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Chemoenzymatic preparation of functionalized bicyclo[3.2.1]octenone and practical utilization

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Abstract—A practical route for the synthesis of both enantiomers of a functionalized bicyclo[3.2.1]octenone, which is potentially useful as a versatile chiral building block, has been developed from 1,4-cyclohexanedione monoethylene acetal by employing proline-catalyzed diastereoselective intramolecular aldolization and lipase-mediated kinetic resolution as the key steps. The synthetic utility of the bicyclo[3.2.1]octenone has been demonstrated by the conversion into a chiral bicyclo[5.3.0]decane, which should serve as the key intermediate for the synthesis of the pseudoguaianolide class of antitumor sesquiterpenes.

1. Introduction

Molecules that possess steric and stereoelectronic biases render their derivatives useful in organic synthesis.[1,2] We have recently developed enone **1**,[3] and its structural isomer **2**,[4] having a bicyclo[3.2.1]octane framework in both enantiomeric forms starting from racemic norbornadiene-2,5-dione[5] by a route involving either an enzymatic or chemical resolution step. Owing to their chemical nature with a sterically biased structure containing two oxygen functionalities, they exhibit inherent convex-face selectivity enabling the diastereocontrolled modification of their enone functionality and various tactical skeletal rearrangements that make them versatile building blocks. They have already been used in the stereocontrolled syntheses of the antibiotic diterpene (+)-ferruginol,[3a] the morphinan alkaloid (−)-morphine[3b] and (−)-*O*-methylpallidinine,[3c] the hormonal substances calcitriol[4a,b] and estrone,[4c] and the indole alkaloid (−)-dihydrocorynantheol.[4e] Since we are further interested in developing the synthetic utility of enone **2**, and since the acquisition of **2** requires an additional three-step sequence[4a] from enone **1** involving alkaline epoxidation, Wharton rearrangement, and manganese(IV) oxidation of the resulting alcohol, we planned to develop a more efficient route to **2**. The masked aldol functionality embedded in **2** prompted us to study the stereocontrolled construction of **3** via organocatalytic intramolecular aldolization[6] of the σ-symmetrical ketoaldehyde **4**. We report here a new chemoenzymatic preparation of **2** in both enantiomeric forms and the diastereocontrolled conversion of **2** to a chiral bicyclo[5.3.0]decane, which should serve as a key intermediate for the synthesis of the pseudoguaianolide class of antitumor sesquiterpenes,[7,8] to extend its versatility as a chiral building block (Scheme 1).

2. Result and discussion

2.1. Organocatalytic construction of *endo*-7-hydroxybicyclo[3.2.1]octan-2-one

The σ-symmetrical ketoaldehyde **4** was readily prepared from commercially available 1,4-cyclohexanedione monoethylene acetal **5** in five steps. Thus, the Horner–Wadsworth–Emmons olefination of **5** with triethyl phosphonoacetate and the following catalytic hydrogenation afforded ester **6**. The lithium aluminum hydride reduction of **6**, the hydrolytic deprotection of an acetal group, and Swern oxidation of the resulting alcohol **7**[9] furnished ketoaldehyde **4** (Scheme 2).

At first, the chemical and diastereofacial preferences of the σ-symmetrical ketoaldehyde **4** for the intramolecular aldolization were evaluated using K_2CO_3 or pyrrolidine as the

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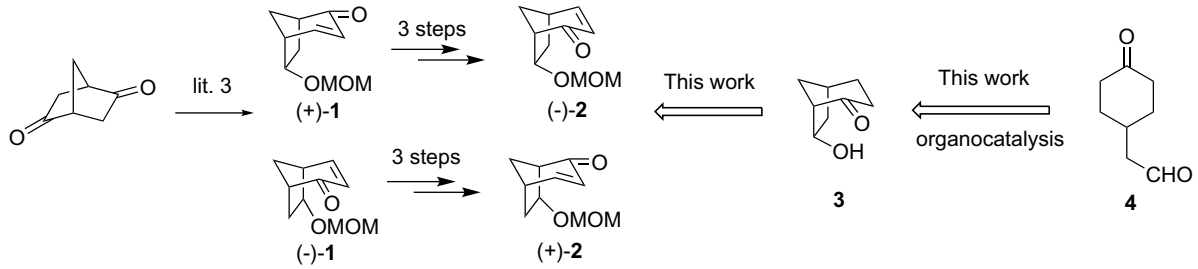
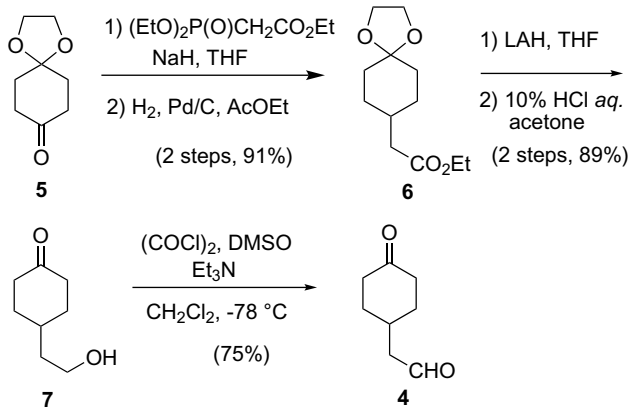
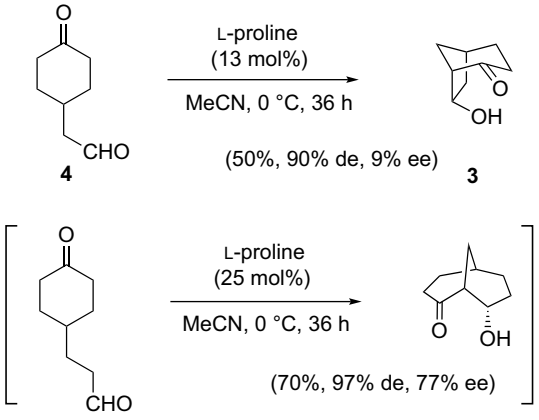


Scheme 1. Synthetic outlines of chiral bicyclo[3.2.1]octenones.



Scheme 2. Synthesis of σ-symmetric ketoaldehyde **4**.

catalyst. In both cases, the bicyclo[3.2.1]octane product **3** was produced as a 1:1 and 1.6:1 mixture of *endo*/*exo*-diastereomers, and no bicyclo[2.2.1]octane products were detected. We were, therefore, pleased to find that L-proline catalyzed[10] the diastereoselective aldolization of **4** to furnish *endo*-**3** in 50% yield with 90% de, although the enantioselectivity was 9% ee (Scheme 3).

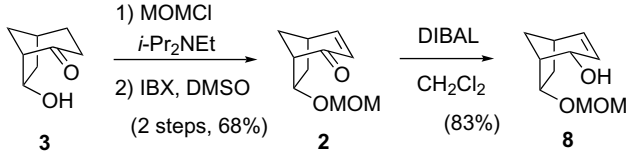


Scheme 3. L-Proline-catalyzed aldolization of **4**.

Then, suitable conditions for increasing enantioselectivity were investigated. However, we were unable to find conditions that would allow us to obtain an ee exceeding 33%.[10] In light of the fact that the homologous σ-symmetrical ketoaldehyde affords the corresponding aldolization product in 77% ee under identical conditions,[10] the discovery of catalysts and cofactors that bring about a practical level of asymmetric induction poses a serious challenge, which is now a subject of our intensive studies.

2.2. Enzymatic kinetic resolution

With our several successes in the lipase-mediated kinetic resolution of closely related bicyclo[3.2.1]octane derivatives,[11] aldol **3** was transformed into allylic alcohol **8** in three steps. Thus, the hydroxyl group of **3** was protected with a methoxymethyl group to give a MOM ether, which was oxidized by IBX[12] in warm DMSO to enone **2** in 68% yield. The treatment of **2** with DIBAL furnished the *endo*-alcohol **8** (Scheme 4).

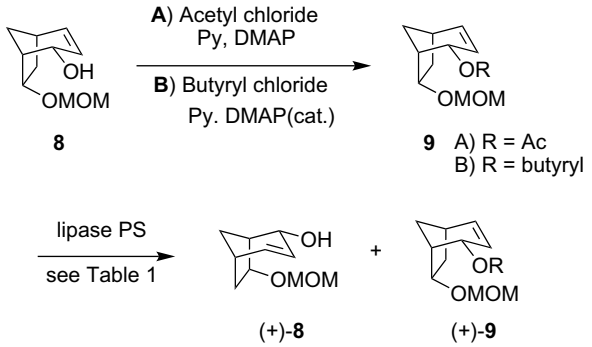


Scheme 4. Conversion of **3** to *endo*-alcohol **8**.

Unfortunately, all attempts at the enzymatic transesterification of the alcohol were unsatisfactory; that is, no reaction was observed using lipase MY, AK, PS, and vinyl acetate. Only a moderate level of resolution was promoted by lipase LIP, giving acetate **9A** in 43% yield with 70% ee after 15 days. We then examined the lipase-mediated enantioselective hydrolysis of ester derivatives **9A** and **9B** (Scheme 5).

Table 1 summarizes the results of the attempted hydrolysis in 0.1 M phosphate buffer (pH 7.0) and acetone (9:1) in the presence of lipase PS. It is interesting to note that both the acyl portion and temperature exert critical effects on the resolution of this particular bicyclo[3.2.1]octane.

Under optimized conditions, the butyryl ester (±)-**9B** was hydrolyzed by lipase PS in phosphate buffer-acetone at 45 °C to afford (+)-**8** and (+)-**9B** with an *E*-value[13] of 451. Thus, **9B** was resolved in a clear-cut manner in the presence of twice (w/w) the amount of lipase PS at 45 °C for 5 days to give an ester in 43% yield with 99% ee. The remaining butyrate (+)-**9B** with a purity of 90% ee was resolved again under hydrolysis conditions to give the enantiopure butyrate (+)-**9B**. Finally, the enantiopure enone (+)-**2** was obtained

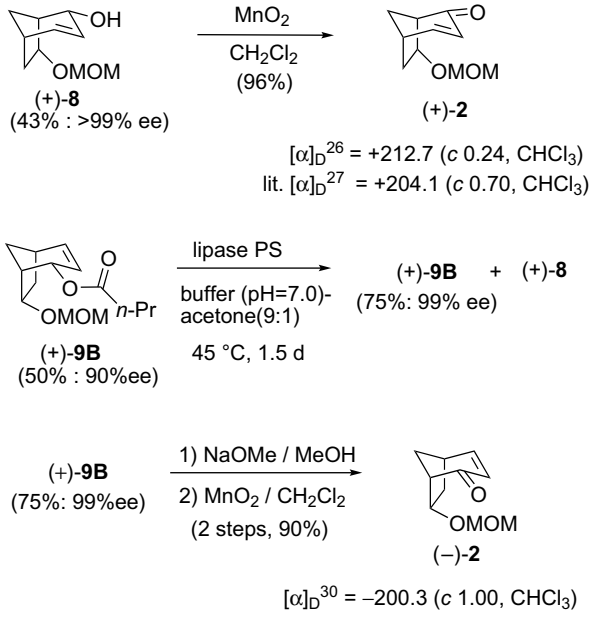


Scheme 5. Synthesis and lipase-mediated enantioselective hydrolysis of **9**.

Table 1. Lipase-mediated enantioselective hydrolysis of **9**

Substrate	Lipase PS (w/w)	Time (day)	Temp	Conversion (%)	ee (%)	*E*-value
9A	1	12	30	44	74	12
9B	1	60	30	39	99	383
9B	4	5	30	41	90	377
9B	2	5	45	43	99	451

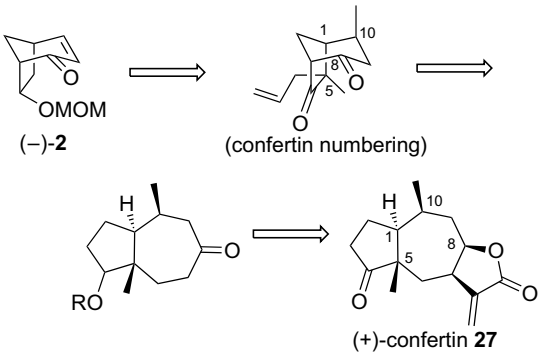
from the former by oxidation, and the enantiomer (−)-**2** was obtained from the latter by the sequential alkaline methanolysis and the oxidation of the resulting alcohol (−)-**8**, both in satisfactory yields (Scheme 6).



Scheme 6. Synthesis of both enantiomers of the bicyclo[3.2.1]octenone **2**.

2.3. Synthetic transformation to the bicyclo[5.3.0]decane system

To demonstrate the synthetic potential of **2**, its conversion to a chiral bicyclo[5.3.0]decane, which has served as a key intermediate[14] for the synthesis of confertin,[15] a pseudo-guaianolide-class antitumor sesquiterpene lactone, was examined on the basis of its functionality and stereochemical background (Scheme 7).



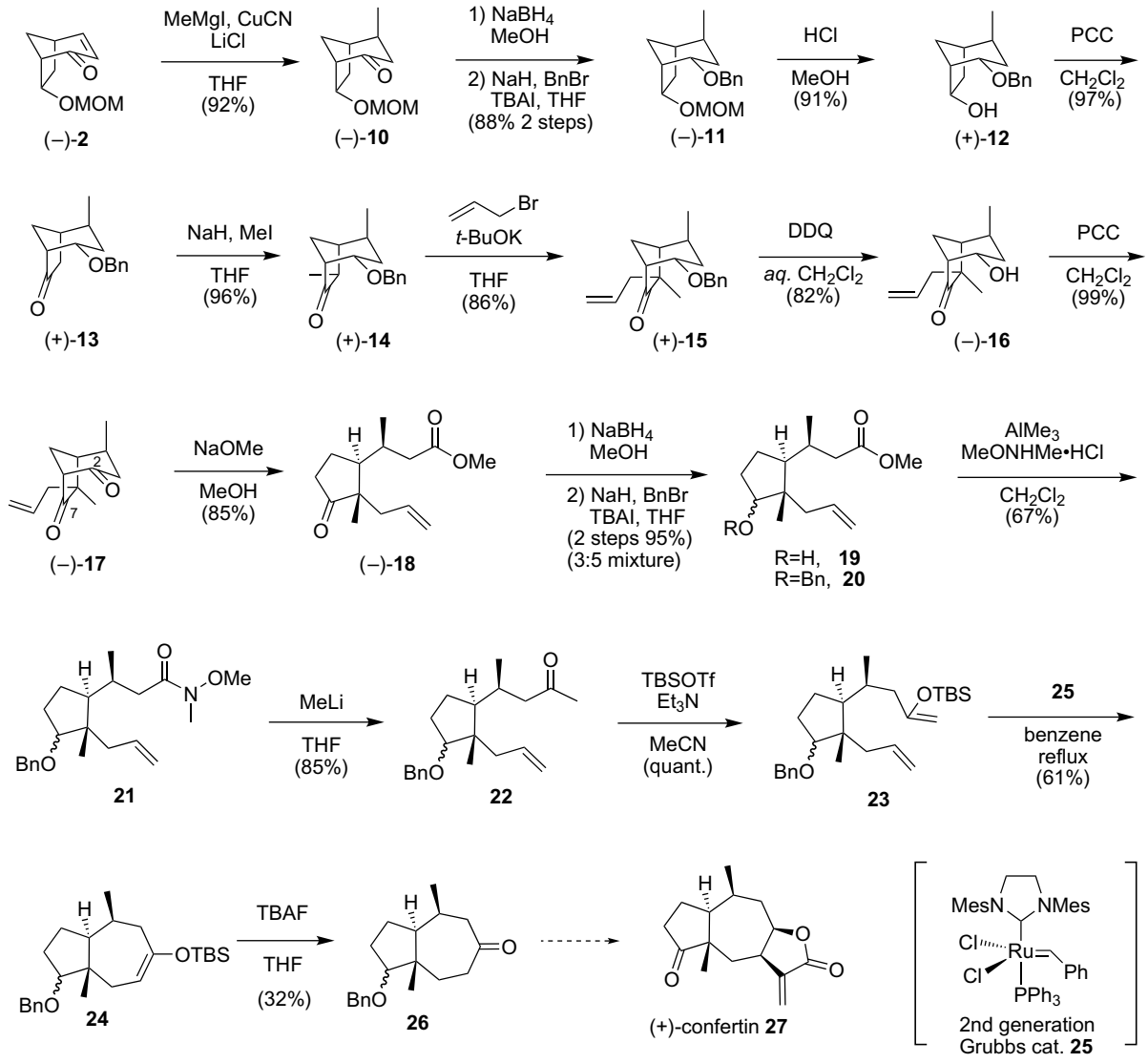
Scheme 7. Synthesis plan for the key intermediate of (+)-confertin.

Thus, the treatment of (−)-**2** with a cuprate, which was generated in situ from methylmagnesium iodide in the presence of copper(I) cyanide and LiCl, furnished ketone (−)-**10** in 92% yield as a single stereoisomer. To prepare for the installation of a quaternary center corresponding to C-5 (confertin numbering), a formal 'aldol transposition' was conducted in a four-step sequence involving $NaBH_4$ reduction, protection of the resulting secondary alcohols by a benzyl group, the deprotection of the MOM group, and PCC oxidation to furnish (+)-**13**. Again ketone **13** exhibited an inherent convex-face selectivity to allow the diastereoselective construction of a quaternary stereogenic center next to the carbonyl functionality. Thus, sequential methylation and allylation proceeded in turn from the convex face to furnish ketone (+)-**15**.

Having constructed the requisite C-10 tertiary and C-5 quaternary centers (confertin numbering), we then focussed our attention to the construction of a seven-membered ring. To this end, the *O*-benzyl group was removed and the resulting alcohol (−)-**16** was oxidized to give diketone (−)-**17**. When sodium methoxide was added to a stirred solution of (−)-**17** in MeOH, a facile and regioselective retro-Dieckmann reaction occurred instantly to afford ketoester (−)-**18** in 85% yield exclusively. The observed regioselectivity might be a consequence of the preferential attack of a methoxide anion onto the sterically more accessible C-2 carbonyl group. Ketone (−)-**18** was reduced with $NaBH_4$, and the resulting alcohol was protected by a benzyl group. Upon Weinreb amide formation and the reaction of **20** with methyllithium and with TBSOTf in the presence of triethylamine, **20** furnished the silyl enol ether **23**. The ring-closing metathesis[16] of **23** using the second generation Grubbs' catalyst[17] enabled us to obtain bicyclo[5.3.0]decane **24**, which furnishes a comparable functionality to the key synthetic intermediate of confertin[14] (Scheme 8).

3. Conclusion

In summary, we developed an alternative method for the efficient chemoenzymatic synthesis of a 7-oxybicyclo-[3.2.1]octenone-type chiral building block from commercially available 1,4-cyclohexanedione monoethylene acetal. The results of the current work are as follows: (1) A nearly racemic 7-hydroxybicyclo[3.2.1]octan-2-one **2** was easily prepared in a diastereocontrolled manner via an L-proline-



Scheme 8. Synthesis of the key intermediate of (+)-confertin.

catalyzed intramolecular aldolization of the σ-symmetric ketoaldehyde **4**. (2) The highly enantiomerically enriched bicyclo[3.2.1]octenones (+)-**2** and (−)-**2** were synthesized by a lipase-mediated enantioselective hydrolysis of racemic **9B**. (3) The newly developed synthesis route for (+)-**2** entails operationally facile 12 steps, enabling more straightforward access to (+)-**2** compared with the previously reported 14-step route. The synthetic use of **2** was demonstrated by converting it into a key intermediate of antitumor sesquiterpene (+)-confertin **27**. We are presently continuing this study for the expansion of the use of (+)-**2** and (−)-**2** in the enantio- and diastereo-controlled syntheses of various natural products.

4. Experimental

4.1. General methods

Unless otherwise mentioned, all reactions were performed in oven-dried glassware under argon atmosphere. Anhydrous THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Organic extracts were dried by stirring them over anhydrous $MgSO_4$, filtered through a Celite pad, and concentrated under reduced pressure using a rotary evaporator. Column chromatography was carried out using Merck 60N (63–210 mesh) silica gel. Reactions were analyzed on precoated silica gel 60 F_{254} plates (Merck) and compounds were visualized with a UV lamp (254 nm) and by staining with *p*-anisaldehyde in EtOH or phosphomolybdic acid (in EtOH). Melting point (mp) was uncorrected. IR spectra were recorded on a JASCO IR-700 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Gemini 2000 (300 MHz) or JEOL AL-400 (400 MHz) spectrometer. Mass spectra were recorded on a JEOLJMS-DX303 instrument. Optical rotation was measured with a JASCO DIP-370 digital polarimeter.

4.2. Ethyl 2-{4,4-(ethylenedioxy)cyclohexylidene}acetate

To a stirred suspension of sodium hydride (60%, 1.0 g, 25.2 mmol) in dry THF (75 mL) was added dropwise

triethyl phosphonoacetate (5 mL, 25.2 mmol) at 0 °C and the resulting mixture was stirred for 30 min. Then, 1,4-cyclohexanedione monoethylene acetal (3.28 g, 21 mmol) in THF (30 mL) was added to the mixture at 0 °C and stirred for 30 min. The mixture was diluted with Et_2O and H_2O. The mixture was extracted with EtOAc, and the extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/6) to give an ester (colorless oil; yield: 4.62 g, 20 mmol, 97%). IR ν_{max} (neat) cm^{-1}: 1712. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.67 (1H, s), 4.15 (2H, q, $J = 7.1$ Hz), 3.98 (4H, s), 3.00 (2H, t, $J = 7.4$ Hz), 2.37 (2H, t, $J = 6.4$ Hz), 1.76 (4H, td, $J = 7.4$, 6.4 Hz), 1.24 (3H, t, $J = 7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 160.0, 114.2, 107.9, 64.4, 59.6, 35.8, 35.0, 34.6, 26.1, 14.4. MS *m/z*: 226 (M^+, 100%). HRMS Calcd for $C_{12}H_{18}O_4$(M^+): 226.1204. Found: 226.1190.

4.3. Ethyl 2-{4,4-(ethylenedioxy)cyclohexyl}acetate 6

A solution of ester (4.62 g, 20 mmol) in AcOEt (100 mL) was hydrogenated on 10% Pd–C (460 mg) using a H_2 balloon for 2 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/6) to give **6** (colorless oil; yield: 4.27 g, 18.7 mmol, 94%). IR ν_{max} (neat) cm^{-1}: 1731. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.12 (2H, q, $J = 7.1$ Hz), 3.93 (4H, s), 2.22 (2H, d, $J = 7.1$ Hz), 1.86–1.82 (1H, m), 1.78–1.69 (4H, m), 1.57 (2H, td, $J = 12.7$, 3.6 Hz), 1.30 (2H, dd, $J = 12.7$, 9.52 Hz), 1.25 (3H, t, $J = 7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.7, 108.5, 64.2, 60.2, 41.0, 34.3, 33.4, 30.0, 14.3. MS *m/z*: 228 (M^+), 99 (100%). HRMS Calcd for $C_{12}H_{20}O_4$ (M^+): 228.1360. Found: 228.1355.

4.4. 4-(2-Hydroxyethyl)cyclohexanone 7

To a stirred suspension of $LiAlH_4$ (532 mg, 14 mmol) in THF (37 mL) was added **6** (4.27 g, 18.7 mmol) in THF (10 mL) at 0 °C, and the mixture was continuously stirred at the same temperature. After 10 min, the mixture was diluted with Et_2O and H_2O. The resulting mixture was filtered through a Celite pad. The filtrate was evaporated under reduced pressure.

The residue was dissolved in acetone (28 mL) and 10% aq HCl (1.8 mL) was added to the solution. Then, the mixture was refluxed for 20 min. A saturated aqueous $NaHCO_3$ solution was added to the cooled reaction mixture and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc/hexane, 1/1) to give **7** (colorless oil; yield: 2.37 g, 16.7 mmol, 89%, 2 steps). IR ν_{max} (neat) cm^{-1}: 3408, 1704. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.75 (2H, t, $J = 6.6$ Hz), 2.36 (2H, dd, $J = 11.0$, 3.9 Hz), 2.37–2.31 (2H, m), 2.08 (2H, dd, $J = 13.1$, 2.9 Hz), 1.98–1.92 (1H, m), 1.62–1.55 (3H, m), 1.43 (2H, dd, $J = 11.9$, 5.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.3, 60.7, 40.8, 38.3, 32.7, 32.6. MS *m/z*: 142 (M^+), 98 (100%). HRMS Calcd for $C_8H_{14}O_2$(M^+): 142.0977. Found: 142.1004.

4.5. (4-Oxocyclohexyl)acetaldehyde 4

A solution of oxalyl chloride (7.27 mL, 83.3 mmol) in CH_2Cl_2 (300 mL) at −78 °C was treated with DMSO (11.8 mL, 167 mmol) dropwise and the mixture was stirred for 10 min. Alcohol **7** (3.00 g, 20.8 mmol) in CH_2Cl_2 (50 mmol) was then added to the mixture at −78 °C. After 15 min, Et_3N (34.9 mL, 250 mmol) was added dropwise at the same temperature. The mixture was then warmed to room temperature and H_2O was added. The mixture was extracted with AcOEt, washed with brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc/hexane, 1/2) to give **4** (colorless oil; yield: 2.19 g, 15.6 mmol, 75%). IR ν_{max} (neat) cm^{-1}: 1712. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.81 (1H, s), 2.50 (2H, dd, $J = 6.3$, 1.8 Hz), 2.45–2.39 (4H, m), 2.12 (2H, dt, $J = 14.7$, 3.3 Hz), 1.65 (1H, s), 1.52–1.47 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.6, 200.9, 49.3, 40.5, 32.4, 30.5. MS *m/z*: 140 (M^+), 96 (100%). HRMS Calcd for $C_8H_{12}O_2$ (M^+): 140.0837. Found: 140.0807.

4.6. (1*R**,5*S**,7*S**)-7-Hydroxybicyclo[3.2.1]octan-2-one 3

To a stirred solution of aldehyde **4** (623 mg, 4.45 mmol) in MeCN (4.45 mL) was added L-proline (64.0 mg, 0.56 mmol) at 0 °C. After 36 h, H_2O was added and the mixture was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (EtOAc/hexane, 1/2) to give **3** (colorless oil; yield: 313 mg, 2.24 mmol, 50%, 90% de, 9% ee). IR ν_{max} (neat) cm^{-1}: 3417, 1697. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.60 (0.95H, m), 4.32 (0.05H, d, $J = 5.8$ Hz), 2.88 (0.1H, s), 2.80 (1.9H, s) 2.68–2.59 (1H, m) 2.50–2.26 (2.85H, m), 2.19 (0.15H, dd, $J = 14.7$, 6.8 Hz), 2.10–1.83 (3H, m), 1.82–1.63 (2H, m), 1.57 (1H, dt $J = 13.5$, 3.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.8, 73.9, 57.7, 40.4, 36.2, 33.4, 31.5, 30.6. MS *m/z*: 140 (M^+), 80 (100%). HRMS Calcd for $C_8H_{12}O_2$ (M^+): 140.0837. Found: 140.0816.

4.7. (1*R**,5*S**,7*S**)-7-Methoxymethoxybicyclo[3.2.1]-octan-2-one

To a stirred solution of alcohol **3** (118 mg, 0.844 mmol) in CH_2Cl_2 (12 mL) was added *i*-Pr_2NEt (0.6 mL, 3.36 mmol) at 0 °C, and the mixture was stirred for 10 min at the same temperature. To the mixture was then added dropwise methoxymethylchloride (0.13 mL, 1.68 mmol). After 12 h, H_2O was added to the mixture and the mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated to give a crude product, which was chromatographed on silica gel (EtOAc/hexane, 1/6) to give a MOM ether (colorless oil; yield 145 mg, 0.79 mmol, 94%). IR ν_{max} (neat) cm^{-1}: 1712. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.61–4.56 (2H, m), 4.41 (1H dt, $J = 12.2$, 4.3 Hz), 3.33 (3H, s), 2.94 (1H, t, $J = 5.1$ Hz), 2.68–2.58 (1H, m) 2.44–2.33 (3H, m), 2.45–2.33 (2H, m), 1.99–1.87 (2H, m), 1.73 (1H, dt, $J = 8.9$, 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.0, 95.5, 78.4, 55.5, 36.3, 35.9, 34.7, 33.0, 31.7, 30.6. MS *m/z*: 184 (M^+), 45 (100%). HRMS Calcd for $C_{10}H_{16}O_3$ (M^+): 184.1094. Found: 184.1080.

4.8. (1*R**,5*S**,7*S**)-7-Methoxymethoxybicyclo[3.2.1]oct-3-en-2-one 2

To a stirred solution of an MOM ether (1.6 g, 8.73 mmol) in DMSO (12 mL) was added IBX (28 g, 35.4 mmol) at 0 °C. The mixture was then heated at 60 °C for 36 h. After cooling to rt, saturated aqueous $NaHCO_3$ was added to the mixture, which was then extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc/hexane, 1/2) to give **2** (colorless oil; yield: 1.12 g, 6.25 mmol, 72%). IR ν_{max} (neat) cm^{-1}: 1680. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38 (1H, ddd, $J = 9.6$, 6.9, 1.6 Hz), 5.96 (1H, dd, $J = 9.6$, 1.6 Hz), 4.65 (1H, ddd, $J = 8.7$, 6.4, 2.7 Hz), 4.64 (1H, d, $J = 6.9$ Hz), 4.51 (1H, d, $J = 6.9$ Hz), 3.33 (3H, s), 3.26 (1H, t, $J = 6.4$ Hz), 2.77 (1H, dd, $J = 6.6$, 4.2 Hz), 2.32 (1H, ddd, $J = 13.7$, 9.3, 6.6 Hz), 2.10 (1H, dd, $J = 11.8$, 3.0 Hz), 1.70–1.78 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.1, 157.0, 128.7, 95.6, 75.6, 55.5, 55.2, 39.2, 37.2, 36.0. MS *m*/*z*: 182 (M^+), 45 (100%). HRMS Calcd for $C_{10}H_{14}O_3$ (M^+): 182.0942. Found: 182.0960.

4.9. (1*R**,2*R**,5*S**,7*S**)-7-Methoxymethoxybicyclo-[3.2.1]oct-3-en-2-ol 8

To a stirred solution of enone **2** (394 mg, 2.16 mmol) in CH_2Cl_2 (43 mL) was added DIBAL in hexane (1.0 M, 2.89 mL, 4.33 mmol) at −78 °C and the mixture was continuously stirred at the same temperature. After 30 min, the mixture was diluted with Et_2O and H_2O was added to the mixture. The mixture was filtered through a Celite pad, and the filtrate was concentrated, and chromatographed on silica gel (EtOAc/hexane, 1/2) to give **8** (colorless oil; yield: 286 mg, 1.56 mmol, 83%). IR ν_{max} (neat) cm^{-1}: 3508. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.01 (1H, ddt, $J = 9.5$, 7.8, 1.7 Hz), 5.62 (1H, td, $J = 9.5$, 1.7 Hz), 4.68 (1H, d, $J = 6.8$ Hz), 4.66 (1H, d, $J = 6.8$ Hz), 4.59–4.48 (1H, m), 4.24 (1H, d, $J = 11.0$ Hz), 3.39 (3H, s), 2.76 (1H, dd, $J = 10.7$, 5.1 Hz), 2.31(1H, dd, $J = 9.8$, 5.6 Hz), 2.12 (1H, ddd, $J = 13.2$, 9.5, 5.9 Hz), 1.79 (1H, dd, $J = 13.2$, 2.7 Hz), 1.72–1.63 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.9, 130.2, 95.7, 82.0, 72.3, 55.8, 43.7, 41.9, 36.9, 34.5. MS *m*/*z*: 152 (M^+−OMe−H), 78 (100%). HRMS Calcd for $C_9H_{12}O_2$ (M^+−OMe−H): 152.0837. Found: 152.0844.

4.10. (1*R**,2*R**,5*S**,7*S**)-Butyric acid 7-methoxy-methoxy bicyclo[3.2.1]oct-3-en-2-yl ester 9B

To a stirred solution of allyl alcohol **8** (3.00 g, 16.3 mmol) in CH_2Cl_2 (82 mL) was added pyridine (3.55 mL, 48.9 mmol), butyryl chloride (3.39 mL, 32.6 mmol), and DMAP (199 mg, 1.63 mmol) at 0 °C. After 6 h, saturated aqueous $NaHCO_3$ was added to the mixture, which was then extracted with AcOEt. The organic extract was washed with 10% aqueous NaOH, brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc/hexane, 4/1) to give **9B** (colorless oil; yield: 3.52 g, 13.9 mmol, 85%). IR ν_{max} (neat) cm^{-1}: 1725. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.14 (1H, dd, $J = 9.5$, 7.8 Hz), 5.80 (1H, s), 5.51 (1H, d, $J = 9.5$ Hz), 4.67 (1H, d, $J = 6.8$ Hz), 4.60 (1H, d, $J = 6.8$ Hz), 4.59–4.56 (1H, m), 3.36 (3H, s), 2.81 (1H, d, $J = 5.1$ Hz), 2.35–2.20 (2H, m), 2.28 (2H, dt, $J = 14.9$, 7.7 Hz), 2.02 (1H, dd, $J = 11.7$, 3.2 Hz), 1.77 (2H, td, $J = 12.1$, 3.2 Hz), 1.66 (2H, q, $J = 7.3$ Hz), 0.95 (3H, t, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.3, 137.5, 124.8, 95.3, 78.3, 76.3, 55.1, 41.8, 41.0, 36.9, 36.4, 34.1, 18.4, 13.8. MS *m*/*z*: 254 (M^+), 134 (100%). HRMS Calcd for $C_{14}H_{22}O_4$ (M^+): 254.1517. Found: 254.1508.

4.11. (1*S*,2*R*,5*S*,7*S*)-7-Methoxymethoxybicyclo[3.2.1]oct-3-en-2-ol (+)-8

4.11.1. (1*S*,2*S*,5*R*,7*R*)-Butyric acid-7-methoxymethoxybicyclo-[3.2.1]-oct-3-en-2-yl ester (+)-9B. To a stirred solution of ester (±)-**9B** (1.0 g, 3.9 mmol) in 0.1 M phosphate buffer (pH 7.0, 35 mL) and acetone (4 mL) was added lipase PS (2 g) at 45 °C. After 5 days, the mixture was diluted with AcOEt and filtered through a Celite pad. The filtrate was extracted with AcOEt, and the organic extract was washed with brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (eluent: EtOAc/hexane, 1/4 or 1/2, respectively) to give ester (+)-**9B** (colorless oil; yield: 495 mg, 1.95 mmol, 50%) and allyl alcohol (+)-**8** (colorless oil; yield: 309 mg, 1.68 mmol, 43%).

The spectroscopic data of (+)-**9B** and (+)-**8** thus obtained were identical with those of the racemates.

The enantiomeric excess was determined to be esters (+)-**9B** (90% ee) and (+)-**8** (99% ee) by HPLC using a column with a chiral stationary phase (CHIRALCEL OD-H, eluent: *i*-PrOH/hexane, 4:96 v/v), as described above, after transformation into enone **2**.

Allyl alcohol (+)-**8**: $[\alpha]_D^{29} = +78.1$ (*c* 0.15, $CHCl_3$).

To a stirred mixture of ester **9B** (495 mg, 1.95 mmol, 90% ee) in 0.1 M phosphate buffer (pH 7.0, 18 mL) and acetone (2 mL) was added lipase PS (990 mg) at 45 °C. After 1.5 days, the mixture was diluted with AcOEt and filtered through a Celite pad. The filtrate was extracted with AcOEt, and the organic extract was washed with brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/hexane, 1/2) to give (+)-**9B** (colorless oil; 371 mg, 1.46 mmol, 75%).

Ester (+)-**9B**: $[\alpha]_D^{27} = +57.8$ (*c* 1.00, $CHCl_3$).

Enantiomeric excess was determined to be ester (+)-**9B** (99% ee) by HPLC as above after transformation into **2**.

4.12. (1*R*,5*S*,7*S*)-7-Methoxymethoxybicyclo[3.2.1]oct-3-en-2-one (+)-2

To a stirred solution of (+)-**8** (532 mg, 14 mmol) in CH_2Cl_2 (22 mL) was added MnO_2 (815 mg) at rt. After 10 min, the mixture was diluted with Et_2O, and filtered through a Celite pad. The filtrate was evaporated and chromatographed on silica gel (EtOAc/hexane, 1/2) to give (+)-**2** (colorless oil; yield: 76.9 mg, 0.42 mmol, 96%).

(+)-**2** $[\alpha]_D^{26} = +212.7$ (*c* 0.24, $CHCl_3$).

4.13. (1*S*,5*R*,7*R*)-7-Methoxymethoxybicyclo[3.2.1]oct-3-en-2-one (−)-2

To a stirred solution of (+)-**9B** (87.5 mg, 0.34 mmol) in MeOH (17 mL) was added NaOMe (13.8 mg, 0.034 mmol) at 0 °C for 5 min. After evaporating the solvent, the residue was treated with saturated aqueous NH_4Cl and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave crude alcohol.

The crude alcohol was dissolved in CH_2Cl_2 (17 mL), and MnO_2 (632 mg) was added to the mixture. The mixture was stirred for 10 min, diluted with Et_2O and filtered through a Celite pad. The filtrate was evaporated and chromatographed on silica gel (EtOAc/hexane, 1/2) to give (−)-**2** (colorless oil; yield: 55.7 mg, 0.31 mmol, 90%).

(−)-**2** $[\alpha]_D^{30} = -200.3$ (*c* 1.00, $CHCl_3$).

4.14. (1*R*,4*S*,5*S*,7*S*)-7-Methoxymethoxy-4-methyl-bicyclo-[3.2.1]octan-2-one (−)-10

To a stirred solution of CuCN (1.48 g, 16.5 mmol) and LiCl (1.40 g, 33.0 mmol) in dry THF (38 mL) was added methylmagnesium iodide (8.8 mL, 2.5 M in Et_2O) at −78 °C. After 30 min, enone **2** (1.00 g) in THF (10 mL) was added dropwise to the mixture at −78 °C. After 30 min, the mixture was diluted with Et_2O, water was added to the mixture and the mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/6) to give ketone **10** (colorless oil; yield: 1.00 g, 5.0 mmol, 92%). $[\alpha]_D^{29} = -92.7$ (*c* 1.5, $CHCl_3$); IR (neat): 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.58 (2H, dd, $J = 12.6$, 6.8 Hz), 4.39 (1H, m), 3.31 (3H, s), 2.91 (1H, dd, $J = 5.1$, 5.1 Hz), 2.82 (1H, dd, $J = 16.4$, 8.2 Hz), 2.50–2.42 (1H, m), 2.23 (1H, m), 2.09–1.96 (2H, m), 1.02 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 216.5, 95.9, 77.9, 55.7, 55.6, 43.8, 39.2, 36.6, 35.8, 30.1, 20.6; MS *m*/*z*: 198 (M^+), 45 (100%); HRMS Calcd $C_{11}H_{18}O_3$: 198.1256. Found: 195.1282.

4.15. (1*R*,2*S*,4*S*,5*R*,6*R*)-4-Benzyloxy-6-methoxymethoxy-2-methylbicyclo[3.2.1]octane (−)-11

To a solution of **10** (407 mg, 2.06 mmol) in MeOH (10.3 mL) was added $NaBH_4$ (58.5 mg, 1.55 mmol) at −78 °C, and the mixture was stirred for 2 h at the same temperature. Then, the mixture was diluted with Et_2O and acetone was added to the mixture. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/4) to give an alcohol (colorless oil; yield: 378 mg, 1.89 mmol, 92%). $[\alpha]_D^{27} = -87.6$ (*c* 0.50, $CHCl_3$); IR (neat): 3547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.65 (2H, d, $J = 4.39$ Hz), 4.37 (1H, dd, $J = 6.59$ Hz), 3.74 (1H, br s), 3.39 (3H, s), 3.23 (1H, d, $J = 11.0$ Hz) 2.45 (1H, br s), 2.24–2.16 (1H, m), 2.00–1.82 (3H, m), 1.74 (1H, dd, $J = 12.9$, 5.61 Hz), 1.59 (1H, d, $J = 12.56$, 5.61 Hz), 1.41 (1H, d, $J = 13.7$ Hz), 1.33–1.28 (2H, m), 1.00 (3H, d, $J = 6.59$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.1, 80.4, 71.0, 55.7, 44.7, 39.7, 37.1, 36.0, 34.8, 29.2, 19.8; MS *m*/*z*: 182 ($M^+ - H_2O$), 94 (100%); HRMS Calcd $C_{11}H_{18}O_2$: 182.1306. Found: 182.1292.

To a stirred solution of the alcohol (100 mg, 0.5 mmol) in dry THF (2.5 mL) was added sodium hydride (40 mg, 1.00 mmol) at 0 °C. After 30 min, benzyl bromide (0.01 mL, 1.13 mmol) and tetrabutyl ammonium iodide (18.5 mg, 0.05 mmol) were added to the mixture at 0 °C. The mixture was heated at reflux overnight. After cooling to rt, the mixture was diluted with Et_2O, and H_2O was added to the mixture. The mixture was extracted with EtOAc, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give (−)-**11** (colorless oil; yield: 138 mg, 48 mmol, 96%). $[\alpha]_D^{23} = -20.6$ (*c* 1.3 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.21 (5H, m), 4.75 (1H, d, $J = 6.83$ Hz), 4.56 (1H, d, $J = 6.59$ Hz), 4.52 (2H, s), 4.34 (1H, ddd, $J = 10.72$, 5.36, 5.36 Hz), 3.60 (1H, ddd, $J = 11.71$, 5.37, 2.20 Hz), 3.35 (3H, s), 2.54 (1H, br s), 2.27 (1H, ddd, $J = 13.78$, 11.10, 7.07 Hz), 2.18 (1H, dt, $J = 12.14$, 6.59 Hz), 1.91–1.83 (2H, m), 1.65 (1H, dd, $J = 12.56$, 5.61 Hz), 1.56 (1H, dd, $J = 12.44$, 3.17 Hz), 1.43 (2H, m), 0.98 (3H, d, $J = 7.07$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.3, 128.1, 127.2, 127.0, 95.6, 77.8, 76.7, 70.2, 55.1, 40.4, 39.3, 37.5, 34.7, 31.9, 30.0, 19.9. MS *m*/*z*: 290 (M^+), 91 (100%). HRMS Calcd for $C_{18}H_{26}O_3$: 290.1882. Found: 290.1854.

4.16. (1*R*,2*S*,4*S*,5*S*,6*R*)-4-Benzyloxy-2-methylbicyclo-[3.2.1]octan-6-ol (+)-12

To a solution of ether (−)-**11** (139 mg, 0.48 mmol) in MeOH (2.0 mL) was added saturated HCl in MeOH (0.5 mL) at 0 °C. After 5 h, the solvent was evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give **12** (colorless oil; yield: 107 mg, 43 mmol, 91%). $[\alpha]_D^{27} = +24.7$ (*c* 1.2 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 3508. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.26 (5H, m), 4.57 (2H, dd, $J = 14.64$, 11.95 Hz), 4.43 (1H, m), 4.22 (1H, d, $J = 4.88$ Hz), 3.87–3.83 (1H, ddd, $J = 10.55$, 6.52, 3.35 Hz), 2.55 (1H, dd, $J = 5.38$, 3.38 Hz), 2.27 (1H, ddd, $J = 13.86$, 10.59, 7.08 Hz), 2.09 (1H, m), 1.96–1.92 (2H, m), 1.80 (1H, dd, $J = 13.17$, 6.10 Hz), 1.58 (1H, s), 1.54 (1H, dd, $J = 12.32$, 2.81 Hz), 1.44–1.36 (2H, m), 0.99 (3H, d, $J = 7.08$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 128.3, 127.5, 127.4, 77.4, 74.7, 70.1, 41.8, 40.3, 40.1, 34.4, 32.3, 29.1, 19.8. MS *m*/*z*: 246 (M^+), 91 (100%). HRMS Calcd for $C_{16}H_{22}O_2$: 246.1620. Found: 246.1627.

4.17. (1*R*,2*S*,4*S*,5*R*)-4-Benzyloxy-2-methylbicyclo-[3.2.1]octan-6-one (+)-13

A mixture of alcohol (+)-**12** (459 mg, 1.86 mmol), PCC (802 mg, 3.72 mmol), and silica gel (459 mg) in CH_2Cl_2 (9.3 mL) was stirred at rt for 2 h. The mixture was then

diluted with Et_2O and filtered through a Celite pad. The filtrate was evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give (+)-**13** (colorless oil; yield: 439 mg, 1.80 mmol, 97%). $[\alpha]_D^{23} = +140.1$ (*c* 2.0 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 1739. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.26 (5H, m), 4.71 (1H, d, $J = 11.95$ Hz), 4.47 (1H, d, $J = 12.20$ Hz), 3.70 (1H, ddd, $J = 11.71$, 5.87, 3.42 Hz), 2.66 (1H, s), 2.33 (1H, s), 2.29 (1H, d, $J = 6.83$), 2.09–1.70 (2H, m), 1.91–1.76 (3H, m), 1.66 (1H, ddd, $J = 12.93$, 12.93, 6.83 Hz), 1.10 (2H, m), 1.65 (1H, dd, $J = 12.56$, 5.61 Hz), 1.56 (1H, dd, $J = 12.44$, 3.17 Hz), 1.43 (3H, d, $J = 7.08$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 217.8, 128.3, 127.5, 127.4, 75.9, 69.8, 49.5, 45.1, 37.6, 33.1, 32.8, 28.8, 19.8. MS *m*/*z*: 244 (M^+), 91 (100%). HRMS Calcd for $C_{16}H_{20}O_2$: 244.1463. Found: 244.1448.

4.18. (1*S*,2*S*,4*S*,5*R*,7*S*)-4-Benzyloxy-2,7-dimethylbicyclo-[3.2.1]octan-6-one (+)-14

To a stirred solution of ketone (+)-**13** (74 mg, 0.3 mmol) in dry THF (1.5 mL) was added sodium hydride (18 mg, 0.45 mmol) at 0 °C. After 30 min, to the mixture was added methyl iodide (0.19 mL, 3.0 mmol) at rt for 3 h. The mixture was diluted with Et_2O, and H_2O was added to the mixture. The mixture was extracted with EtOAc, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give **14** (colorless oil; yield: 74 mg, 28.8 mmol, 96%). $[\alpha]_D^{23} = +121.9$ (*c* 0.7 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 1736. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.21 (5H, m), 4.69 (1H, d, $J = 12.20$), 4.44 (1H, d, $J = 11.95$ Hz), 3.69 (1H, ddd, $J = 11.71$, 5.85, 3.42 Hz), 2.66 (1H, br s), 2.05–1.96 (2H, m), 1.94–1.97 (2H, m), 1.82–1.71 (2H, m), 1.61 (1H, ddd, $J = 14.15$, 11.71, 6.83 Hz), 1.11 (3H, d, $J = 7.56$ Hz), 1.07 (3H, d, $J = 7.32$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 220.5, 138.4, 128.2, 127.4, 127.4, 127.3, 76.1, 69.8, 50.1, 48.8, 45.0, 33.6, 33.3, 26.1, 20.0, 16.1. MS *m*/*z*: 258 (M^+), 91 (100%). HRMS Calcd for $C_{17}H_{22}O_2$: 258.1620. Found: 258.1614.

4.19. (1*S*,2*S*,4*S*,5*R*,7*S*)-7-Allyl-4-benzyloxy-2,7-dimethyl bicyclo[3.2.1]octan-6-one (+)-15

To a stirred solution of ketone (+)-**14** (272 mg, 1.05 mmol) in dry THF (5.3 mL) was added *t*-BuOK (177 mg, 1.58 mmol) at rt. After 30 min, to the mixture was added 3-bromopropene (0.2 mL, 2.1 mmol), and the mixture was stirred for 5 min. The mixture was diluted with Et_2O and saturated aqueous NH_4Cl was added to the mixture. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give **15** (colorless oil; yield: 258 mg, 0.90 mmol, 86%). $[\alpha]_D^{26} = +74.5$ (*c* 0.7 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 1734. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.22 (5H, m), 5.75 (1H, m), 5.11 (1H, d, $J = 8.54$ Hz), 5.05 (1H, dd, $J = 16.83$, 1.46 Hz), 3.71 (1H, ddd, $J = 11.71$, 6.10, 3.42 Hz), 2.80–2.75 (1H, m), 2.19 (2H, dd, $J = 14.15$, 8.05 Hz), 2.14–2.20 (2H, m), 1.93 (2H, br s), 1.77 (1H, dd, $J = 15.98$, 14.5 Hz), 1.67 (1H, d, $J = 12.93$ Hz), 1.58–1.46 (2H, m), 1.10 (3H, d, $J = 7.08$ Hz), 1.06 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 220.5, 138.4, 132.9, 128.2, 127.4, 127.4, 127.3, 118.6, 76.1, 69.8, 52.1, 50.1, 48.8, 45.0, 33.6, 33.3, 26.1, 20.0, 16.1. MS *m*/*z*: 298 (M^+), 91 (100%). HRMS Calcd for $C_{20}H_{26}O_2$: 298.1933. Found: 298.1944.

4.20. (1*R*,2*S*,4*S*,5*R*,7*S*)-7-Allyl-4-hydroxy-2,7-dimethyl-bicyclo[3.2.1]octan-6-one (−)-16

A mixture of benzyl ether (+)-**15** (85 mg, 0.29 mmol), H_2O (0.15 mL), and DDQ (194 mg, 0.85 mmol) in CH_2Cl_2 (1.3 mL) was stirred at rt overnight. The mixture was diluted with Et_2O, and saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/4) to give **16** (colorless oil; yield: 49 mg, 23.7 mmol, 82%). $[\alpha]_D^{31} = -32.2$ (*c* 0.4 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 3424, 1733. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.89–5.77 (1H, m), 5.13 (1H, dd, $J = 10.12$, 0.85 Hz), 5.07 (1H, dd, $J = 17.08$, 0.85 Hz), 3.98–3.88 (1H, m), 2.52 (1H, br s), 2.22 (1H, dd, $J = 14.15$, 8.05 Hz), 2.16–2.01 (3H, m), 1.94 (1H, br s), 1.89 (1H, d, $J = 9.03$ Hz), 1.84 (1H, dd, $J = 14.27$, 6.22 Hz), 1.74 (1H, d, $J = 13.17$ Hz), 1.28 (1H, ddd, $J = 14.03$, 11.59, 7.08 Hz), 1.12 (3H, d, $J = 7.08$ Hz), 1.05 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 220.7, 138.4, 133.3, 128.3, 127.6, 127.4, 118.3, 69.7, 51.7, 48.8, 45.1, 41.0, 33.8, 28.9, 25.7, 20.6, 14.6. MS *m*/*z*: 208 (M^+), 114 (100%). HRMS Calcd for $C_{13}H_{20}O_2$: 208.1463. Found: 208.1484.

4.21. (1*R*,4*S*,5*S*,6*S*)-6-Allyl-4,6-dimethyl-bicyclo[3.2.1]-octane-2,7-dione (−)-17

A mixture of alcohol **16** (49 mg, 0.24 mmol), PCC (101 mg, 0.47 mmol), and silica gel (49 mg) in CH_2Cl_2 (1.12 mL) was stirred for 2 h. The mixture was diluted with Et_2O and filtered through a Celite pad. The filtrate was evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give **17** (colorless oil; yield: 48 mg, 23.8 mmol, 99%). $[\alpha]_D^{31} = -201.5$ (*c* 0.8 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 1743, 1711. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.82–5.71 (1H, m), 5.17 (1H, dt, $J = 10.25$, 0.98 Hz), 5.11 (1H, ddd, $J = 16.83$, 3.05, 1.46 Hz), 3.25 (1H, dt, $J = 5.12$, 1.46 Hz), 2.45–2.34 (3H, m), 2.26 (1H, dd, $J = 14.15$, 8.29 Hz), 2.22–2.12 (2H, m), 1.55 (2H, s), 1.22 (3H, s), 1.16 (3H, d, $J = 7.07$ Hz). MS *m*/*z*: 206 (M^+). HRMS Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1279.

4.22. (*S*)-Methyl 3-{(1*S*,2*S*)-2-allyl-2-methyl-3-oxo-cyclo-pentyl}butanoate (−)-18

To a solution of diketone (−)-**17** (48 mg, 0.23 mmol) in MeOH (1.17 mL) was added NaOMe (15 mg, 0.28 mmol) at −20 °C. After stirring for 10 min, the mixture was diluted with Et_2O, and saturated aqueous NH_4Cl was added to the mixture. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$),

and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/6) to give **18** (colorless oil; yield: 47 mg, 0.20 mmol, 85%). $[\alpha]_D^{31} = -101.5$ (*c* 1.3 $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 3424, 1735. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.62–5.46 (1H, m), 5.05 (1H, d, $J = 10.98$ Hz), 5.01 (1H, d, $J = 18.79$ Hz), 3.69 (3H, s), 2.57 (1H, dd, $J = 14.03$, 5.98 Hz), 2.51 (1H, dd, $J = 19.27$, 8.29 Hz), 2.43–2.32 (1H, m), 2.19 (1H, dd, $J = 14.03$, 9.15 Hz), 2.15–1.94 (5H, m), 1.54–1.42 (1H, m), 1.07 (3H, d, $J = 6.10$ Hz), 0.96 (3H, s). MS *m*/*z*: 238 (M^+). HRMS Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1568.

4.23. (*S*)-Methyl 3-{(1*S*,2*S*,3*RS*)-2-allyl-3-hydroxy-2-methylcyclopentyl}butanoate 19

To a solution of **18** (306 mg, 1.29 mmol) in MeOH (6.45 mL) was added $NaBH_4$ (37 mg, 0.97 mmol) at −78 °C, and the mixture was stirred for 3 h at the same temperature. Then, the mixture was diluted with Et_2O and acetone was added to the mixture. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/4) to give **19** (colorless oil; yield: 297 mg, 1.25 mmol, 97%).

IR ν_{max} (neat) cm^{-1}: 3514, 1722. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.04–5.88 (1H, m), 5.12 (1H, t, $J = 6.95$ Hz), 5.06 (1H, d, $J = 10.00$ Hz), 3.84 (0.36H, t, $J = 8.54$ Hz), 3.77 (0.6H, d, $J = 5.12$ Hz), 3.67 (3H, s), 2.50–2.28 (1.5H, m), 2.12–1.86 (5H, m), 1.80–1.65 (1.5H, m), 1.55–1.23 (3H, m), 1.02 (3H, t, $J = 6.83$ Hz), 0.85 (3H, d, $J = 7.81$ Hz). MS *m*/*z*: 222 (M^+–H_2O), 107 (100%). HRMS Calcd for $C_{14}H_{24}O_3$: 222.1620. Found: 222.1606.

4.24. (*S*)-Methyl 3-{(1*S*,2*S*,3*RS*)-2-allyl-3-benzyloxy-2-methylcyclopentyl}butanoate 20

To a stirred solution of **19** (13 mg, 0.054 mmol) in dry THF (0.27 mL) was added sodium hydride (4.32 mg, 0.1 mmol) at 0 °C. After 30 min, benzyl bromide (0.01 mL, 0.12 mmol) and tetrabutyl ammonium iodide (2 mg, 0.005 mmol) were added to the mixture at 0 °C. The mixture was heated at reflux overnight. After cooling to rt, the mixture was diluted with Et_2O, and H_2O was added to the mixture. The mixture was extracted with EtOAc, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give **20** (colorless oil; yield: 11 mg, 0.033 mmol, 61 %). IR ν_{max} (neat) cm^{-1}: 1734. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.23 (5H, m), 5.87–5.74 (1H, m), 4.54 (1H, t, $J = 12.69$ Hz), 4.39 (0.41H, d, $J = 11.95$ Hz), 4.39 (0.59H, d, $J = 11.71$ Hz), 3.66 (3H, s), 3.54 (0.41H, t, $J = 8.12$ Hz), 3.43 (0.59H, q, $J = 2.20$ Hz), 2.55 (0.59H, dd, $J = 13.66$, 6.34 Hz), 2.45 (1H, dd, $J = 19.64$, 8.29 Hz), 2.34 (0.41H, dd, $J = 14.15$, 7.81 Hz), 2.23–1.24 (10H, m), 1.01 (3H, dd, $J = 7.81$, 6.34 Hz), 0.94 (1.23H, s), 0.84 (1.77H, s). MS *m*/*z*: 330 (M^+), 91 (100%). HRMS Calcd for $C_{21}H_{30}O_3$: 330.2195. Found: 330.2186.

4.25. (*S*)-3-{(1*S*,2*S*,3*RS*)-2-Allyl-3-benzyloxy-2-methylcyclopentyl}-*N*-methoxy-*N*-methylbutanamide 21

To a stirred solution of MeNHOMeHCl (0.64 mg, 0.66 mmol) in dry CH_2Cl_2 (0.55 mL) was added $AlMe_3$ (1.0 M in *n*-hexane, 0.66 mL, 0.66 mmol) at −15 °C. After 30 min, ester **20** (33 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at 0 °C and stirred for 3 h. The mixture was diluted with Et_2O, and H_2O was added to the mixture. The mixture was extracted with EtOAc, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/4) to give **21** (colorless oil; yield: 22 mg, 0.074 mmol, 67%). IR ν_{max} (neat) cm^{-1}: 1660. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.22 (5H, m), 5.90–5.75 (1H, m), 5.06–4.99 (2H, m), 4.68 (1H, s), 4.53 (1H, t, $J = 12.08$ Hz), 4.39 (0.39H, d, $J = 11.95$ Hz), 4.29 (0.61H, d, $J = 11.71$ Hz), 3.64 (3H, s), 3.54 (0.39H, t, $J = 7.82$ Hz), 3.43 (0.61H, d, $J = 2.68$ Hz), 3.17 (3H, s), 2.60–2.52 (1H, m), 2.50–2.06 (5H, m), 2.01–1.64 (5H, m), 1.54–1.38 (2H, m), 1.01 (1.21H, d, $J = 7.07$ Hz), 0.99 (1.79H, d, $J = 6.83$ Hz), 0.91 (1.21H, s), 0.81(1.79H, s). MS *m*/*z*: 359 (M^+), 91 (100%). HRMS Calcd for $C_{22}H_{33}NO_3$: 359.2460. Found: 359.2447.

4.26. (*S*)-4-{(1*S*,2*S*,3*RS*)-2-Allyl-3-benzyloxy-2-methylcyclopentyl}pentan-2-one 22

To a solution of amide **21** (22 mg, 0.06 mmol) in THF (1 mL) was added MeLi (0.99 M in Et_2O, 0.14 mL, 0.15 mmol) at −78 °C. After stirring for 1 h, the mixture was diluted with Et_2O and saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: EtOAc/hexane, 1/10) to give **22** (colorless oil; yield: 16 mg, 0.051 mmol, 85%). IR ν_{max} (neat) cm^{-1}: 1712. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.22 (5H, m), 5.88–5.72 (1H, m), 5.06–4.88 (2H, m), 4.53 (1H, t, $J = 12.20$ Hz), 4.39 (0.40H, d, $J = 11.95$ Hz), 4.30 (0.60H, d, $J = 11.71$ Hz), 3.53 (0.4H, t, $J = 8.17$), 3.43 (0.60H, dd, $J = 4.39$, 1.95 Hz), 2.58–2.49 (1H, m), 2.47 (0.6H, d, $J = 2.45$ Hz), 2.32 (0.4H, dd, $J = 7.81$ 14.15 Hz), 2.24–2.04 (3H, m), 2.12 (1.2H, s), 2.11 (1.8H, s), 1.99–1.20 (6H, m), 0.96 (1.20H, d, $J = 4.64$ Hz), 0.95 (1.80H, d, $J = 6.34$ Hz), 0.90 (1.20H, s), 0.80(1.80H, s). MS *m*/*z*: 314 (M^+), 91 (100%). HRMS Calcd for $C_{21}H_{30}O_2$: 314.2246. Found: 314.2240.

4.27. (1*S*,5*S*)-1-Allyl-2-methoxy-1-methyl-5-{(*S*)-4-(2,3,3-trimethylbutan-2-yloxy)pent-4-en-2-yl}cyclopentane 23

To a stirred solution of **22** (15 mg, 0.048 mmol) in dry MeCN (0.24 mL) were added Et_3N (40 μL, 0.28 mmol) and TBSOTf (40 μL, 0.19 mmol) at rt. After 10 min, the mixture was diluted with Et_2O, and saturated aqueous NH_4Cl was added to the mixture at 0 °C. The mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product, which was chromatographed on silica gel (eluent: hexane) to give **23** (colorless oil; yield: 20 mg, 0.048 mmol, quant.). ^1H NMR (400 MHz, $CDCl_3$) δ:

7.19–7.12 (5H, m), 5.72–5.57 (1H, m), 4.88–4.70 (2H, m), 4.38 (1H, d, $J = 11.46$ Hz), 4.23 (0.60H, d, $J = 11.95$ Hz), 4.13 (0.40H, d, $J = 11.71$ Hz), 3.86 (1.2H, s), 3.81 (0.80H, s), 3.37 (0.4H, t, $J = 8.29$ Hz), 3.26 (0.6H, d, $J = 5.00$ Hz), 2.37 (0.4H, dd, $J = 12.69$, 5.61 Hz), 2.19 (0.6H, dd, $J = 13.91$, 8.05 Hz), 1.98 (0.6H, dd, $J = 14.15$, 6.83 Hz), 2.15–1.03 (7H, m), 0.85–0.60 (15H, m), 0.17 (6H, d, $J = 2.44$ Hz). MS *m*/*z*: 428 (M^+), 199 (100%). HRMS Calcd for $C_{27}H_{44}OSi$: 428.3111. Found: 428.3097.

4.28. (1*RS*,3a*S*,8a*S*,4*S*)-1-Benzyloxy-4,8a-dimethyl-6-*tert*-butyl-dimethylsilyloxy-1,2,3,3a,4,5,8,8a-octahydroazulen 24

To a stirred solution of **23** (23 mg, 0.054 mmol) in benzene (5.37 mL) was added second generation Grubbs's catalyst (4.5 mg, 0.005 mmol) at rt. After 20 h, the solvent was evaporated to leave a crude product, which was chromatographed on silica gel (eluent: hexane) to give **24** (colorless oil; yield: 13 mg, 0.033 mmol, 61%). MS *m*/*z*: 400 (M^+), 185 (100%). HRMS Calcd for $C_{25}H_{40}O_2Si$: 400.2797. Found: 400.2811.

4.29. (1*RS*,3*S*,4*S*,8a*S*)-1-Benzyloxy-4,8a-dimethyl-octahydroazulen-6-one 26

To a stirred solution of **24** (13 mg, 0.03 mmol) in dry THF (0.163 mL) was added TBAF (1.0 M in THF, 0.05 mL, 0.05 mmol) at rt. After 3 h, the solvent was evaporated under reduced pressure to leave a crude product, which was chromatographed on silica gel (eluent: hexane) to give **26** as a colorless oil; yield: 3 mg, 9.6 μmol (32%). IR ν_{max} (neat) cm^{-1}: 1695. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.52–7.25 (5H, m), 4.61 (0.6H, d, $J = 9.61$ Hz), 4.53 (0.4H, d, $J = 12.91$ Hz), 4.42 (0.6H, d, $J = 11.26$ Hz), 4.32 (0.40H, d, $J = 12.36$ Hz), 3.36 (0.40H, d, $J = 7.97$ Hz), 3.30 (0.60H, d, $J = 5.31$ Hz), 2.82 (0.6H, t, $J = 11.26$ Hz), 2.62–1.86 (5.4H, m), 1.82–1.44 (6H, m), 0.95 (3H, d, $J = 7.42$ Hz), 0.80 (1.8H, s), 0.73 (1.2H, s). MS *m*/*z*: 286 (M^+), 91 (100%). HRMS Calcd for $C_{19}H_{26}O_2$: 286.1933. Found: 286.1903.

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