Anti-addition of Dimethylsulfoxonium Methyldie to Acyclic $\alpha,\beta$-Unsaturated Ketones and Its Application in Formal Synthesis of an Eicosanoid

Venkatchalam Angamuthu, Wen-Jung Chang, and Duen-Ren Hou

Department of Chemistry, National Central University, No. 300 Jhong-Da Road, Jhong-li, Taoyuan 32001, Taiwan

Supporting Information

ABSTRACT: Cyclopropanation using dimethylsulfoxonium methyldie (Corey–Chaykovsky reaction) was examined with a series of linear $\alpha,\beta$-unsaturated ketones, and the results showed that the major trajectory for the addition of the sulfur ylide to the enones is anti, related to the $\gamma$-substituent. The stereochemical assignment for the generated cyclopropanes was achieved by X-ray crystallography or comparing with the reported spectroscopic data. We found that the diastereoselectivity is influenced by several factors, including the protecting groups, solvents, and temperatures, and good anti/syn ratios (>10:1) were often obtained using the tert-butylidemethylsilyl and tert-butylidiphenylsilyl-protected substrates. The method was applied to a formal synthesis of a natural eicosanoid with good efficiency.

INTRODUCTION

The structure of cyclopropane is prevalent in natural products, biologically active compounds, and organic materials. As highly strained molecules, cyclopropane and its derivatives are also useful building blocks or precursors to access various structures downstream. Substituted cyclopropanes, like many cyclic compounds, often possess the elements of stereochemistry, which influence the physical, chemical, and biological properties of target compounds. Therefore, chemists are interested in and continue to develop various methods to prepare cyclopropanes with good stereochemical control. Common methods include metal-mediated carbene insertion, the Simmons–Smith reaction, Wadsworth–Emmons cyclopropanations, Kulinkovich–de Meijere reactions, and various Michael-induced ring closure reactions. Among these methods, the Michael addition of dimethylsulfoxonium methyldie to $\alpha,\beta$-unsaturated carbonyl compounds and the following intramolecular displacement of dimethyl sulfoxide (Corey–Chaykovsky reaction) is a convenient way to prepare cyclopropyl ketones or esters. Because the addition of dimethylsulfoxonium methyldie to an enone produced the same enolate intermediate regardless of the E- or Z-geometry of the original enones, the following ring closure usually gives a thermodynamically stable trans-1,2-disubstituted cyclopropane. Therefore, the stereochemistry of the products is determined at the first step, 1,4-addition of sulfur ylides, which is known to go through the less hindered face of the cyclic enones (Scheme 1). However, the diastereoselectivity for the addition of sulfur ylides to $\gamma$-substituted, linear/acyclic enones is complicated. For example, Wills et al. reported the anti-addition as the major pathway, but Ma’s, Krief’s, and Gurjar’s groups reported that acetonide-protected $\gamma$-alkoxy-$\alpha,\beta$-unsaturated esters or ketones gave the syn-adducts as the major products. These contradictory results were further confirmed during our synthesis of (-)-brevipolide H, in which the opposite diastereoselectivities of the cyclopropanations were observed when the protecting groups for the $\gamma$-alkoxy groups were altered from the acetonide group to others. However, only one type of enones, bearing $\gamma,\delta$-disterocenters, was studied in our previous work.

Herein, we present our systematic studies on the diastereoselectivity of the cyclopropanation with dimethylsulfoxonium methyldie using a series of linear, $\gamma$-substituted $\alpha,\beta$-unsaturated enones. Our results verify that the anti-addition is the major trajectory for the addition of sulfur ylides to acyclic enones although the diastereomeric ratio may vary by the reaction factors applied, such as protecting groups, solvents, and temperature. A formal synthesis of a cyclopropane-containing eicosanoid was achieved with this anticyclopropanation.

RESULTS AND DISCUSSION

Various $\gamma$-hydroxyl group-protected (-)-ethyl L-lactates (1a–f) were prepared according to the reported methods. The following disobutylaluminium hydride (DIBAL-H) reduction and Wittig olefination yielded a series of $\alpha,\beta$-unsaturated phenyl ketones, in which the $\gamma$-hydroxyl groups were protected as silyl ethers (2a–c), ethoxy methyl ether (2d), benzy! ether (2e), and triphenylmethyl ether (2f) (Scheme 2). The catalytic amount (10 mol%) of benzoic acid in the Wittig reactions gave the E-olefins only.

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The results derived from the reactions of the γ-silyloxy- or alkoxyl-substituted, α,β-unsaturated phenyl ketones 2 and dimethyloxosulfonium methylide are summarized in Table 1. After the removal of the protecting groups, all of the reactions provided the same major diastereomer (5), which was separated and characterized by 1H and 13C NMR. The stereochemistry of the cyclopropane moiety related to the hydroxyl group of compound 5 was unambiguously assigned as anti by X-ray crystallography of its 1-adamantyl carbamate derivative 7 (Figure 1), prepared in eq 1. When we applied the reaction conditions developed in our previous study of cyclopropanation, −30 °C and different ratios of dimethylformamide (DMF)/tetrahydrofuran (THF) as the solvents, good yields but moderate diastereoselectivities were observed (entries 1−3, Table 1). It is interesting to note that the diastereoselectivity improved as the ratio of DMF increased and the reaction using the single solvent (DMF) gave the best ratio of the anti/syn for the cyclopropanes derived from phenyl ketone 2a (12:1, entry 4). tert-Butylmethylylsil (TBS)-protected enone 2b was also an ideal substrate for this cyclopropanation reaction as a good diastereomeric ratio (13:1) was observed (entry 5). Further increasing the steric hindrance of the silyl ether group to triisopropylsilyl (TIPS) did not improve the diastereoselectivity (entry 6). Moderate diastereoselectivities observed for γ-ethoxymethoxy-enone 2d and γ-benzoxyl-enone 2e (entries 7 and 8) indicate that the silyl ether groups, such as −OTBS and OTBDPS, are more helpful than the alkoxyl groups in yielding the conformers of enones favoring anti-addition. Tryptl-group-protected enone 2f only gave slight excess in the antiadduct (entry 9). These results confirm that relative to the γ-substituent, anti-addition of dimethyloxosulfonium methyldie to α,β-unsaturated enone is the major reaction pathway (Figure 2). However, the steric hindrance of the protecting groups may not be the only factor to account for the anti-addition as the two most bulky substrates, TIPS and trityl protected enones (2c and 2f, respectively), only gave moderate selectivities. We further prepared a series of γ-(tert-butyldimethylsilyloxy)-substituted, α,β-unsaturated ketones to study the diastereoselectivity of their cyclopropanations. The results are summarized in Table 2. For the aryl ketones bearing different functional groups, such as halogen, ester, and isolated olefin (8−10, respectively), good yields (up to 97%) and diastereoselectivities (dr up to 9) were observed for the reactions conducted in DMF and at −30 °C (condition A, entries 1−3). Although excellent diastereoselectivity was observed for cyclopropanation of methyl ketone 11 under condition A, the reaction yield was rather poor (13%, entry 4). Alkyl ketones 11−15 were indeed less reactive than the aryl ketones for cyclopropanations. We found that the DMF/THF mixed solvents were helpful in obtaining a good yield while maintaining the desired diastereoselectivity (entries 5 and 6). This trend was also observed for the tert-butyl ketone (12, entries 7−9) and is consistent with our previous studies with α,β-unsaturated alkyl ketones. Therefore, the DMF/THF mixed solvents were applied to the rest of the ketones (13 and 14, entries 10−11) and synthetically useful results were obtained for these ketones with a 3-butenyl or 2-phenylethyl group. Although benzyl-protected enone 15 only gave a 1:4:1 diastereomeric ratio of cyclopropane adducts (entry 12), the 1H NMR of the major diastereomer is consistent with the spectroscopic data of the reported anti-15C, in which the cyclopropane was derived from the cyclization of a chiral, homoallylic triflate and supported by X-ray crystallography. Compound 11C, prepared in this study, was also converted to the same anti-15C after the removal of its TBS group and the following benzylation (eq 2), which provides a solid basis to support the antistereochemical assignment. This method was applied to our formal synthesis of cyclopropyl-containing eicosanoid 16, which was isolated by the incubation of...
arachidonic acid with an acetone powder of the Caribbean soft coral *Plexaura homomalla* and showed an inhibitory activity to lipoxygenases. These properties of stimulated several synthetic studies on this compound. The structural features of this eicosanoid include a six-membered lactone bearing a cyclopropyl ketone group, whose stereochemistry matches the outcome preparing from the anti-addition of the sulfur ylide to \(\alpha,\beta\)-unsaturated enone in this study, and makes eicosanoid 16 a good target to demonstrate its efficiency (Scheme 3).

Homoallylic alcohol 21 was prepared from D-mannitol in three steps. The following TBS protection of the hydroxyl group, acidic hydrolysis, and oxidative cleavage of the acetonide provided intermediate aldehyde 23, which was converted to key enone 24 with 65% from (Scheme 4).

The addition of the sulfur ylide to enone 24 generated cyclopropane 19 with the diastereoselectivity of 9:1 and 57% yield (Scheme 5). The anti-isomer was isolated after the removal of the TBS group by hydrogen fluoride pyridine and converted to acrylate 20. The following ring closing metathesis yielded unsaturated lactone 26, which was hydrogenated with Pd/C to provide reported precursor 17 for the synthesis of eicosanoid 16. This synthesis shows that the anti-addition of dimethyloxosulfonium methylide to \(\alpha,\beta\)-unsaturated enone is a convenient and stereoselective method to prepare cyclopropyl ketones, such as eicosanoid 16.

### CONCLUSIONS

The anti-addition should be the major pathway for cyclopropanations using dimethyloxosulfonium methylide and acyclic \(\gamma\)-substituted, \(\alpha,\beta\)-unsaturated enone, and good diastereoselectivities, anti/syn >10:1, could be obtained with TBS- or tert-butyldiphenylsilyl (TBDPS)-protected substrates. The choice of the reaction solvents is important as synthetically useful results were obtained with DMF and DMF/THF (1:10) for the aryl ketones and alkyl ketones, respectively. The key
intermediate for the synthesis of cycloproyl eicosanoid 16 was efficiently prepared by this cyclopropanation.

■ EXPERIMENTAL SECTION

All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen in oven-dried glassware. All reagents and solvents were obtained from commercial suppliers and used without further purification, if not mentioned otherwise. THF and diethyl ether were dried over sodium, monitored with benzophenone ketyl radical, and distilled prior to use. Dichloromethane (DCM) and toluene were dried over CaH2 and distilled prior to use. Thin layer chromatography was done using precoated silica gel 60 F254 plates containing a fluorescent indicator; purification by chromatography was done using silica gel (230–400 mesh). 1H and 13C chemical shifts are reported in parts per million and referenced to the residual solvent. All spectra were obtained at 25 °C. Compounds 1a, 1b, 1c, 1d, 1e, and 1f were prepared according to the literature procedures.

Scheme 3. Retrosynthetic Analysis of Eicosanoid 16

Table 2. Cyclopropanation of α,β-Unsaturated Enones

| entry | enone | product | condition\(\text{a}\) | anti:syn\(\text{b}\) | yield (%)\(\text{b}\) |
|-------|-------|---------|------------------|-----------------|-------------|
| 1     | 1 OTBS 8 Br | 8C TBSO | A | 9 : 1 | 92 |
| 2     | 9 CO2CH2 OPh | 9C | A | 7 : 1 | 69 |
| 3     | 10 OTBS | 10C | A | 4 : 1 | 97 |
| 4     | 11 OTBS | 11C | A | 12 : 1 | 33 |
| 5     | 11 | 11C | B | 18 : 1 | 13 |
| 6     | 12 | 12C | C | 9 : 1 | 63 |
| 7     | 12 | 12C | A | 9 : 1 | 49 |
| 8     | 12 | 12C | B | >20 : 1 | 13 |
| 9     | 12 | 12C | C | 7 : 1 | 64 |
| 10    | 14 | 14C | C | 9 : 1 | 64 |
| 11    | 15 | 15C | C | 5 : 1 | 71 |
| 12    | 16 | 16C | C | 1.4 : 1 | 68 |

\(\text{a}\)Reagents: NaH (2 equiv) and Me₃S(O)I (2 equiv), condition A: −30 °C in DMF; condition B: −30 °C in DMF/THF (1:10); condition C: 25 °C in DMF/THF (1:10). \(\text{b}\)Determined by 1H NMR of crude reaction mixtures. \(\text{c}\)Isolated yields.

(5S,4E)-4-(((tert-Butyldiphenylsilyl)oxy)-1-phenylpent-2-en-1-one (2a). DIBAL-H (1 M in hexane, 3.8 mL, 3.8 mmol) was added to a solution of ethyl-(S)-2-(((tert-butyldiphenylsilyl)oxy)propionate (1a, 1.2 g, 3.36 mmol) and diethyl ether (30 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate (20 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (25 mL × 2). The combined organic layers were washed with sat. NaCl (10 mL), dried over Na2SO4 and concentrated. The obtained crude aldehyde without further purification was added to a solution of ylide (1-phenyl-2-(triphenylphosphoranylidene)ethanone)31 (1.8 g, 4.71 mmol) and benzoic acid (40.0 mg, 0.33 mmol), and toluene (20 mL) at room temperature under a N2 atmosphere. The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature, and toluene was removed under reduced pressure. The crude product was purified by column chromatography (SiO2, ethyl acetate (EtOAc)/hexanes, 1:19, Rf 0.70) to give 2a (1.18 g, 2.84 mmol, 85% over two steps) as a yellow oil. 1H NMR (CDCl3, 300 MHz) δ 7.71–7.82 (m, 2H), 7.46–7.52 (m, 4H), 7.58–7.66 (m, 4H), 7.71–7.82 (m, 2H).
7.32 (m, 8H), 7.07 (dd, \(J = 15.5\) Hz, \(J = 1.4\) Hz, 1H), 6.96 (dq, \(J = 15.0\) Hz, \(J = 4.5\) Hz, \(J = 4.5\) Hz, \(J = 0.75\) Hz, 1H), 4.63−4.55 (m, 1H), 1.23 (d, \(J = 6.6\) Hz, 3H), 1.12 (s, 9H); 13C NMR (CDCl3, 75 MHz) \(\delta\) 190.8, 151.7, 137.9, 136.0, 135.9, 133.9, 133.7, 132.9, 130.0, 129.9, 128.7, 127.9, 127.8, 123.9, 123.4, 126.7, 126.5, 123.3, 69.4, 27.2, 23.5, 19.4; high-resolution mass spectrometry-electrospray ionization (HRMS-ESI) (m/z) calcd for [M + Na]+ (C27H30NaO2Si), 437.1913, found 437.1919.

\((S,E)-4-((\text{tert-Butyldimethylsilyl})\text{oxy})-1\text{-phenylpent-2-en-1-one} (2b)\). DIBAL-H (1 M in hexane, 19.3 mL, 19.2 mmol) was added to a solution of \((S)-\text{ethyl-2-((\text{tert-butyldimethylsilyl})\text{oxy})propanoate} (1b, 4 g, 17.21 mmol) and diethyl ether (120 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate (aq) (80 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (50 mL × 3). The combined organic layers were washed with sat. NaCl (aq) (40 mL), dried over Na2SO4, and concentrated. The obtained crude aldehyde without further purification was a yellowish oil. \([\alpha]_{D}^{20} = -0.8\) (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) \(\delta\) 7.94 (d, \(J = 7.3\) Hz, 2H), 7.56−7.47 (m, 3H), 7.14−6.99 (m, 2H), 4.57−4.56 (m, 1H), 1.33 (d, \(J = 6.4\) Hz, 3H), 0.97 (s, 9H), 0.12 (s, 6H); 13C NMR (CDCl3, 75 MHz) \(\delta\) 190.8, 152.1, 138.0, 132.7, 128.6, 122.8, 68.2, 25.8, 23.6, 18.2, −4.8; HRMS-ESI (m/z) calcd for [M + Na]+ (C17H26NaO2Si), 313.1600, found 313.1594.

\((S,E)-1\text{-Phenyl-4-((\text{triisopropylsilyl})\text{oxy})pent-2-en-1-one} (2c)\). DIBAL-H (1 M in hexane, 7.7 mL, 7.7 mmol) was added to a solution of \((S)-\text{ethyl-2-((\text{triisopropylsilyl})\text{oxy})propanoate} (1c, 1.9 g, 6.92 mmol) and diethyl ether (30 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate (30 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with sat. NaCl (30 mL), dried over Na2SO4, and concentrated. The obtained crude aldehyde without further purification was a yellowish oil. \([\alpha]_{D}^{20} = 0.8\) (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) \(\delta\) 7.94 (d, \(J = 7.3\) Hz, 2H), 7.56−7.47 (m, 3H), 7.14−6.99 (m, 2H), 4.57−4.56 (m, 1H), 1.33 (d, \(J = 6.4\) Hz, 3H), 0.97 (s, 9H), 0.12 (s, 6H); 13C NMR (CDCl3, 75 MHz) \(\delta\) 190.8, 152.1, 138.0, 132.7, 128.6, 122.8, 68.2, 25.8, 23.6, 18.2, −4.8; HRMS-ESI (m/z) calcd for [M + Na]+ (C17H26NaO2Si), 313.1600, found 313.1594.
yellowish oil. [α]120D = −22.2 (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 7.95 (d, J = 7.3 Hz, 2H), 7.58–7.45 (m, 3H), 7.17 (d, J = 15.3 Hz, 1H), 7.05 (dd, J = 15.3 Hz, J = 3.8 Hz, 1H), 4.70 (p, J = 6.5 Hz, 1H), 1.36 (d, J = 6.5 Hz, 3H), 1.10–1.09 (m, 21H); 13C NMR (CDCl3, 75 MHz) δ 191.0, 152.6, 132.7, 128.6, 128.5, 122.7, 60.7, 23.9, 18.0, 17.8, 12.3, 12.1; HRMS-atmospheric pressure chemical ionization (APCI) (m/z) calc'd for [M + H]+ (C20H33O2Si), 333.2250, found 333.2247.

(S,E)-4-(Ethoxymethoxy)-1-phenylpent-2-en-1-one (2d). DIBAL-H (1 M in hexane, 6.6 mL, 6.6 mmol) was added to a solution of (S)-ethyl-2-(ethoxymethoxy)propanoate (1d, 1.03 g, 5.84 mmol) and diethyl ether (20 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate(aq) (20 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (20 mL × 3). The combined organic layers were washed with sat. NaCl(aq) (20 mL), dried over Na2SO4 and concentrated. The obtained crude aldehyde without further purification was added to a solution of ylide (1-phenyl-2-(triphenylphosphoranylidene)ethanone) 31 as a colorless oil. [α]120D = −69.0 (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 7.75–7.72 (m, 2H), 7.54–7.51 (m, 7H), 7.48–7.40 (m, 20H), 7.32–7.26 (m, 6H), 7.2–7.16 (m, 3H), 6.63 (dd, J = 15.5 Hz, J = 15.2 Hz, 1H), 6.45 (d, J = 15.2 Hz, 1H), 4.37 (p, J = 6.4 Hz, 1H), 1.20 (d, J = 6.4 Hz, 3H); 13C NMR (CDCl3, 75 MHz) δ 190.7, 151.0, 144.7, 137.8, 132.5, 128.9, 128.4, 127.9, 127.2, 122.1, 87.5, 70.2, 22.4; HRMS-ESI (m/z) calc'd for [M + Na]+ (C30H26NaO2), 441.1830, found 441.1824.

General procedure for cyclopropanation reactions. Condition A. In a flame-dried round-bottomed flask, a solution of sodium hydride (0.42 mmol), trimethylsulfoxonium iodide (0.42 mmol), and DMF (1 mL) was stirred at room temperature for 45 min under an atmosphere of nitrogen. The reaction mixture was cooled to −30 °C, added with a solution of enone (2a–f, 8, 9, 10, or 11, 0.21 mmol) in DMF (1 mL), stirred for another 16 h at −30 °C, quenched with saturated NH4Cl(aq) (3 mL), and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (1% EtOAc/hexanes) to give the cyclopropyl ketones.

Condition B. In a flame-dried flask, a solution of sodium hydride (0.42 mmol), trimethylsulfoxonium iodide (0.42 mmol), and DMF (0.2 mL) was stirred at room temperature for 45 min under an atmosphere of nitrogen. The reaction mixture was diluted with THF (1 mL), cooled to −30 °C, added with a solution of enone (11 or 12, 0.21 mmol) in THF (1 mL), stirred for another 16 h at −30 °C, quenched with saturated NH4Cl(aq) (3 mL), and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (1% EtOAc/hexanes) to give the cyclopropyl ketones.

Condition C. Condition C was the same as condition B except that the reactions were performed at 25 °C during the whole process (5 h).

(S,E)-1-Phenyl-4-(trityloxy)pent-2-en-1-one (2f). DIBAL-H (1 M in hexane, 5.9 mL, 5.90 mmol) was added to a solution of (S)-ethyl-2-(trityloxy)propanoate (1f, 1.9 g, 5.27 mmol) and diethyl ether (30 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate(aq) (30 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with sat. NaCl(aq) (30 mL), dried over Na2SO4 and concentrated. The obtained crude aldehyde without further purification was added to a solution of ylide (1-phenyl-2-(triphenylphosphoranylidene)ethanone) as a yellowish oil. [α]120D = −81% over two steps) as a colorless oil.

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3.85 (ddd, J = 4.3 Hz, J = 6.3 Hz, J = 12.5 Hz, 1H), 2.73 (ddd, J = 4.5 Hz, 4.7 Hz, 12.5 Hz, 1H), 1.73 (ddd, J = 4.3 Hz, J = 3.6 Hz, 5.5 Hz, 12.5 Hz, 1H), 1.40 (ddd, J = 3.5, J = 6.0 Hz, J = 8.9 Hz, 1H), 1.24 (d, J = 6.0 Hz, 3H), 1.09 (ddd, J = 3.5, J = 6.0 Hz, J = 8.9 Hz, 1H), 0.88 (s, 9H), 0.067 (s, 3H), 0.05 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 200.2, 138.1, 132.6, 128.5, 128.0, 67.6, 33.8, 25.8, 24.2, 20.1, 18.1, 15.0, −4.3, −4.7; HRMS-ESI (m/z) calcld for [M + Na]+ (C17H26BrO2Si), 369.0885, found 369.0891.

((1R,2R)-2-((S)-1-Hydroxyethyl)cyclopropyl)(phenyl)methanone (5). A solution of hydrogen fluoride pyridine (250 μL) was added to a mixture of 3b and 4b (51.0 mg, 0.17 mmol) and acetonitrile (250 μL) at room temperature. The reaction mixture was stirred at 25 °C for 12 h, quenched with sat. NaHCO3(aq) (4 mL), and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with sat. CuSO4(aq) and acetonitrile (250 °C). The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature. The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature, and the crude product was purified by column chromatography (SiO2, EtOAc/hexanes, 1:9, Rf 0.6) to give 8 (1.41 g, 3.81 mmol, 68% over two steps) as a yellowish oil. [α]20D +0.9 (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 7.80 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.06 (t, J = 1.0 Hz, 2H), 4.57 (dq, J = 1.6 Hz, J = 6.6 Hz, 1H), 1.32 (d, J = 6.6 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 189.7, 150.5, 137.9, 133.7, 132.0, 129.8, 128.5, 128.1, 69.6, 33.4, 23.1, 22.5, 15.5; HRMS-ESI (m/z) calcld for [M + Na]+ (C17H25NNaO3Si), 369.0885, found 369.0891.

((R)-Methyl-5-(tert-butyldimethylsilyloxy)-8-oxo-8-phenyloct-6-enoate (9). (R)-Methyl-5-((tert-butyldimethylsilyloxy)oxy)-6-oxohexanoate (500 mg, 1.25 mmol) was added to a solution of ylide (1-phenyl-2-(triphenylphosphoranylidene)ethanone) (618.2 mg, 1.62 mmol), benzoic acid (15 mg, 0.12 mmol), and toluene (10 mL) at room temperature under a N2 atmosphere. The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature, and the crude product was purified by column chromatography (SiO2, EtOAc/hexanes, 1:9, Rf 0.63) to give 9 (487 mg, 0.97 mmol, 77% over two steps) as a yellowish oil. [α]20D +22.8 (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 7.78–7.76 (m, 2H), 7.69–7.64 (m, 4H), 7.54–7.52 (m, 1H), 7.45–7.32 (m, 8H), 6.97 (d, J = 15.4 Hz, 1H), 6.92 (d, J = 15.4 Hz, 1H), 4.51 (q, J = 5.0 Hz, 1H), 3.62 (s, 3H), 2.20 (t, J = 5.0 Hz, 2H), 1.63–1.55 (m, 4H), 1.12 (s, 9H); 13C NMR (CDCl3, 75 MHz) δ 190.4, 173.6, 149.6, 137.8, 135.9, 133.6, 132.7, 130, 129.8, 128.5, 127.3, 127.1, 72.6, 51.5, 36.1, 33.9, 27.0, 19.7, 19.4; HRMS-ESI (m/z) calcld for [M + Na]+ (C17H25NNaO3Si), 523.2281, found 523.2283.

(S,E)-1-(4-Bromophenyl)-4-((tert-butylidimethylsilyloxy)pent-2-en-1-one (8). Dibal-H (1 M in hexane, 6.3 mL, 0.6 mmol) was added to a solution of (S)-ethyl-2-((tert-butylidimethylsilyloxy)propionate (1b, 1.3 g, 5.59 mmol) and diethyl ether (25 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium tertartrate (25 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (30 mL × 3). The obtained crude aldehyde without further purification was added to a solution of ylide (1-(4-bromophenyl)-2-(triphenylphosphoranylidene)ethanone) (3.34 g, 7.27 mmol), benzoic acid (68 mg, 0.56 mmol), and toluene (25 mL) at room temperature under a N2 atmosphere. The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature, and the crude product was purified by column chromatography (SiO2, EtOAc/hexanes, 1:9, Rf 0.6) to give 10 (1.7 g, 6.99 mmol) as a yellowish oil. [α]20D +5.64 (c 1.0, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 7.94–7.92 (m, 2H), 7.57–7.43 (m, 3H), 7.11 (dd, J = 1.0 Hz, J = 15.0 Hz, 1H), 7.03 (dd, J = 3.5 Hz, J = 15.0 Hz, 1H), 5.85–5.74 (m, 1H), 5.12–5.06 (m, 2H), 4.94–4.84 (m, 1H, 3.36 (tt, J = 1.1 Hz, J = 6.1 Hz, 2H), 0.95 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 190.5, 150.5, 137.9, 133.7, 132.8, 128.6, 123.9, 117.9, 71.8, 42.0, 25.8, 25.7, 18.2, −4.6, −4094 DOI: 10.1021/acsomega.7b00663

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−4.8; HRMS-ESI (m/z) calcd for [M + H]+ (C_{19}H_{29}O_{2}Si), 317.1937, found 317.1938.

(S,E)-5-((tert-Butyldimethylsilyl)oxy)hex-3-en-2-one (11). DIBAL-H (1 M in hexane, 12.1 mL, 12.04 mmol) was added to a solution of (S)-ethyl-2-((tert-butyldimethylsilyl)oxy)propiionate (1b, 2.5 g, 10.75 mmol) and diethyl ether (50 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate(aq) (50 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with sat. NaCl(aq) (30 mL), dried over Na_{2}SO_{4} and concentrated. The obtained crude aldehyde without further purification was added to a solution of ylide (1-(triphenylphosphoranylidene)-2-propanone 34 (4.5 g, 14.1 mmol), benzoic acid (79 mg, 0.64 mmol), and toluene (30 mL) at −78 °C, quenched with sat. potassium sodium tartrate(aq) (1.3 g, 4.80 mmol, 75% over two steps) as a colorless oil. [α]_{D}^{20} +3.02 (c 1.27, CHCl_{3}); 1^H NMR (CDCl_{3}, 300 MHz) δ 6.78 (dd, J = 1.1 Hz, J = 4.1 Hz, J = 15.7 Hz, 1H), 6.25 (dd, J = 1.4 Hz, J = 15.7 Hz, 1H), 5.87–5.78 (m, 1H), 5.07–4.95 (m, 2H), 4.46 (p, J = 1.65 Hz, 1H), 2.65 (dd, J = 0.7 Hz, 7.5 Hz, 2H), 2.40–2.32 (m, 2H), 1.26 (dd, J = 1.1 Hz, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); 13C NMR (CDCl_{3}, 75 MHz) δ 199.8, 149.8, 137.1, 126.9, 115.1, 67.8, 39.7, 28.0, 25.8, 23.6, 18.2, −4.9; HRMS-APCI (m/z) calcd for [M + H]+ (C_{17}H_{25}O_{2}Si), 269.1624, found 269.1620.

(S,E)-6-((tert-Butyldimethylsilyl)oxy)-1-phenylhept-4-en-3-one (14). DIBAL-H (1 M in hexane, 7.2 mL, 7.22 mmol) was added to a solution of (S)-ethyl-2-((tert-butyldimethylsilyl)oxy)propiionate (1b, 1.5 g, 6.45 mmol) and diethyl ether (30 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate(aq) (30 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (20 mL × 3). The combined organic layers were washed with sat. NaCl(aq) (30 mL), dried over Na_{2}SO_{4} and concentrated. The obtained crude aldehyde without further purification was added to a solution of ylide (1-(triphenylphosphoranylidene)-4-phenyl-butan-2-one) 12 (3.42 g, 8.37 mmol), benzoic acid (79 mg, 0.64 mmol), and toluene (30 mL) at room temperature under a N_{2} atmosphere. The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature, and toluene was removed under reduced pressure. The crude product was purified by column chromatography (SiO_{2}, EtOAc/hexanes, 1:19, Rf 0.83) to give 14 (1.56 g, 4.90 mmol, 76% over two steps) as a colorless oil. [α]_{D}^{20} +2.02 (c 1.025, CHCl_{3}); 1^H NMR (CDCl_{3}, 300 MHz) δ 7.10–7.17 (m, 7.5H), 6.78 (dd, J = 4.2 Hz, J = 15.7 Hz, 1H), 6.35 (dd, J = 1.7 Hz, J = 6.6 Hz, 3H), 4.50–2.85 (m, 4H), 1.26 (dd, J = 6.5 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); 13C NMR (CDCl_{3}, 75 MHz) δ 199.7, 150.8, 128.0, 67.7, 27.2, 25.7, 23.6, 18.1, −4.9; HRMS-APCI (m/z) calcd for [M + H]+ (C_{18}H_{25}O_{2}Si), 319.2093, found 319.2094.

(S,E)-8-((tert-Butyldimethylsilyl)oxy)nona-1,6-dien-5-one (13). DIBAL-H (1 M in hexane, 7.2 mL, 7.22 mmol) was added to a solution of (S)-ethyl-2-((tert-butyldimethylsilyl)oxy)propiionate (1b, 1.5 g, 6.45 mmol) and diethyl ether (30 mL) at −78 °C. The resulting solution was stirred for 6 h at −78 °C, quenched with sat. potassium sodium tartrate(aq) (30 mL), and warmed to room temperature. Two layers were separated, and the aqueous layer was extracted with diethyl ether (20 mL × 3). The combined organic layers were washed with sat. NaCl(aq) (30 mL), dried over Na_{2}SO_{4} and concentrated. The obtained crude aldehyde without further purification was added to a solution of ylide (1-(triphenylphosphoranylidene)-2-propanone 10 (3.0 g, 9.43 mmol), benzoic

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acid (88 mg, 0.72 mmol) and toluene (30 mL) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C and cooled to room temperature, and toluene was removed under reduced pressure. The crude product was purified by column chromatography (SiO2, EtOAc/hexanes, 1:10, Rf 0.70) to give 1S (11.1 g, 5.43 mmol, 75% over two steps) as a colorless oil. 1H NMR (CDCl3, 300 MHz) δ 7.38–7.25 (m, 5H), 6.70 (dd, J = 6.2 Hz, J = 16.7 Hz, 1H), 6.24 (dd, J = 1.2 Hz, J = 16.7 Hz, 1H), 4.51 (dd, J = 11.9 Hz, J = 30.4 Hz, 2H), 4.14 (dq, J = 1.2 Hz, J = 6.5 Hz, 1H), 2.27 (s, 3H), 1.35 (s, J = 6.5 Hz, 3H). 13C NMR (CDCl3, 75 MHz) δ 198.5, 148.1, 138.1, 130.3, 128.5, 127.7, 127.6, 74.1, 70.8, 27.2, 21.7; HRMS-APCI (m/z) calcld for [M + H]+ (C18H28BrO2Si), 383.1042, found 383.1035.

(4-Bromophenyl)((1R,2R)-2-((S)-1-((tert-butyldimethylsiloxy)ethyl)cyclopropyl)methanone (8C). The reaction was carried out according to the general procedure (condition A): starting with enone 8 (100 mg, 0.42 mmol), compound 8C (149.0 mg, 92%, dr = 9) was produced after column chromatography (SiO2, EtOAc/hexanes, 1:19, Rf 0.62) as a colorless liquid. 1H NMR (CDCl3, 300 MHz) δ 7.85 (br, J = 4.3 Hz, 3H), 4.48 (s, J = 8.1 Hz, 1H), 2.57 (d, J = 8.1 Hz, 2H), 2.37 (J = 6.2 Hz, 1H), 1.85 (s, 3H), 0.85 (s, 3H), 0.05 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 199.3, 136.7, 131.8, 129.6, 119.0, 118.3, 112.7, 76.8, 54.2, 28.8, 10.3, 18.0, 14.2; HRMS-ESI (m/z) calcld for [M + Na]+ (C19H30NaO2Si), 383.1042, found 383.1037.

(1R,2R)-2-((S)-1-((tert-butyldimethylsiloxy)oxy)pentanoate (9C). The reaction was carried out according to the general procedure (condition A): starting with enone 9 (100.1 mg, 0.37 mmol), compound 9C (71.0 mg, 69%, dr = 7) was produced after column chromatography (SiO2, EtOAc/hexanes, 1:19, Rf 0.64) as a colorless liquid. 1H NMR (CDCl3, 300 MHz) δ 7.78–7.62 (m, 5H), 7.58–7.53 (m, 2H), 7.44–7.41 (m, 4H), 7.37–7.34 (m, 4H), 7.26–7.15 (m, 4H), 3.63 (s, 3H), 3.35 (dd, J = 5.4 Hz, J = 6.5 Hz, 1H), 6.08 (s, 1H), 1.90 (d, J = 6.2 Hz, 1H), 1.23 (d, J = 6.2 Hz, 1H), 0.95 (d, J = 3.5 Hz, 1H), 0.87 (s, 3H), 0.06 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 199.8, 136.5, 131.8, 129.6, 129.5, 128.2, 128.0, 127.8, 127.7, 127.6, 74.9, 37.3, 34.1, 29.7, 26.8, 26.6, 25.6, 23.1, 20.5; HRMS-ESI (m/z) calcld for [M + Na]+ (C19H30NaO2Si), 383.1042, found 383.1037.
Periodic acid (1.16 g, 5.08 mmol) was added to a solution of the major diastereomer were consistent with the reported data.21b

Conversion of 11C to 15C. A cold solution of hydrogen fluoride pyridine (0.74 mL) was added to a solution of 15C (120 mg, 0.49 mmol) and acetonitrile (0.75 mL). The reaction mixture was stirred at 25 °C for 12 h, quenched with sat. NaHCO3 (4 mL), and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with sat. CuSO4, added with sodium hydride (15.0 mg, 0.38 mmol), and DCM (10 mL) at 0 °C, stirred for another 30 min, and added with benzyl bromide (204 μL, 1.72 mmol) and tetraethylammonium iodide (13.0 mg, 0.040 mmol). The reaction mixture was stirred for another 3 h at 25 °C, quenched with water (3 mL), and extracted with diethyl ether (5 mL × 5). The combined organic layers were washed with sat. NaN3 and concentrated. The crude product was purified by column chromatography (SiO2, EtOAc/hexanes, 1:10, Rf 0.73) to give 15C (69.0 mg, 0.32 mmol, 64%, two steps).

tert-Butyl(((S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-yl)oxy)dimethylsilane (22). tert-Butyl(tert-butyl(dimethyl)silyl) chloride (5.25 g, 34.8 mmol) was added to a solution of enone (998.0 mg, 3.48 mmol) and diethyl ether (50 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 6 h, filtered through a pad of celite, and concentrated to give crude aldehyde (23), which was used in the next step without purification. 1-(Triphenylphosphoranylidene)propan-2-one34 (1.40 g, 4.40 mmol) and benzoic acid (31.0 mg, 0.25 mmol) were added to the solution of the above aldehyde in toluene (20 mL). The reaction mixture was stirred in an oil bath (100 °C) for 2 h and concentrated. The residue was separated by column chromatography (SiO2, EtOAc/hexanes, 1:19, Rf 0.76) to afford trans-enone 24 (576.0 mg, 2.26 mmol, 65%) as a colorless liquid. 1-{(1R,2R)-2-[(S)-1-Hydroxybut-3-en-1-yl]cyclopropyl}ethanone (19). In a flame-dried round-bottomed flask, a solution of sodium hydride (37.7 mg, 1.57 mmol), trimethylsulfoxonium iodide (346.0 mg, 1.57 mmol), and DMF (2 mL) was stirred at room temperature for 30 min under an atmosphere of nitrogen. The reaction mixture was diluted with THF (10 mL), added with a solution of enone 24 (200.0 mg, 0.78 mmol) in THF (20 mL), stirred for another 4 h at 25 °C, quenched with saturated NH4Cl (20 mL), and extracted with EtOAc (40 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (SiO2, EtOAc/hexanes, 1:49, Rf 0.81) to give cyclopropyl ketone 19 (120.0 mg, 0.44 mmol, 57%, anti/syn = 9:1). [α]D 20 = −13.0 (c 0.75, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 5.88–5.74 (m, 1H), 5.06–5.01 (m, 2H), 3.53 (q, J = 5.6 Hz, 1H), 2.28 (t, J = 6.6 Hz, 2H), 2.22 (s, 3H), 1.94 (ddd, J = 4.5 Hz, J = 4.4 Hz, J = 8.0 Hz, 1H), 1.54 (ddd, J = 5.0 Hz, J = 5.3 Hz, J = 7.3 Hz, J = 9.5 Hz, 1H), 1.17 (ddd, J = 3.8 Hz, J = 5.0 Hz, J = 9.5 Hz, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 208.3, 134.3, 113.7, 71.4, 42.9, 30.8, 30.3, 25.8, 25.4, 18.1, 14.2, −4.4, −4.6; HRMS-ESI (m/z) calcd for [M + Na]+ (C15H28NaO2Si), 291.1780, found 291.1783.

1-{((1R,2R)-2-[(S)-1-(Triphenylphosphoranylidene)propan-2-yl)oxy]but-3-en-1-yl}cyclopropyl)ethanone (25). A cold solution of hydrogen fluoride pyridine (0.74 mL) was added to a solution of 22 (250.0 mg, 1.42 mmol, 96%). [α]D 20 = −56.0 (c 1.1, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 5.84–5.69 (m, 1H), 5.08–5.02 (m, 2H), 3.16 (q, J = 6.3 Hz, 1H), 2.79 (s, 1H, br), 2.30–2.19 (m, 2H), 2.17 (s, 3H), 1.98–1.92 (m, 1H), 1.53–1.45 (m, 1H), 1.20–1.09 (m, 1H), 0.88–0.82 (m, 1H); 13C NMR (CDCl3, 75 MHz) δ 208.7, 134.1, 118.0, 72.3, 41.8, 30.8, 26.2, 14.8; HRMS-ESI (m/z) calcd for [M + Na]+ (C17H14NaO2Si), 297.1774, found 297.1785.

1-((1R,2R)-2-((S)-1-Benzoyloxyethyl)cyclopropyl)ethanone (15C). The reaction mixture was carried out according to the general procedure (condition C): starting with enone 15 (200.1 mg, 0.98 mmol), compound 15C (145.1 mg, 68%, dr = 1.4) was produced after column chromatography (SiO2, EtOAc/hexanes, 1:10, Rf 0.72) as a colorless liquid. [α]D 20 = −14.5 (c 1.03, CHCl3); 1H NMR (CDCl3, 300 MHz) δ 7.35–7.24 (m, 5H), 4.55 (dd, J = 9.1 Hz, J = 12.1 Hz, 2H), 3.26–3.13 (m, 1H), 2.22 (s, 3H), 1.96 (ddd, J = 4.4 Hz, J = 4.6 Hz, J = 8.1 Hz, 1H), 1.63 (m, 1H), 1.27 (d, J = 6.2 Hz, 3H), 1.25–1.18 (m, 1H), 1.02 (ddd, J = 3.9 Hz, J = 5.6 Hz, J = 8.2 Hz, 1H, minor), 0.84 (ddd, J = 3.9 Hz, J = 5.6 Hz, J = 8.3 Hz, 1H, major); 13C NMR (CDCl3, 75 MHz) δ 207.8, 138.7, 128.4, 127.6, 127.5, 75.7, 70.4, 30.4, 30.3, 27.3, 20.0, 13.8. The NMR spectroscopic data of the major diastereomer were consistent with the reported data.21b

(S,E)-5-((t-Butyl(dimethyl)silyl)oxy)octa-3,7-dien-2-one (24). Periodic acid (1.16 g, 5.08 mmol) was added to a solution of 22 (998.0 mg, 3.48 mmol) and diethyl ether (50 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 6 h.
was stirred at −78 °C for 1 h and for another 2 h at 25 °C, quenched with saturated NaHCO₃(aq) (5 mL) at 0 °C, and extracted with DCM (10 mL × 3). The combined organic layers were washed with sat. NaCl(aq) (10 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was further purified by column chromatography (SiO₂, EtOAc/hexanes, 1:19, Rf 0.76) to give 20 (57.0 mg, 0.27 mmol, 84%) as a colorless liquid. [α]D²⁰ = −64.1 (c 1.0, CHCl₃): ¹H NMR (CDCl₃, 500 MHz) δ 6.56 (dd, J = 17.2 Hz, J = 0.9 Hz, 1H), 6.39 (dd, J = 17.2 Hz, J = 1.3 Hz, 1H), 5.84 (dd, J = 10.4 Hz, J = 1.3 Hz, 1H), 5.79–5.71 (m, 1H), 5.08 (tt, J = 1.5 Hz, J = 17.1 Hz, 2H), 4.51 (dt, J = 6.3 Hz, J = 8.5 Hz, 1H), 2.44 (t, J = 6.5 Hz, 2H), 2.21 (s, 3H), 2.11 (ddd, J = 4.6 Hz, J = 4.8 Hz, J = 8.1 Hz, 1H), 1.65 (dd, J = 4.1 Hz, J = 5.4 Hz, J = 8.5 Hz, J = 9.0 Hz, 1H), 1.28 (ddd, J = 4.7 Hz, J = 5.1 Hz, J = 9.0 Hz, 1H), 0.89 (ddd, J = 4.4 Hz, J = 5.4 Hz, J = 9.0 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 207.4, 165.7, 132.8, 131.0, 128.4, 118.3, 75.3, 38.9, 30.7, 28.1, 26.7, 14.9; HRMS-ESI (z/m) calc for [M + Na]+ (C₄H₆O₈Na₂) 231.0997, found 231.0996.

(S)-6-[(1R,2R)-2-Acetylcyclopropyl]-5,6-dihydro-2H-pyran-2-one (26). The reaction mixture of 20 (110.0 mg, 0.52 mmol), Grubbs' catalyst, second generation (44.0 mg, 0.052 mmol), and DCM (16 mL) was heated to reflux for 12 h and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/hexanes, 1:32, Rf 0.81) to give 26 (67.0 mg, 0.37 mmol, 70%) as a viscous liquid. [α]D²⁰ = −126.0° (c 0.85, CHCl₃): ¹H NMR (CDCl₃, 300 MHz) δ 6.86 (dd, J = 4.2 Hz, J = 4.9 Hz, J = 9.7 Hz, 1H), 5.97 (dt, J = 9.8 Hz, J = 1.6 Hz, 1H), 3.88 (q, J = 7.8 Hz, 2H), 2.47–2.42 (m, 1H), 2.26 (s, 3H), 2.12 (ddd, J = 4.5 Hz, J = 5.2 Hz, J = 8.0 Hz, 1H), 1.73 (ddd, J = 4.0 Hz, J = 5.0 Hz, J = 8.7 Hz, J = 8.5 Hz, 1H), 1.23 (ddd, J = 4.5 Hz, J = 5.0 Hz, J = 9.0 Hz, 1H), 0.93 (dd, J = 4.3 Hz, J = 5.2 Hz, J = 8.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 206.9, 163.9, 144.9, 121.4, 79.3, 30.9, 29.4, 27.4, 26.0, 14.1; HRMS-ESI (m/z) calc for [M + H]+ (C₁₂H₁₄O₃) 181.0865, found 181.0864.

(S)-6-[(1R,2R)-2-Acetylcyclopropyl]tetrahydro-2H-pyran-2-one (17). The reaction mixture of 26 (60.0 mg, 0.33 mmol), palladium on activated charcoal (10% 36 mg), and EtOAc (6 mL) was stirred under an atmosphere of hydrogen at 25 °C for 12 h, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/hexanes, 2:3, Rf 0.82) to give 17 (59.0 mg, 0.32 mmol, 98%) as a light brown liquid. [α]D²⁰ = −71.2° (c 0.5, CHCl₃): ¹H NMR (CDCl₃, 300 MHz) δ 3.80 (ddd, J = 10.4 Hz, J = 7.7 Hz, J = 3.15 Hz, 1H), 2.60–2.55 (m, 1H), 2.47 (ddd, J = 17.87 Hz, J = 8.8 Hz, J = 7.0 Hz, 1H), 2.26 (s, 3H), 2.08 (ddd, J = 8.4 Hz, J = 4.6 Hz, J = 4.6 Hz, 1H), 2.03–1.99 (m, 1H), 1.98–1.93 (m, 2H), 1.91–1.88 (m, 1H), 1.84–1.74 (m, 1H), 1.70–1.60 (m, 1H), 1.22 (ddd, J = 9.0 Hz, J = 4.7 Hz, J = 4.7 Hz, 1H), 0.90 (ddd, J = 8.4 Hz, J = 6.2 Hz, J = 4.23 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 207.1, 171.2, 81.9, 30.9, 29.5, 28.5, 28.0, 26.1, 18.3, 14.0; HRMS-ESI (m/z) calc for [M + Na]+ (C₁₀H₁₄NaO₃) 205.0841, found 205.0846.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00663.

NMR spectra for all new compounds (PDF)
X-ray crystallographic data for 7 (CIF)
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