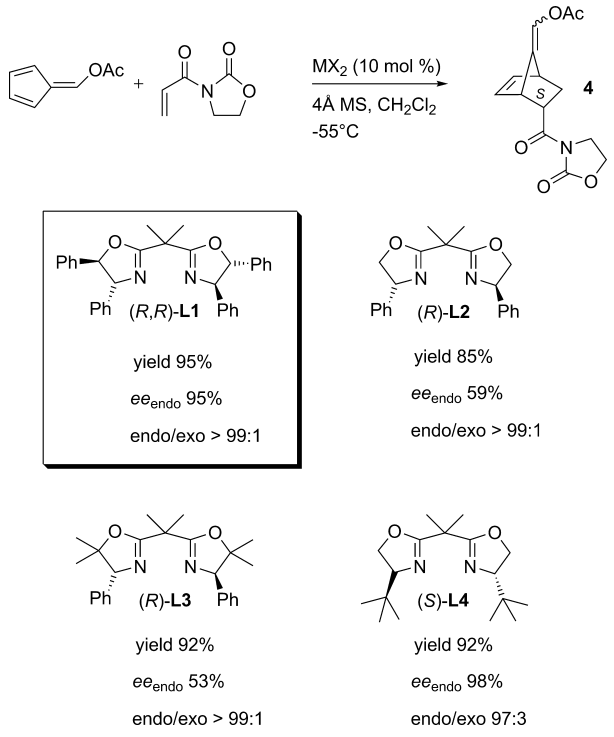
Table 1. Lewis Acid Promoted Diels–Alder Reaction between Acetoxyfulvene and 3-Acryloyl-1,3-oxazolidin-2-one To Afford Cycloadduct 4[a]

entry	catalyst	yield (%)	*endo*/*exo*
1	$Mg(ClO_4)_2$	89	80:20
2	$MgBr_2$	51	77:23
3	$Mg(OSO_2CF_3)_2$	35	81:19
4	$Zn(ClO_4)_2$	57	49:51
5	$Zn(OSO_2CF_3)_2$	34	81:19
6	$Cu((OSO_2CF_3)_2$	70	85:15[b]

[a]Reactions were carried out at rt with metal catalyst (30 mol %) and 4 Å molecular sieves in CH_2Cl_2. [b]Reaction was carried out at 4 °C.

Indeed, compared with other catalysts, both $Mg(ClO_4)_2$ and $Cu(OTf)_2$ afforded cycloadducts in better yields and higher *endo*/*exo* selectivity (determined by HPLC), respectively. Buoyed by the ligand-accelerated catalysis concept,[11] chiral C_2-symmetric bis(oxazoline) ligands were selected on the basis of their ability to promote the Diels–Alder reaction in a catalytic asymmetric fashion.[12] Indeed, the combination of $Mg(ClO_4)_2$ and ligand (*R*,*R*)-**L1** (Chart 1) afforded the *endo* adduct **4** in 90% isolated yield with 95% ee and *endo*/*exo* ratio >99:1. Enantiomeric excesses and *endo*/*exo* ratios were determined by chiral HPLC on a Chiralpak IA-3 column, after conversion of cycloadduct **4** into methyl ester acetal **3**, as detailed below. Under this condition, the *exo* isomer was not detected. The enantiomeric excess of the *endo* cycloadduct was then increased using the combination of $Cu(OTf)_2$ and ligand (*S*)-**L4** (Chart 1), which afforded the *endo* adduct **4** in 92% isolated yield and 98% ee, albeit with slightly lower diastereoselectivity (*endo*/*exo* 97:3).

Chart 1. Performance of a Group of C_2-Symmetric Bis(oxazoline) Ligands in the Enantioselective Diels–Alder Cycloaddition between Acetoxyfulvene and 3-Acryloyl-1,3-oxazolidin-2-one[a]

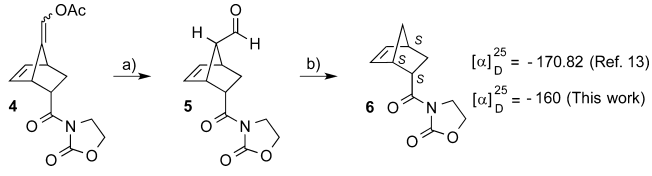


[a]MS = molecular sieves, MX_2 metal salt (see text).

The absolute stereochemistry of (1*S*,2*S*,4*S*)-cycloadduct **4** was established by comparing the optical rotation of the corresponding bicyclo[2.2.1]oxazolidinone derivative **6** (Scheme 1) with the literature.[13] Norbornane **6** was obtained from cycloadduct **4**, via Ir(I)-mediated decarbonylation of free aldehyde **5** (Scheme 1).[14]

In order to gain insight into the high *endo* preference for the complex $Mg(ClO_4)_2$-(*R*,*R*)-**L1**, DFT calculations were carried out using the B3LYP method with the 6-31G(d,p) basis set for

Scheme 1. Absolute Configuration Determination of Cycloadduct 4[a]



[a]Reagents and conditions: (a) MeOH, cat. PTSA, 60 °C, 3 h, 80%; (b) [IrCl(cod)$_2$], Ph_3P, dioxane, 110 °C, 24 h, 30%.

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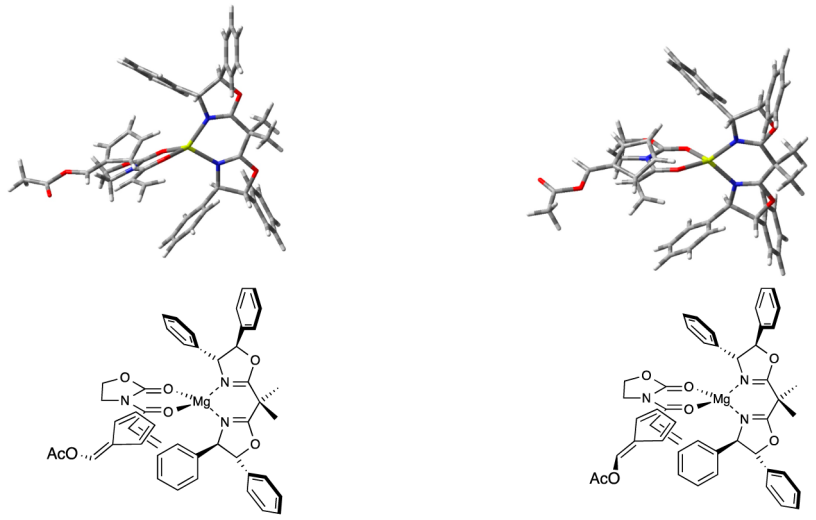


TS-A TS-B

Figure 2. Transition states for the $Mg(ClO_4)_2$-(*R*,*R*)-**L1** catalyzed Diels–Alder cycloaddition between acetoxyfulvene and 3-acryloyloxazolidin-2-one. The two low-energy orientations of the diene inside the catalyst chiral cavity are shown.

H, O, N, C and the 6-31+G(d,p) basis set for the Mg cation (for computational details see the Supporting Information). Calculations for the reaction leading to the *exo* adduct were unable to locate the corresponding transition state (TS), which might be due to steric hindrance between the acetoxy group of fulvene and one of the phenyl group on the (*R*,*R*)-**L1** ligand. On the other hand, two *endo* TSs could be located on the potential energy surface, which corresponded to two different orientations of the diene inside the catalyst chiral cavity, both positioning the acetoxy group far from the phenyl ring (Figure 2).

The energy difference between TS-A and TS-B was only 1 kcal/mol; however, both TS geometries clearly showed that acetoxyfulvene attacked the more accessible C(α) *re* diastereoface of the dienophile.

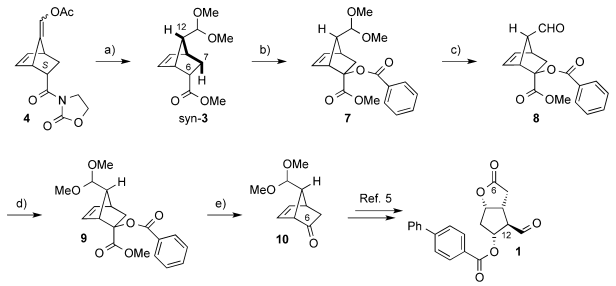
Although the complex Cu(II)-(*S*)-**L4** provided an almost complete enantiocontrol for the *endo* adduct **4**, we preferred to use the complex $Mg(ClO_4)_2$-(*R*,*R*)-**L1** to continue our synthetic route; although it afforded the *endo* adduct with slightly lower ee, it provided higher diastereocontrol (cf. **L4** and **L1** in Chart 1).

As a matter of fact, both the *endo* and *exo* stereoadducts, which belonged to the opposite enantiomeric series, subsequently converged to the same intermediates **10** (Scheme 2) and **14** (Scheme 3). As a consequence, the reaction catalyzed by $Mg(ClO_4)_2$-(*R*,*R*)-**L1**, in which no *exo* stereoisomer was formed, afforded a higher overall ee for **10** and **14** than the reaction catalyzed by Cu(II)-(*S*)-**L4**, which provided the *endo*/*exo* cycloadducts in a 97:3 ratio.

Interestingly, both enantiomeric catalysts Cu(II)-(*S*)-L4 and $Mg(ClO_4)_2$-(*R*,*R*)-**L1** showed the same sense of asymmetric induction, as reported in the literature,[12b] providing the same enantiomeric cycloadduct (*S*)-**4**.

With a robust enantioselective Diels–Alder protocol in hand, the stereodivergent synthesis of the two key building blocks **1** and **2** for prostaglandin and isoprostanoid synthesis, respectively, proceeded straightforwardly, at first by conversion of cycloadduct (*S*)-**4** into the common methyl ester intermediate **3**, followed by the stereodivergent manipulation

Scheme 2. Preparation of Key Intermediates for Prostaglandin Synthesis[a]



[a]Reagents and conditions: (a) (i) MeOH, cat. PTSA, 60 °C, 3 h, 80%; (ii) MeOMgBr, MeOH/THF (2:1), 0 °C, 2 h, 70%; (b) (i) NaHMDS, THF, −78 to 0 °C, 1 h, then O_2, −78 °C, 1 h, then DMS, −78 to −20 °C, 16 h; (ii) PhCOCl, pyridine, 4-DMAP, CH_2Cl_2, rt, 24 h, 75%; (c) 2.17 M $NaHSO_4$ in CH_3CN/H_2O (9:1), rt, 84%; (d) (i) 6 M HCl, dioxane, 75 °C, 72 h, 72%; (ii) MeOH, PTSA, 60 °C, 3 h, 90%; (e) (i) 1 M $LiAlH_4$ in THF, 0 °C to rt, 16 h; (ii) $NaIO_4$, THF/H_2O/pH 7 buffer (2:1:1), rt, 4 h, 57%.

of **3** to bicyclic ketones **10** and **14**, respectively. Two major tasks, however, had to be accomplished to fulfill our synthetic plan: (1) the adjustment of the oxidation state at C-6 of adduct **3** for the subsequent transformations and (2) the careful inversion of the stereochemistry at the C-12 stereocenter of **3** or the conservation of its stereochemical integrity to achieve the prostaglandin or the isoprostanoid stereochemistry, respectively (see compounds **1** and **2**, respectively, in Figure 1).[15]

2.1. Prostaglandin Approach. The strategy for the prostaglandin approach was based upon the preparation of the bicyclic ketone **10**, which has been used for the preparation of building block **1** and then prostaglandins (Scheme 2).[5] (*S*)-Cycloadduct **4** was transformed into the corresponding masked aldehyde-methyl ester **3** simply upon exposure to a catalytic amount of *p*-toluenesulfonic acid (PTSA) in methanol at 60 °C for 3 h (80% yield), followed by treatment with Evans' MeOMgBr reagent (prepared *in situ* from MeMgBr and MeOH)[12a] in THF at 0 °C for 1 h (70% yield). Noteworthy, only the *syn* diastereoisomer **3** was obtained, as confirmed by

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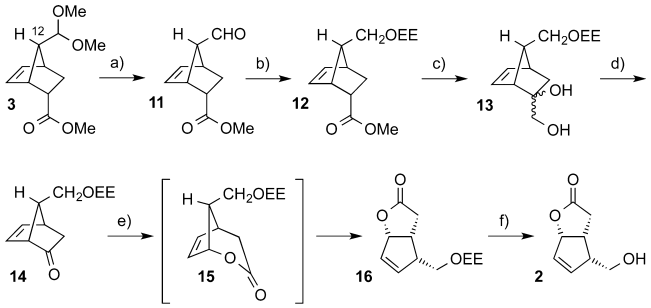
Scheme 3. Preparation of the Key Intermediate 2 for Isoprostanoid Synthesis[a]



[a]Reagents and conditions: (a) 2.17 M $NaHSO_4$ in CH_3CN/H_2O (9:1), rt, 99%; (b) (i) $NaBH(AcO)_3$, THF, rt; (ii) ethyl vinyl ether, CH_2Cl_2, PPTS, rt, 78%; (c) (i) NaHMDS, THF, −78 to 0 °C, 1 h, then O_2, −78 °C, 1 h, then DMS, −78 to −20 °C, 16 h; (ii) 1 M $LiAlH_4$ in THF, THF, 0 °C to rt, 4 h, 61%; (d) $NaIO_4$, THF/H_2O/pH 7 buffer (2:1:1), rt, 4 h, 80%; (e) 10 M H_2O_2 in H_2O, $NaHCO_3$, MeOH/MTBE (1:1), 0 °C, then SiO_2, CH_2Cl_2/hexane (3:1), 40 °C, 57%; (f) MeOH, PPTS, 16 h, rt, 80%.

$^1H-^1H$ COSY and ^{11}H NMR experiments showing a diagnostic J_w of 1.5 Hz[5] between 12-H and 7-H_{endo}.[15]

After a few experiments, the key oxidation level of C-6 (cf. compound **10**) was adjusted via a one-pot oxidation of the C(α)-carbon of methyl ester **3**, using a modified Corey protocol.[16] In the event, a current of O_2 was bubbled through a solution of the enolate formed upon treatment of **3** with NaHMDS (sodium hexamethyldisilazide) at −78 °C, followed by dimethyl sulfide (DMS) quenching of the corresponding hydroperoxide. Subsequently, the crude product was treated with benzoyl chloride in the presence of pyridine and 4-dimethylaminopyridine at rt, to afford the expected α-benzoyloxy methyl ester **7** in a gratifying 76% overall yield as a 6:1 mixture of *endo*:*exo* C-6 epimers. Aldehyde functionality was restored at C-12 of compound **8** in 84% yield, with complete conservation of the stereochemical integrity, by exposing **7** to 2.17 M $NaHSO_4$ in CH_3CN/H_2O (9:1) at rt.

The crucial epimerization of the C-12 stereocenter was then smoothly accomplished by treating aldehyde **8** with 6 M HCl in dioxane at 75 °C for 72 h.

The successful stereochemical inversion was witnessed by the absence of the diagnostic J_w coupling between 12-H and 7-H_{endo}[5] in the *anti* diastereoisomer **9**, which was obtained from **8** in 90% isolated yield upon exposure to a catalytic amount of PTSA in MeOH. Computational studies showed that *anti* diastereoisomer **9** was more stable then the corresponding *syn* isomer by 2.7 kcal/mol.

Finally, ketone **10** was obtained in a single sequence by reducing ester **9** with $LiAlH_4$ in THF at rt for 4 h, followed by sodium metaperiodate cleavage of the resulting diol in aqueous THF (buffered to pH 7) at rt for 4 h. Optically active ketone **10**, a key intermediate in the ICI prostaglandin synthesis,[6] was thus achieved in 57% overall yield from **9** with an enantiomeric excess of 97.6% (chiral HPLC).

Comparison between the optical rotation of our sample of **10** $[\alpha]^{20}_D$ = 550 (*c* 0.15, CH_2Cl_2) with the literature value for enantiopure **10**, $[\alpha]^{20}_D$ = 545 (*c* 0.16, $CHCl_3$)[5] clearly confirmed the correct assignment of the absolute configuration.

2.2. Isoprostanoid Approach. The approach to the synthesis of isoprostanoids exploited the advantage offered by the stereoselective formation of the *syn* masked aldehyde **3** in which the C-12 stereocenter had the correct configuration required for isoprostanoid synthesis. The key building block **2**[3] was then prepared using the synthetic sequence depicted in Scheme 3, which was mainly focused on the modification of the C-6 oxidation level.

In the event, $NaHSO_4$-mediated hydrolysis of acetal **3** afforded *syn* aldehyde **11** in quantitative yield, which was reduced by $NaBH(OAc)_3$ in THF at rt, followed by *in situ* protection of the resulting alcohol as ethoxyethyl ether upon exposure to ethyl vinyl ether (EVE) in CH_2Cl_2 in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The expected ethoxyethyl ether **12** was thus obtained in 78% isolated yield over two steps.

The proper oxidation state at C-6 was then adjusted using the protocol previously optimized for compound **3**. Hydroxylation of the α-carbon of methyl ester **12** followed by reduction with $LiAlH_4$ provided diol **13** in 61% overall yield, which was subsequently exposed to $NaIO_4$ (buffered to pH 7) to give the corresponding ketone **14** in 80% isolated yield.

Baeyer−Villiger oxidation of ketone **14** by slightly basic hydrogen peroxide ($NaHCO_3$, H_2O_2)[17] gave the expected [3.2.1]-bicyclic lactone **15**, accompanied by chromatographically inseparable desired lactone **16** in 9:1 ratio (^1H NMR). SiO_2-mediated rearrangement of labile lactone **15** in CH_2Cl_2/hexane (3:1) at 40 °C for 18 h afforded pure lactone **16** in 68% isolated yield.[18]

The key building block (+)-(3a*R*,4*R*,6a*S*)-γ-lactone **2**, required for isoprostanoid synthesis, was eventually produced, in 80% yield and 97% ee, by simple deprotection of ethoxyethyl ether **16** using a catalytic amount of PPTS in MeOH. Compound **2** was identical in all respects with an authentic sample prepared via a different route.[3]

3. CONCLUSION

In summary, an unified stereodivergent synthetic strategy for the efficient preparation of both prostaglandins and isoprostanoids has been developed. The common key intermediate **4** was prepared in excellent enantiomeric excess through an unprecedented asymmetric Diels−Alder reaction between acetoxyfulvene and 3-acryloyloxazolidin-2-one promoted by a chiral C_2-symmetric bis(oxazoline) complex of $Mg(ClO_4)_2$.

Two other stereoselective reactions, namely, the hydrolysis of the enol-acetate cycloadduct **4** and the epimerization of the stereocenter in the α-position to aldehyde **8**, secured a fast route to prostaglandin and isoprostanoids via the key lactones **1** and **2**, respectively. Further studies on the extension of this methodology and its synthetic utility are in progress and will be reported in due course.

4. EXPERIMENTAL SECTION

General Procedures. All solvents were of commercial quality and were purified by distillation over the drying agents indicated: THF (Na/benzophenone), CH_2Cl_2 and hexane (CaH_2), toluene (Na/K). All other reagents were used as supplied. All moisture-sensitive reactions were carried out under a positive static atmosphere of Ar in flame-dried glassware. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Routine monitoring of reactions was performed using silica gel 60 (0.25 mm) aluminum-supported TLC plates. Compounds were visualized by UV irradiation at a wavelength of 254 nm or stained by exposure to a 0.5% solution of vanillin in H_2SO_4/EtOH, followed by charring. Flash column chromatography (FCC) was performed on silica gel (40−63 μm). Yields are reported for isolated compounds with >96% purity established by NMR unless otherwise indicated. ^1H

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and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) are in hertz. The solvent signals were used as references, and the chemical shifts were converted to the TMS scale ($CDCl_3$: δC 77.00; residual $CHCl_3$ in $CDCl_3$: δH 7.26; CD_2Cl_2: δC 53.8; residual CH_2Cl_2 in CD_2Cl_2: δH 5.32 ppm). COSY, DEPT, and NOESY spectra were recorded using a standard pulse program library. The number of H-atoms attached to each C-atom (s = 0H, d = 1H, t = 2H, q = 3H) was determined by DEPT experiments. Optical rotations were recorded on a digital polarimeter at 589 nm, with concentration (c) in g/100 mL. Mass spectrometry was performed by Q-TOF using electrospray ionization (ESI) mode [M + H^+].

Diels–Alder: General Procedure without Chiral Ligands. Molecular sieves type 4 Å (700 mg) and 3-acryloil-1,3-oxazolidin-2-one (200 mg, 1.417 mmol) were mixed with dry dichloromethane under an argon atmosphere (6 mL). The salt (0.425 mmol, 30% mol) was then added to this suspension, and the resulting slurry was stirred at room temperature for 40 min. Acetoxyfulvene solution (392 mg, 2.834 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to the slurry. The reaction was stirred at rt for 48 h and then quenched with saturated aqueous NH_4Cl (15 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (6:4) gave the desired diastereomeric mixture *rac*-**4** (see the Table 1 for yields and *endo*/*exo* ratios) as a pale yellow oil.

Asymmetric Diels–Alder Reaction with Chiral Ligand Complex. *Synthesis of (E)-((1S,4S,5S)-5-(2-Oxooxazolidine-3-carbonyl)bicyclo[2.2.1]hept-2-en-7-ylidene)methyl Acetate (**4**).* In a dry Schlenk flask under an argon atmosphere were added, in this order, molecular sieves type 4 Å (700 mg), 3-acryloil-1,3-oxazolidin-2-one (200 mg, 1.417 mmol), chiral ligand (0.142 mmol, 10% mol), and dry CH_2Cl_2 (6 mL). To this slurry was then added the salt (0.142 mmol, 10% mol), and the resulting suspension was stirred at room temperature for 40 min. The slurry was then cooled at −55 °C, and acetoxyfulvene solution (392 mg, 2.834 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. The reaction was stirred at −55 °C for 72 h and then quenched with saturated aqueous NH_4Cl (15 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (6:4) gave the desired norbornene cycloadducts **4** (see Chart 1 for yields, ee, and *endo*/*exo* ratios) as a pale yellow oil. The *endo*/*exo* ratio and the ee were determinated by HPLC after the conversion of **4** into the compound *syn*-**3**. TLC (SiO_2): R_f = 0.23 (hexane/EtOAc 7:3). FTIR (neat): 2989, 2360, 1778, 1696, 1478, 1388, 1312, 1225, 1077, 1043, 998, 923, 894, 859, 826, 762, 736, 709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.64 (s, 1H), 6.32–6.41 (m, 1H), 6.03–6.41 (m, 1H), 4.42 (dt, J = 2.2, 7.7 Hz, 2H) 3.92–4.02 (m, 3H), 3.60 (d, J = 3.28 Hz, 2H), 2.08 (bs overlyed with m, 4H), 1.65 (dd, J = 4.6, 11.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 173.3 (s)*, 173.2 (s), 168.2 (s), 153.2 (s), 139.3 (s), 137.9 (d)*, 136.7 (d), 132.5 (d), 131.4 (d)*, 116.3 (d), 116.0 (d)*, 62.0 (t), 46.1 (d), 44.0 (d)*, 43.2 (d), 42.8 (t), 42.2 (d)*, 41.0 (d), 30.7 (t)*, 29.7 (t), 20.6 (q) [an asterisk indicates doubled signals due to the presence of diastereoisomers]. HRMS: calcd for $C_{14}H_{15}NO_5$ 277.095; found 277.093

Determination of Absolute Configuration. *Synthesis of Norbornene Acetal 3-((1S,2S,4S)-bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxazolidin-2-one (**6**).* Compound **4** (903 mg, 3.235 mmol) was dissolved in dry MeOH (32 mL) at room temperature. PTSA (62 mg, 0.324 mmol) was then added, and the solution was heated to 60 °C for 4 h. The reaction mixture was cooled to room temperature, solid $NaHCO_3$ was added (27 mg, 0.325 mmol), and MeOH was then removed under reduced pressure. The residue was dissolved with saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (15 mL) under vigorous stirring. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash cromatography on silica gel. Elution with CH_2Cl_2/EtOAc 95:5 gave desired product (728 mg, yield = 80%). TLC (SiO_2): R_f = 0.27 (CH_2Cl_2/EtOAc 95:5). IR (liquid film): 2950, 1760, 1490, 1350, 1100, 1030, 750, and 680 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ (ppm) 6.25 (dd, J = 3.07, 5.6 Hz, 1H), 5.95 (dd, J = 2.91, 5.64 Hz, 1H), 4.41 (m, 2H), 4.15 (m, 1H), 4.11–3.85 (m, 2H), 3.39 (s, 3H), 3.30 (s, 3H), 3.20 (m, 1H), 3.15 (bs, 1H), 2.70 (bs, 1H), 1.95 (m, 1H), 1.80 (dd, J = 1.38, 8.76 Hz, 1H), 1.60–1.50 (ddd, J = 1.09 (J_w), 4.11, 5.44 Hz, 1H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 174.5 (s), 154.8 (s), 139.3 (d), 134.8 (d), 104.5 (d), 63.6 (d), 63.4 (t), 54.8 (q), 53.7 (q), 47.6 (d) 44.5 (d), 44.2 (t), 42.4 (d), 27.6 (t). ESI (m/z) = 304.20 [(M + Na)$^+$, 100], 585.06 [(2M + Na)$^+$, 20]. HRMS: calcd for $C_{14}H_{19}NO_5$ 281.1263; found 281.1261

Decarbonylation Reaction. The acetal of norbornene (220 mg, 0.782 mmol) was dissolved in 9:1 CH_3CN/H_2O (15 mL), aqueous $NaHSO_4$ (2.17M, 540 μL, 1.173 mmol) was added, and the reaction was stirred at room temperature until complete deprotection of acetal. The reaction was quenched with phosphate buffered solution (pH = 6.8, 15 mL), and the CH_3CN was removed under vacuum. The residue was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered using a little amount of silica gel with CH_2Cl_2/EtOAc 95:5 as eluent to afford aldehyde **5**.

Dioxane solution (1.5 mL) of $[IrCl(cod)]_2$ (13 mg, 0.020 mmol) and PPh_3 (10 mg, 0.040 mmol) was stirred at room temperature for 30 min. Dioxane solution (0.5 mL) of **5** was added, and the reaction was stirred at 110 °C until TLC (hexane/CH_2Cl_2/Et_2O 6:2:2 as eluent) showed a significative amount of desired product **6**. The reaction mixture was cooled to room temperature and diluted with water (7 mL) and hexane/Et_2O 7:3 (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash cromatography on silica gel. Elution with hexane/CH_2Cl_2/Et_2O 6:2:2 gave desired product **6** (48 mg, yield = 30% over two steps) as a pale yellow oil. $[\alpha]^{20}_D$ = −160 (c 0.13, $CHCl_3$). ESI (m/z) = 230.08 [(M + Na)$^+$, 100]. The spectroscopic data were in agreement with the literature.[5]

*Methyl (1R,2S,4S,7S)-7-(Dimethoxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (syn-**3**).* To a solution of the imide-acetal of **4** (283 mg, 1 mmol) in a mixture of MeOH (5 mL) and THF (2.5 mL) at 0 °C was added via cannula a suspension of MeOMgBr prepared by addition of methylmagnesium bromide (370 μL, 3.2 M in diethyl ether, 0.118 mmol) to anhydrous methanol (50 mL). After the reaction mixture was stirred for 1 h at 0 °C, it was quenched by the addition of satured NH_4Cl (5 mL). Volatiles were removed *in vacuo*. The residue was dissolved with water and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel, CH_2Cl_2/EtOAc 95:5 as eluent, afforded the desired methyl ester *syn*-**3** (210 mg, 92%) as a colorless oil. TLC (SiO_2): R_f = 0.27 (CH_2Cl_2/EtOAc 95:5). $[\alpha]^{20}_D$ = −66.4 (c 2.76, CH_2Cl_2). FTIR (neat): 3436, 1735, 1652, 1436, 1140, 1061 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ (ppm) δ 6.30–6.18 (dd, J = 3.2, 5.6 Hz 1H), 5.90 (dd, J = 3.3, 5.5 Hz, 1H), 4.20 (d, J = 8.85 Hz 1H), 3.62 (s, 3H), 3.30 (2s, 6H), 3.05 (m, 2H), 2.70 (bs, 1H) 2.05–1.85 (m, 1H), 1.70 (d, J = 8.77 1H), 1.57–1.42 (dd, J = 2.3, 12.28 Hz 1H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 175.2 (s), 139.9 (d), 135.0 (d), 103.8 (d), 62.6 (d), 53.6 (q), 53.4 (q), 52.0 (q), 47.1 (d), 44.1 (d), 42.1 (d), 27.5 (t). ESI (m/z) = 249.12 [(M + Na)$^+$, 100]. HRMS: calcd for $C_{12}H_{18}O_4$ 226.1205; found 226.1207

*Methyl (1R,2R,4S,7S)-2-(Benzoyloxy)-7-formylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**8**). Oxidation of C-6.* To a stirred solution of NaHMDS (1730 μL, 1.730 mmol) in dry THF (6 mL) under an argon atmosphere was added dry hexane (1 mL). The resulting clear solution was cooled at −78 °C, and a THF solution (4 mL) of *syn*-**3** (230 mg,

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1.018 mmol) was added dropwise via cannula. The reaction mixture was warmed to 0 °C and stirred at this temperature for 1 h, and after recooling to −78 °C dry O_2 was bubbled inside the enolate solution for 1 h. The hydroperoxide was reduced using an excess of Me_2S (750 μL, 10.18 mmol) at −40 °C for 1 h, the reaction was then quenched with phosphate buffered solution at pH = 6.8 (10 mL), and the resulting mixture was stirred at −20 °C for 16 h. The reaction mixture was warmed to room temperature and diluted with ether (15 mL) and water (5 mL), the organic phase was collected, and the aqueous phase was extracted with Et_2O (3 × 8 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was solved in dry CH_2Cl_2 (10 mL) under Ar, and at 0 °C were added Py (165 μL, 2.036 mmol), BzCl (155 μL, 1.323 mmol), and DMAP. The reaction was allowed to reach the room temperature and was stirred for 24 h. It was quenched with saturated aqueous $NaHCO_3$ (10 mL) and was diluted with CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers reunited were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column cromatography on silica gel using CH_2Cl_2/EtOAc 95:5 as eluent to afford the product **7** (260 mg, yield = 75% over two steps).

The residue was purified by column cromatography on silica gel using CH_2Cl_2/EtOAc 95:5 as eluent to afford the oxidized product (260 mg, yield = 75% over two steps). TLC (SiO_2): R_f = 0.25 (CH_2Cl_2/EtOAc 95:5). FTIR (neat): 2952, 2829, 2754, 1721, 1602, 1452, 1287, 1161, 1111, 1072, 1010, 961, 876, 849, 801, 770 cm^{-1}. ^1H NMR (300 MHz, CD_2Cl_2): δ (ppm) 8.16−8.12 (m, 2H), 7.68−7.61 (m, 1H), 7.56−7.45 (m, 2H), 6.49 (dd, *J* = 5.8, 3.2 Hz, 1H), 6.02 (dd, *J* = 5.6, 3.4 Hz, 1H), 4.68−4.63 (m, 1H), 3.67 (bs, 3H), 3.34−3.28 (m, 7H), 2.97 (bs, 1H), 2.63 (dd, *J* = 13.6, 1.5 Hz, 1H), 2.32 (dd, *J* = 9.3, 1.3 Hz, 1H), 2.04 (dd, *J* = 13.7, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm)171.4 (s), 166.5 (s), 142.9 (d), 134.2 (d), 132.7 (d), 130.5 (2 × d), 130.4 (s), 129.2 (2 × d), 102.4 (d), 87.6 (s), 64.5 (d), 53.3 (d), 52.9 (q), 52.7 (q), 52.5 (q), 44.0 (d), 36.6 (t). HRMS: calcd for $C_{19}H_{22}O_6$ 346.1416; found 346.1414

Acetal Deprotection. Oxidized acetal (157 mg, 0.453 mmol) was dissolved in 9:1 CH_3CN/H_2O (9 mL), aqueous $NaHSO_4$ 2.17 M (500 μL, 0.5 mmol) was added and the reaction was stirred at room temperature until complete deprotection of acetal. The reaction was quenched with phosphate buffered solution (pH = 6.8, 15 mL), and the CH_3CN was removed under vacuum. The residue was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered using a little amount of silica gel with *n*-hexane/EtOAc 8:2 as eluent to afford the product **8** (114 mg, yield = 84%). TLC (SiO_2): R_f = 0.24 (hexane/EtOAc 8:2). FTIR (neat): 2954, 1722, 1602, 1584, 1452, 1317, 1283, 1236, 1151, 1108, 1069, 1030, 1001, 962, 890, 846, 802, 715, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.77 (s, 1H), 7.96−7.93 (m, 2H), 7.60−7.58 (m, 1H), 7.49−7.44 (m, 2H), 6.50 (dd, *J* = 5.8, 3.1 Hz, 1H), 6.07 (dd, *J* = 5.6, 3.4 Hz, 1H), 3.75 (dd, *J* = 1.4, 1.2 Hz, 1H), 3.72−3.71 (s, 3H), 3.38 (bs, 1H), 2.78 (bs, 1H), 2.53 (dd, *J* = 13.7, 2.1 Hz, 1H), 2.15 (dd, *J* = 13.7, 3.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 199.0 (d), 170.3 (s), 165.6 (s), 141.4 (d), 133.6 (d), 130.8 (d), 129.8 (2 × d), 128.9 (s), 128.6 (2 × d), 86.3 (s), 71.4 (d), 52.5 (d), 52.4 (q). 41.7 (d), 36.8 (t). ESI (*m*/*z*) = 323.14 [$(M + Na)^+$, 12], 355.19 [$(M + Na + MeOH)^+$, 33], 687.14 [$(2M + Na + 2MeOH)^+$, 100]. HRMS: calcd for $C_{17}H_{16}O_5$ 300.0998; found 300.0996

*Methyl (1R,2R,4S,7R)-2-(Benzoyloxy)-7-(dimethoxymethyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**9**). Aldehyde **8** Epimerization.* HCl (6 M, 130 μL, 0.79 mmol) was added to a solution of aldehyde **8** (95 mg, 0.316 mmol) in dioxane (2 mL) under an argon atmosphere and then was heated at 75 °C for 96 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and a phosphate buffer (10 mL, pH) 6.95) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O (10 mL) and brine (15 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with CH_2Cl_2/EtOAc/hexane 47:3:50 as eluent gave the desired aldehyde epimer (69 mg, yield = 72%). TLC (SiO_2): R_f = 0.24 (CH_2Cl_2/EtOAc/hexane 47:3:50). FTIR (neat): 2954, 1722, 1602, 1584, 1452, 1317, 1283, 1236, 1151, 1108, 1069, 1030, 1001, 962, 890, 846, 802, 715, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.73 (d, *J* = 1.9 Hz, 1H), 8.09−8.05 (m, 2H), 7.65−7.60 (m, 1H), 7.53−7.46 (m, 2H), 6.47 (dd, *J* = 5.7, 3.0 Hz, 1H), 5.99 (dd, *J* = 5.6, 3.0 Hz, 1H), 3.73−3.66 (s, 3H), 3.60 (bs, 1H), 3.38 (bs, 1H), 3.12 (d, *J* = 1.5 Hz, 1H), 2.59 (d, *J* = 13.5 Hz, 1H), 2.02 (dd, *J* = 13.5, 3.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 203.0 (d), 170.2 (s), 166.0 (s), 139.7 (d), 133.6 (d), 129.8 (2 × d), 129.2 (s), 128.6 (d), 128.5 (d), 85.6 (s), 70.6 (d), 52.7 (q), 52.6 (d), 43.7 (d), 39.3 (t). HRMS: calcd for $C_{17}H_{16}O_5$ 300.0998; found 300.1000

Acetal Protection. Epimeric aldehyde (48 mg, 0.160 mmol) was dissolved in dry MeOH (1.6 mL) at room temperature. PTSA (6 mg, 0.032 mmol) was then added, and the solution was heated to 60 °C for 3 h. The reaction mixture was cooled to room temperature, solid $NaHCO_3$ was added (15 mg, 0.176 mmol), and MeOH was then removed under reduced pressure. The residue was dissolved with saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (15 mL) under vigorous stirring. The layer were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash cromatography on silica gel. Elution with CH_2Cl_2/EtOAc 95:5 gave desired product **9** (50 mg, yield = 90%). TLC (SiO_2): R_f = 0.25 (CH_2Cl_2/EtOAc 95:5). FTIR (neat): 2829, 2754, 1721, 1602, 1452, 1287, 1161, 1111, 1072, 1010, 961, 876, 849, 801, 770 cm^{-1}. ^1H NMR (300 MHz, CD_2Cl_2): δ (ppm) 8.08−8.05 (m, 2H), 7.67−7.62 (m, 1H), 7.54−7.48 (m, 2H), 6.38 (dd, *J* = 5.7, 3.0 Hz, 1H), 5.86 (dd, *J* = 5.4, 2.9 Hz, 1H), 4.36 (d, *J* = 8.2 Hz, 1H), 3.65 (d, *J* = 1.2 Hz, 3H), 3.35−3.31 (m, 6H), 3.29−3.25 (m, 1H), 2.95 (dd, *J* = 1.4, 0.7 Hz, 1H), 2.75 (d, *J* = 8.2 Hz, 1H), 2.46 (d, *J* = 13.3 Hz, 1H), 1.92 (dd, *J* = 13.3, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm) 171.4 (s), 166.8 (s), 140.1 (d), 134.1 (d), 130.5 (s), 130.4 (d), 129.3 (d), 128.4 (d), 103.5 (d), 86.9 (s), 63.4 (d), 54.4 (q), 54.0 (q) 53.0 (2q), 44.3 (d), 40.1 (t). HRMS: calcd for $C_{19}H_{22}O_6$ 346.1416; found 346.1419

*(1R,4S,7R)-7-(Dimethoxymethyl)bicyclo[2.2.1]hept-5-en-2-one (**10**).* $LiAlH_4$ (1 M in THF, 770 μL, 0.773 mmol) was added under an argon atmosphere to a solution of norbornene **9** (69 mg, 0.184 mmol) in dry THF (2 mL) and cooled to 0 °C. The cooling bath was removed, and the reaction mixture was stirred at rt overnight. Rochelle's salt (8 mL, satd aq) was added, and the resulting two layers were vigorously stirred at rt for 4 h. After addition of DCM (8 mL) the organic layer was then collected, the water phase was extracted with DCM (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was filtered through a pad of silica gel, washed with hexane/EtOAc 2:8 (100 mL), and concentrated under reduced pressure to yield the desired diol, which was directly used in the next step. $NaIO_4$ (78 mg, 0.368 mmol) was added to a stirred solution of the diol in THF/H_2O/phosphate buffered solution (pH = 6.8) 2:1:1 (2 mL) at rt, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), after 10 min the mixture was diluted with CH_2Cl_2 (10 mL), and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL), and the combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure (>90 mmHg). The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc 9:1 gave compound **10** (19 mg, yield = 57% over two steps, ee 97%) as a colorless oil. HPLC: (Chiralcel IA-3 column, hexane/*i*-PrOH = 90:10, 1 mL/min, 204 nm/208 nm). TLC (SiO_2): R_f = 0.25 (hexane/EtOAc 9:1). $[\alpha]^{20}_D$ = −424.0 (*c* 0.2, CH_2Cl_2). ^1H NMR (300 MHz, CD_3COCD_3): δ (ppm) 6.50 (dd, *J* = 5.5, 2.8 Hz, 1H), 6.06−6.02 (m, 1H), 4.40 (d, *J* = 8.1 Hz, 1H), 3.31−3.29 (bs, 3H), 3.29−3.24 (bs, 3H), 3.14−3.10 (bs, 1H), 2.85−2.78 (m, 1H), 2.62 (d, *J* = 8.1 Hz, 1H), 2.10−2.01 (m, 1H), 1.86−1.80 (m, 1H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 212.1 (s), 141.7 (d), 128.4 (d), 103.2 (d), 65.3

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(d) 58.8 (d), 53.7 (q), 53.6 (q), 43.0 (d), 39.2 (t). ESI (m/z) = 205.03 [$(M + Na)^+$, 100]. HRMS: calcd for $C_{10}H_{14}O_3$ 182.0943; found 182.0945

*Methyl (1R,2S,4S,7S)-7-Formylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**11**).* Acetal *syn*-**3** (177 mg, 0.783 mmol) was dissolved in 9:1 CH_3CN/H_2O (15 mL), aqueous $NaHSO_4$ (2.17 M, 540 μL, 1.175 mmol) was added, and the reaction was stirred at room temperature until complete deprotection of acetal. The reaction was quenched with phosphate buffered solution (pH = 6.8, 15 mL), and the CH_3CN was removed under vacuum. The residue was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered using a small amount of silica gel with *n*-hexane/EtOAc 9:1 as eluent to afford the product **11** (140 mg, yield = 99%). TLC (SiO_2): R_f = 0.25 (hexane/EtOAc 9:1). $[\alpha]^{20}_D$ = −81.7 (*c* 2.8, CH_2Cl_2). FTIR (neat): 3474, 2954, 1732, 1436, 1325, 1203, 1030, 906, 719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.58 (s, 1H), 6.27 (dd, *J* = 5.5, 3.0 Hz, 1H), 6.05 (dd, *J* = 5.6, 2.9 Hz, 1H), 3.66 (s, 3H), 3.48 (bs, 1H), 3.20 (bs, 1H), 3.02 (dt, *J* = 7.95, 4.0 Hz, 1H), 2.50 (d, J_w = 1.5 Hz, 1H), 1.93 (ddd, *J* = 12.6, 9.3, 3.7 Hz, 1H), 1.58 (dddd, *J* = 12.5, 5.8, 3.8, 1.7 (J_w), 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 200.8 (d), 174.2 (s), 137.7 (d), 133.3 (d), 69.5 (d), 51.7 (q), 44.9 (d), 42.3 (d), 41.1 (d), 26.9 (t). HRMS: calcd for $C_{10}H_{12}O_3$ 180.0786; found 180.0788

*Methyl (1R,2S,4S,7S)-7-((1-Ethoxyethoxy)methyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (**12**).* $Na(AcO)_3BH$ (330 mg, 1.556 mmol) was added under an argon atmosphere to a solution of compound **11** (140 mg, 0.778 mmol) in dry THF (4 mL) cooled to 0 °C. The cooling bath was removed, and the reaction mixture was stirred at rt until complete conversion. The reaction was quenched with a phosphate buffered solution (pH = 6.8, 4 mL) and was diluted with DCM. The organic layer was then collected, the aqueous phase was extracted with DCM (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was directly submitted to the next synthetic step. The crude was dissolved in CH_2Cl_2 (8 mL), and ethyl vinyl ether (1490 μL, 15.56 mmol) and PPTS (39 mg, 0.156 mmol) were added. The resulting mixture was stirred for 2 h, and then excess solid $NaHCO_3$ was added, followed by a saturated solution of $NaHCO_3$ (15 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*Hexane/EtOAc (9:1) gave the desired acetal **12** (166 mg, 84% over two steps, 1:1 mixture of anomers). TLC (SiO_2): R_f = 0.26 (hexane/EtOAc 95:5). FTIR (neat): 3447, 3061, 2979, 1736, 1438, 1381, 1336, 1296, 1274, 1201, 1134, 1059, 982, 930, 872, 846, 753, 709 cm^{-1}. ^1H NMR (300 MHz, CD_3CN): δ (ppm) 6.27 (dd, *J* = 5.7, 3.1 Hz, 1H), 6.00 (dd, *J* = 5.7, 2.9 Hz, 1H), 4.66−4.59 (m, 1H), 3.68−3.57 (bs overlyed m, 4H), 3.50−3.40 (m, 1H), 3.34 (ddt, *J* = 10.1, 7.4, 2.6 Hz, 1H), 3.22 (ddt, *J* = 10.2, 6.8, 3.3 Hz, 1H), 3.02−2.92 (m, 2H), 2.71 (bs, 1H), 1.98−1.86 (m, 2H), 1.46−1.39 (dddd, *J* = 12.3, 5.2, 4.0, 1.3 (J_w) Hz, 1H), 1.26−1.20 (d, *J* = 5.3 Hz, 3H), 1.20−1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CD_3CN): δ (ppm) 174.7 (s), 139.1 (d), 134.1 (d), 99.5 (d), 63.6 (t)*, 63.6 (t), 60.7 (t)*, 60.6 (t), 59.7 (d), 51.0 (d), 46.3 (d), 43.2 (d), 40.6 (d), 25.9 (t), 19.3 (q), 14.7 (q) [an asterisk indicates doubled signals due to the presence of diastereoisomers]. HRMS: calcd for $C_{14}H_{22}O_4$ 254.1518; found 254.1520

*(1R,2R,4S,7S)-7-((1-Ethoxyethoxy)methyl)-2-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**13**).* To a stirred solution of NaHMDS (1.326 mL, 1.326 mmol) in dry THF (5 mL) under an argon atmosphere was added dry hexane (0.8 mL). The resulting clear solution was cooled at −78 °C, and THF solution (2 mL) of **3** (198 mg, 0.780 mmol) was added dropwise via cannula. The reaction mixture was warmed to 0 °C and stirred at this temperature for 1 h, and after recooling to −78 °C dry O_2 was bubbled inside the enolate solution for 1 h. The hydroperoxide was reduced using an excess of $LiAlH_4$ (2 M in THF, 4.056 mmol, 2.028 mL) at −78 °C, and the reaction was stirred at room temperature overnight. Rochelle's salt (8 mL, satd aq) was added, and resulting two layers was vigorously stirred at rt for 4 h. After addition of DCM (8 mL) the organic layer was then collected, the water phase was extracted with DCM (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was filtered through a pad of silica gel, washed with hexane/EtOAc 2:8 (100 mL), and concentrated under reduced pressure to yield the desired diol **13**, which was directly used in the next step. IR (liquid film): 3700−3150 (br), 3060, 2985, 2875, 1465, 1450, 1345, 1275, 1060, 1050, 1030, 990, 910.

*(1R,4S,7S)-7-((1-Ethoxyethoxy)methyl)bicyclo[2.2.1]hept-5-en-2-one (**14**).* $NaIO_4$ (86 mg, 0.428 mmol) was added to a stirred solution of **13** (52 mg, 0.214 mmol) in THF/H_2O/phosphate buffered solution (pH = 6.8) 2:1:1 (1.5 mL) at rt, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), after 10 min the mixture was diluted with CH_2Cl_2 (10 mL), and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL), and the combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure (>90 mmHg). The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc 9:1 gave compound **14** (36 mg, yield = 80% over three steps) as a colorless oil. TLC (SiO_2): R_f = 0.24 (hexane/EtOAc 9:1). FTIR (neat): 3061, 1724, 1708, 1176. cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ (ppm) 6.75−6.60 (dd, *J* = 5.63, 2.94 Hz, 1H), 6.25−6.14 (dd, *J* = 4.5, 3.6 Hz, 1H), 4.75−4.58 (m, 1H), 3.30−4.70 (m, 4H), 3.10 (bs, 1H), 2,80 (bs, 1H), 2.70−2.55 (t, *J* = 7.52 Hz, 1H), 2.15−2.00 (m, 1H), 1.80−1.65 (dd, *J* = 16.7, 2.4 Hz, 1H), 1.25 (d, *J* = 5.31 Hz, 3H), 1.20−1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 214.2 (s), 145.9 (d), 132.6 (d), 100.6 (d), 63.8 (t), 63.6 (t)*, 62.8 (d), 62.7 (d)*, 61.8 (t), 61.6 (t)*, 58.6 (d), 42.4 (d), 33.5 (t), 20.4 (q), 16.0 (q). HRMS: calcd for $C_{12}H_{18}O_3$ 210.1256; found 210.1258

*(3aR,4R,6aS)-4-((1-Ethoxyethoxy)methyl)-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (**16**).* $NaHCO_3$ (287 mg, 3.42 mmol) was added to a solution of **14** (36 mg, 0.171 mmol) in MeOH/methyl *tert*-butyl ether 1:1. The suspension was cooled at 4 °C, and H_2O_2 10 M (171 μL, 1.71 mmol) was added under vigorous stirring. The reaction mixture was stirred at 4 °C for 18 h and then was diluted with Et_2O (10 mL), and organic layer was colected and washed with fresh H_2O (2 × 5 mL). The organic layer was washed with aqueous saturated $Na_2S_2O_3$ (8 mL), aqueous saturated $NaHCO_3$ (8 mL), water (4 mL), and finally brine (4 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/AcOEt (7:3) gave a mixture of lactones **16** and **15** (1:9 ratio). Silica gel (108 mg) was added to a solution of lactones **16** and **15** (1:9 ratio) in dry CH_2Cl_2/hexane 3:1 (0.5 mL). The reaction mixture was stirred at 40 °C, and the conversion was monitorated by ^1H NMR until complete conversion of the [3.2.1] structure into the [3.3.0] structure. The reaction was filtered over a short pad of Celite and concentrated under vacuum to afford the pure lactone **16** (22 mg, yield = 57% over two steps). TLC (SiO_2): R_f = 0.23 (hexane/EtOAc 7:3). FTIR (neat): 3016, 2927, 1764, 1291, 1173, 1139, 1023, 973, 759. cm^{-1}. ^1H NMR (300 MHz, CD_2Cl_2): δ (ppm) 6.02−5.95 (m, 2H), 5.46 (dd, *J* = 7.4, 0.8 Hz, 1H), 4.66 (m, 1H), 3.74−3.36 (m, 4H), 3.30−3.20 (m, 1H), 3.17−3.09 (m, 1H), 2.65−2.55 (m, 2H), 1.28 (d, *J* = 4.6 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 177.4 (s), 138.5 (d), 138.4 (d)*, 129.8 (d), 100.3 (d), 100.0 (d)*, 89.0 (d), 64.8 (t), 64.6 (t)*, 61.2 (t), 47.5 (d), 47.4 (d)*, 38.5 (d), 29.9 (t), 29.9 (t)*, 19.8 (q), 15.5 (q). ESI (m/z) = 249.07 [$(M + Na)^+$, 100], 475.06 [$(2M + Na)^+$, 15]. HRMS: calcd for $C_{12}H_{18}O_4$ 226.1205; found 226.1202

*(3aR,4R,6aS)-4-(Hydroxymethyl)-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (**2**).* PPTS (cat.) was added to a stirred solution of acetal **16** (22 mg, 0.097 mMol) in MeOH (1 mL), and the resulting mixture was stirred for 16 h. An excess of solid $NaHCO_3$ was added, and the resulting mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash

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chromatography on silica gel. Elution with hexane/EtOAc (1:1) gave the desired alcohol **2** (12 mg, yield = 80%, ee = 97%) as a pale yellow oil. HPLC: (Chiralcel AS-H column, hexane/*i*-PrOH = 70:30, 1 mL/min, 204 nm/208 nm). TLC (SiO_2): R_f = 0.22 (hexane/EtOAc 1:1). $[\alpha]^{20}_D$ = +7.17 (*c* 0.265, CH_2Cl_2). ESI (*m*/*z*) = 176.99 [$(M + Na)^+$, 100], 331.08 [$(2M + Na)^+$, 85]. The spetroscopic data were in agreement with the literature.[3]

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H, ^{13}C, HPLC profiles, computational details for the TS-A and TS-B and for the thermodinamic stability of aldehyde **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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