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Palladium-catalyzed sequential alkylation–alkenylation reactions: application towards the synthesis of polyfunctionalized fused aromatic rings

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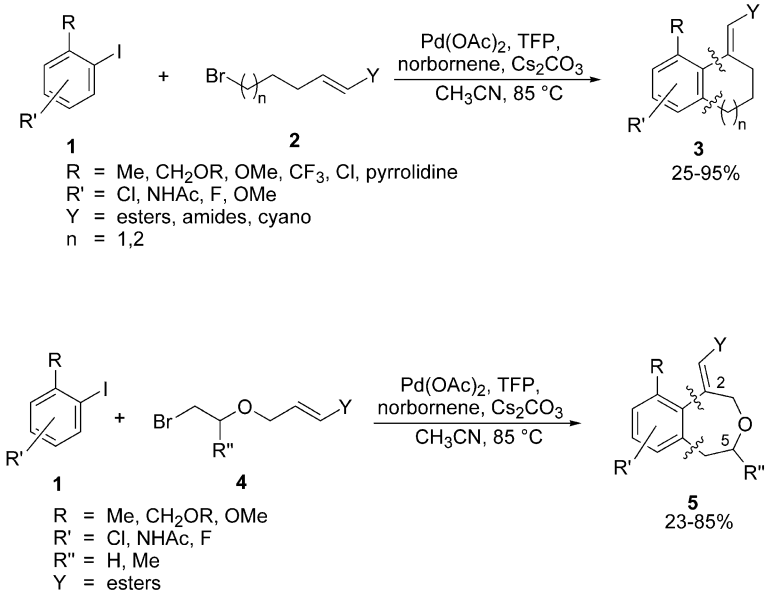
Abstract—The synthesis of polyfunctionalized fused aromatic carbo- and heterocycles from aryl iodides and bromoenoates via a tandem palladium-catalyzed aromatic substitution intramolecular Heck sequence is reported. Using $Pd(OAc)_2$ and tri-2-furylphosphine (TFP) in the presence of norbornene and Cs_2CO_3 in CH_3CN at 85 °C gave a variety of functionalized bi- and tricyclic fused aromatic rings in good yield.

1. Introduction

Carbocyclization is an important and valuable method for the synthesis of carbocyclic and heterocyclic compounds.[1] Over the past few years, palladium has emerged as one of the most reliable and versatile transition metals for the synthesis of fused aromatic carbocycles and heterocycles. In particular, the intramolecular Heck reaction has gained widespread acceptance due to its mild reaction conditions and functional group tolerance.[2]



Scheme 1. Synthesis of fused aromatic carbocycles and 2,5-disubstituted-4-benzoxepines.

Keywords: Palladium; Catalysis; Intramolecular Heck reaction; Norbornene; *ortho* Functionalization; Fused aromatic rings; Catellani reaction.
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Recently, we reported the synthesis of fused aromatic carbocycles from aryl iodides and difunctional acceptors[3] using modified Catellani[4] conditions. A variety of functional groups on the aryl moiety (**1**) were tolerated (Scheme 1)[3] and numerous six and seven-membered polyfunctionalized carbocycles (**3**) were synthesized using a variety of Heck acceptors in the difunctional acceptor **2**. This methodology was also extended towards the synthesis of 2-substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines (**5**) (Scheme 1).[5]

Although our previously reported methodology examined the effect of substitution on the aromatic moiety, the effect of substituents on the carbocyclic ring formed in this tandem process was not evaluated. The resulting substituted fused aromatic carbocyclic core is widely found in natural products exhibiting notable biological and pharmaceutical properties.[6] Having a diverse range of substituents on the carbocyclic moiety provides the opportunity for subsequent modification, thereby accessing a wide range of medicinally important compounds from relatively simple and accessible starting materials. We now report a further extension of our methodology for the synthesis of more highly substituted fused aromatic six- and seven-membered carbocycles **7** (Fig. 1).

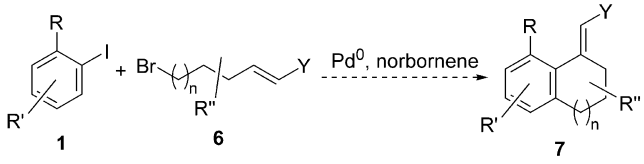


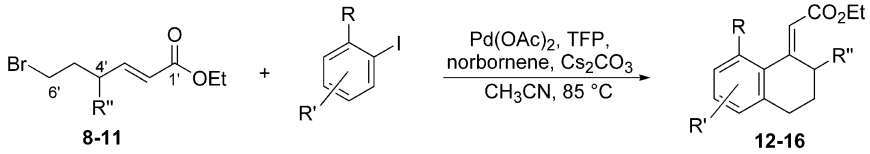
Figure 1.

2. Results and discussion

A number of functionalized bromoenoates (**6**) and aryl iodides were prepared and subjected to standard reaction conditions: $Pd(OAc)_2$ (10 mol%), TFP (20 mol%), norbornene (2 equiv), Cs_2CO_3 (2 equiv), CH_3CN, 85 °C.

We first examined the effect of substituents in the 4′ position of compounds **8–11** (Table 1). Using 2-iodotoluene and bromoenoate **8** (R″=Me), the desired product **12** was obtained in 81% yield (entry 1). While the 4′ hydroxyl derivative yielded decomposition products, protection of the 4′ hydroxyl group as a methoxymethyl (MOM) gave moderate to good yields for 2-iodotoluene and 4-fluoro-2-iodotoluene (entries 2, 3). Use of the tertiary protected methyl amine **10** gave **15** in 22% yield, while the secondary protected amine **11** provided the tricyclic lactam **16** in 45% yield. This result is interesting and insight into the observed product deserves further comment. The *trans* olefin

Table 1. Formation of six-membered carbocycles from 4′-substituted bromoenoates



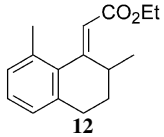
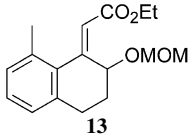
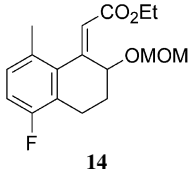
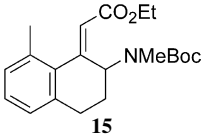
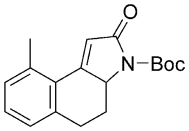
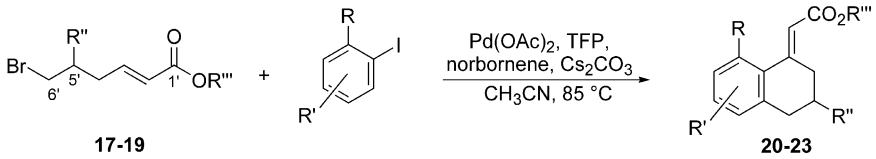
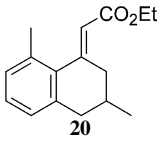
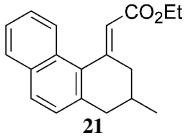
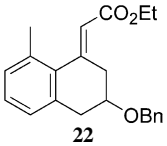
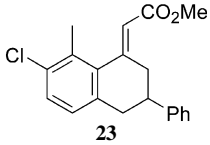
Entry	R″	Bromoenoate	Aryl iodide	Product	Isolated yield (%)
1	Me	**8**	2-Iodotoluene	 **12**	81
2	OMOM	**9**	2-Iodotoluene	 **13**	70
3	OMOM	**9**	4-Fluoro-2-iodotoluene	 **14**	40
4	NMeBoc	**10**	2-Iodotoluene	 **15**	22
5	NHBoc	**11**	2-Iodotoluene	 **16**	45

Table 2. Formation of six-membered carbocycles from 5′-substituted bromoenoates

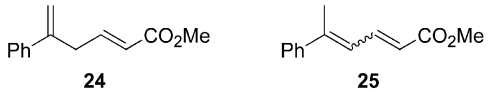


17-19 20-23

Entry	R″	Bromoenoate	Aryl iodide	Product	Isolated yield (%)
1	Me	**17**	2-Iodotoluene	 **20**	83
2	Me	**17**	1-Iodonaphthalene	 **21**	70
3	OBn	**18**	2-Iodotoluene	 **22**	58
4	Ph	**19**	2-Chloro-6-iodotoluene	 **23**	44

geometry of **11** prevents intramolecular attack of the nitrogen onto the carbonyl functionality, thus making the starting substrate unreactive toward lactamization. However, following the benzannulation catalytic cycle, the olefin geometry sets the ester functionality in a position that allows for lactamization to occur. Therefore, although this unexpected product was obtained in modest yield, this result is advantageous since three bonds and two additional rings were formed in a relatively simple one-pot process.

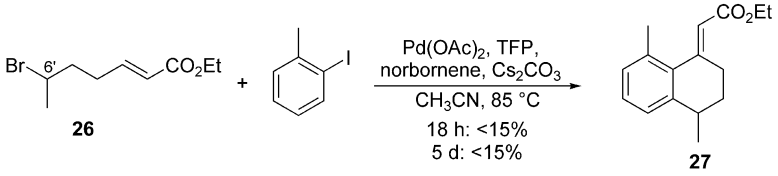
We next investigated the effect of substitution at the 5′ position of the bromoenoate (Table 2). For 2-iodotoluene and 1-iodonaphthalene, methyl substitution at the 5′ position gave the expected carbocycles **20** and **21** in 83 and 70% yields, respectively. Protection of the secondary alcohol using the larger benzyl protecting group afforded **22** in 58% yield, suggesting that steric effects play a role for substituents at the 5′ position. Reaction of **19** with 6-chloro-2-iodotoluene afforded the desired product **23** in 44% yield as well as 33% of elimination products **24** and **25**[7] as identified by ^{1}H NMR spectroscopy and MS (Fig. 2). While product **24** likely arises from the elimination of HBr promoted by Cs_2CO_3, elimination product **25** is presumably an isomerization product of **24**. We note that the low yield of products may be due to competing oxidative addition into the aryl chloride. However, we previously reported the reaction of 6-chloro-2-iodotoluene with bromoenoate **2** ($n=2$, Y = CO_2Et) gave the desired product in 86% yield,[3b] indicating that this process is not likely responsible for reducing the yields. Again, no benzannulation was observed when the unprotected alcohol was used, instead ethyl (2*E*,4*E*)-6-hydroxy-2,4-hexadienoate was isolated.[8]



24 25

Figure 2.

Under typical reaction conditions (for 18 h), use of the 6′ substituted bromoenoate **26** resulted in a very low yield (<15%) of cyclized product **27** (Scheme 2) as well as unreacted starting material. Attempts to increase conversion by increasing reaction time also failed. While disappointing, this result was not surprising since *ortho* insertion under these reaction conditions has been reported to be very slow for secondary alkyl halides.[4a,b]



26 27

Scheme 2. Formation of a six-membered carbocycle **27** from a 6′-substituted bromoenoate.

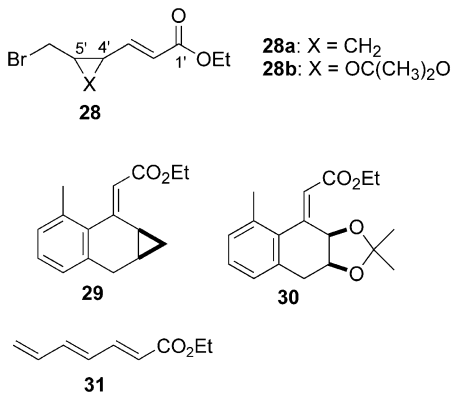


Figure 3. Tricyclic carbo- and heterocycles.

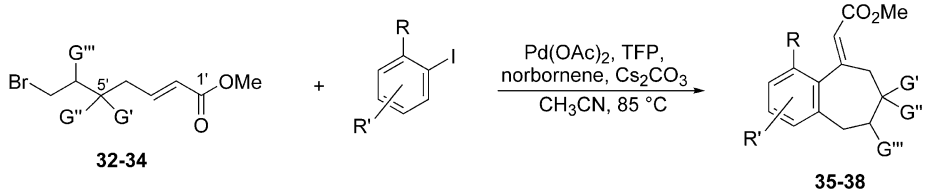
Successful cyclization reactions with substituents in the 4′ position and 5′ position led us to explore the potential of tethered substituents joining positions 4′ and 5′ with the objective of forming tricyclic products. Substrates **28** (**28a**: X=CH_2, **28b**: X=$OC(CH_3)_2O$) were subjected to the reaction conditions with different aryl iodides (Fig. 3). Unfortunately, low yields (<30%) of the cyclized products were obtained for all cases (Fig. 3).

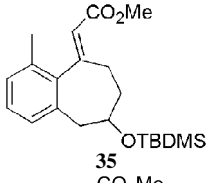
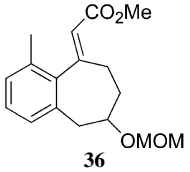
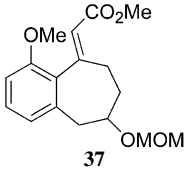
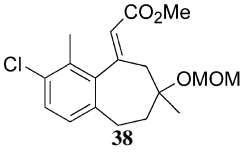
For X=CH_2 (**28a**), triene **31** was obtained in 25% yield in addition to the desired cyclized product **29**. The side-product could arise from insertion of Pd(0) into the carbon–bromine bond, followed by a cyclopropylcarbinyl–homoallyl rearrangement[9] and subsequent β-hydride elimination.

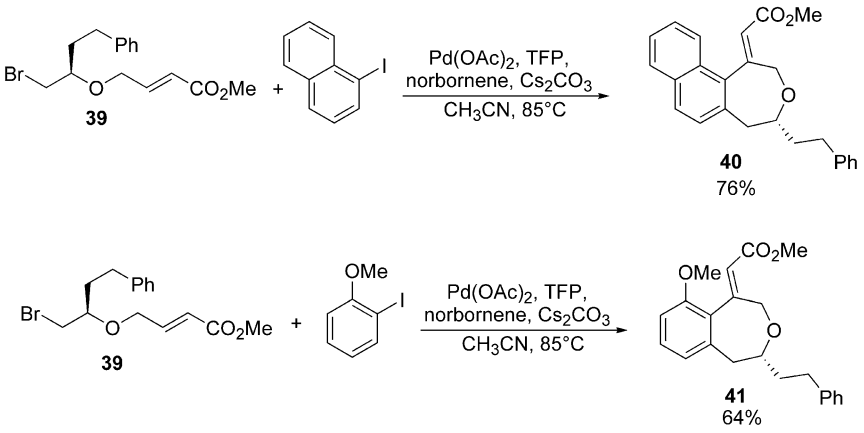
We next focused on the extension of reaction scope for substituted seven-membered rings (Table 3). A *tert*-butyldimethylsilylether (TBDMS) in the 6′ position (**32**) resulted in 54% yield of **35** when 2-iodotoluene was used. Use of the smaller MOM protected alcohol (**33**) provided **36** in a slightly higher yield of 61%, further supporting our steric arguments (vide supra). When **33** was reacted with 2-iodoanisole, a similar yield of 59% was obtained (**37**). Lastly, when bromoenoate **34** and 2-chloro-6-iodotoluene were subjected to the reaction conditions, carbocycle **38** was obtained in a low 33% yield.

Encouraged by the results obtained for the reactions of functionalized bromoenoates, we attempted additional benzannulation reactions using a substituted oxygenated bromoenoate. We reported that when R″=CH_3 (**4**) (Scheme 1), the reaction with 1-iodonaphthalene afforded the benzoxepine product in 72% yield.[5] We therefore synthesized the substituted oxygenated bromoenoate **39** and subjected it to our reaction conditions in the presence of different aryl iodides (Scheme 3). In general, good yields of the expected benzoxepines **40** (76% yield) and **41** (64% yield) were obtained.

Table 3. Formation of seven-membered carbocycles



Entry	G′, G″, G″	Bromoenoate	Aryl iodide	Product	Isolated yield (%)
1	H, H, OTBDMS	**32**	2-Iodotoluene	 **35**	54
2	H, H, OMOM	**33**	2-Iodotoluene	 **36**	61
3	H, H, OMOM	**33**	2-Iodoanisole	 **37**	59
4	Me, H, OMOM	**34**	2-Chloro-6-iodotoluene	 **38**	33



Scheme 3. Formation of 2,5-disubstituted-4-benzoxepines.

3. Conclusions

The palladium-catalyzed synthesis of highly substituted six- and seven-membered fused aromatic carbocycles, as well as 2,5-disubstituted-4-benzoxepines from aryl iodides and substituted oxygenated bromoenoates was described. A variety of functional groups along the chain on the bromoenoate (alkyl, OR, NR_2) are tolerated, affording bi- and tricyclic fused aromatic rings under relatively mild reaction conditions in moderate to good yields. Further manipulation of the functionalized compounds towards the synthesis of more complex as well as bioactive molecules is in progress.

4. Experimental

4.1. General

The following includes general experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for new compounds. Melting points were recorded using a Fisher–Johns melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained using either Varian Gemini 300 MHz or Varian Unity 400 MHz spectrometers. ^{1}H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ^{13}C spectra were referenced to solvent carbons (77.23 ppm for $CDCl_3$). No special notation is used for equivalent carbons. IR spectra were obtained using a Nicolet DX FT IR spectrometer as thin films on NaCl plates. Optical rotations were obtained using a Perkin–Elmer 243 B polarimeter. High-resolution mass spectra were obtained using a VG 70-250S (double focusing) mass spectrometer at 70 eV unless otherwise noted.

Diethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and acetonitrile were distilled under nitrogen from CaH_2 immediately prior to use. Neutral silica (Silicycle, Quebec, Canada) for flash chromatography was used as received. All reagents, metal catalysts and ligands were purchased from Sigma-Aldrich or Strem-Chemical Company and used as received unless otherwise noted. Reactions were performed under an atmosphere of nitrogen.

4.2. General procedure for the cyclization reaction

A round-bottom flask equipped with a condenser was charged with Cs_2CO_3 (0.400 mmol, 2 equiv), $Pd(OAc)_2$ (0.020 mmol, 10 mol%), tri-2-furylphosphine (0.040 mmol, 20 mol%), and norbornene (0.400 mmol, 2 equiv). A solution of bromoenoate (0.400 mmol, 2 equiv) and aryl iodide (0.200 mmol, 1 equiv) in CH_3CN (2 mL) was added. The resulting mixture was heated at 85 °C for 19 h, cooled and then quenched with saturated aqueous NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and filtered. Removal of the solvent gave a crude product that was purified by flash chromatography.

4.2.1. Ethyl (2*E*)-(2,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (12). Following the general procedure for the cyclization reaction using 2-iodotoluene and **8**, **12** was isolated as a pale yellow oil (37.1 mg, 81%) by flash chromatography using 5% EtOAc/hexanes as eluant. R_f=0.68 on silica gel (10% EtOAc/hexanes). IR (neat) ν= 2952, 1714, 1621, 1467, 1371, 1263, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–6.92 (m, 3H), 5.80 (s, 1H), 4.20 (q, 2H, J=7.1 Hz), 4.08 (m, 1H), 2.64–2.36 (m, 2H), 2.43 (s, 3H), 2.22–2.12 (m, 1H), 1.30 (t, 3H, J=7.1 Hz), 1.10 (d, 3H, J=6.8 Hz), 1.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.2, 142.1, 136.1, 135.1, 129.3, 127.8, 124.4, 117.8, 59.8, 32.2, 30.1, 29.4, 21.5, 20.8, 14.4; HRMS calcd for $C_{16}H_{20}O_2$ $[M]^+$ 244.1463, found 244.1463.

4.2.2. Ethyl (2*Z*)-[2-(methoxymethoxy)-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]acetate (13). Following the general procedure for the cyclization reaction using 2-iodotoluene and **9**, **13** was isolated as a colorless oil (41.0 mg, 70%) by flash chromatography using 10% EtOAc/hexanes as eluant. R_f=0.40 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2931, 1714, 1632, 1465, 1374, 1268, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–6.94 (m, 3H), 6.04 (t, 1H, J=3.8 Hz), 5.93 (s, 1H), 4.66 (dd, 2H, J= 15.0, 6.6 Hz), 4.22 (q, 2H, J=7.1 Hz), 3.16 (s, 3H), 3.06–2.95 (m, 1H), 2.80–2.68 (m, 1H), 2.47 (s, 3H), 2.22–2.06 (m, 2H), 1.31 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.2, 154.1, 139.5, 135.8, 134.0, 129.4, 128.1, 125.9, 119.3, 95.4, 69.3, 60.2, 55.4, 29.3, 25.4, 21.2, 14.3;

HRMS calcd for $C_{17}H_{22}O_4$ $[M]^+$ 290.1516, found 290.1518.

4.2.3. Ethyl (2*Z*)-[5-fluoro-2-(methoxymethoxy)-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]acetate (14). Following the general procedure for the cyclization reaction using 4-fluoro-2-iodotoluene and **9**, **14** was isolated as a colorless oil (24.5 mg, 40%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=0.30$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2935$, 1714, 1634, 1476, 1372, 1249, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12–6.84 (m, 2H), 6.04 (t, 1H, $J=3.8$ Hz), 5.93 (s, 1H), 4.64 (dd, 2H, $J=10.7$, 6.6 Hz), 4.23 (q, 2H, $J=7.1$ Hz), 3.13 (s, 3H), 3.06–2.60 (m, 2H), 2.43 (s, 3H), 2.36–1.95 (m, 2H), 1.32 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.3, 18.1, 18.2, 21.0, 28.5, 55.5, 60.4, 68.9, 95.7, 114.3, 114.6, 119.6, 126.0, 126.3, 130.0, 130.1, 130.8, 131.3, 135.1, 135.2, 150.6, 150.7, 153.7, 153.8, 156.8, 160.0, 166.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.88 (s, 1F); HRMS calcd for $C_{17}H_{21}FO_4$ $[M]^+$ 308.1421, found 308.1424.

4.2.4. Ethyl (2*Z*)-[2-[(*tert*-butoxycarbonyl)(methyl)-amino]-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]-acetate (15). Following the general procedure for the cyclization reaction using 2-iodotoluene (0.300 mmol scale) and **10**, **15** was isolated as a colorless oil (25.0 mg, 22%) by flash chromatography using 50% EtOAc/hexanes as eluant. $R_f=0.67$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=$ 2974, 1700, 1457, 1366 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–6.87 (m, 3H), 6.03 (s, 1H), 5.84 (brs, 1H), 4.20 (q, 2H, $J=7.1$ Hz), 2.66–2.56 (m, 2H), 2.55 (s, 3H), 2.48 (s, 3H), 2.44–2.32 (m, 2H), 1.50 (s, 9H), 1.29 (t, 3H, $J=$ 7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.3, 158.9, 149.7, 142.0, 136.4, 134.9, 130.1, 128.2, 124.8, 123.6, 79.6, 77.4, 60.4, 53.4, 30.2, 28.6, 26.7, 21.2, 14.5; HRMS calcd for $C_{17}H_{22}O_4$ $[M]^+$ 359.2101, found 359.2096.

4.2.5. *tert*-Butyl 9-methyl-2-oxo-2,3a,4,5-tetrahydro-3*H*-benzo[*e*]indole-3-carboxylate (16). Following the general procedure for the cyclization reaction using 2-iodotoluene and **11** (0.300 mmol scale), **16** was isolated as a colorless oil (41.0 mg, 45%) by flash chromatography using 25% EtOAc/hexanes as eluant. $R_f=0.36$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2977$, 1770, 1698, 1608 1318 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.04 (m, 3H), 6.21 (s, 1H), 4.62–4.54 (dd, 1H, $J=11.5$, 3.0 Hz), 3.14–3.05 (m, 2H), 2.94–2.82 (m, 1H), 2.48 (s, 3H), 1.83–1.62 (m, 1H), 1.59 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 169.8, 158.2, 149.9, 138.6, 138.5, 130.2, 129.8, 127.7, 127.2, 120.1, 83.1, 62.0, 30.2, 28.9, 28.4, 22.6; HRMS calcd for $C_{18}H_{21}NO_3$ $[M]^+$ 299.1523, found 299.1521.

4.2.6. Ethyl (2*E*)-(3,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (20). Following the general procedure for the cyclization reaction using 2-iodotoluene and **17**, **20** was isolated as a colorless oil (38.8 mg, 83%) by flash chromatography using 5% EtOAc/hexanes as eluant. $R_f=$ 0.59 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2951$, 1715, 1615, 1434, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–6.94 (m, 3H), 5.94 (t, 3H, $J=1.8$ Hz), 3.75 (s, 3H), 3.32 (dd, 1H, $J=16.7$, 6.2 Hz), 2.80–2.70 (m, 2H), 2.48 (s, 3H), 2.34 (dd, 1H, $J=14.9$, 10.7 Hz), 1.98–1.78 (m, 1H), 1.11 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.2, 155.4, 141.2, 136.0, 135.0, 129.8, 128.2, 125.8, 117.9, 51.4, 39.3, 37.5, 29.7, 22.3, 22.2; HRMS calcd for $C_{15}H_{18}O_2$ $[M]^+$ 230.1316, found 230.1306.

4.2.7. Ethyl (2*E*)-(2-methyl-2,3-dihydrophenanthren-4(1*H*)-ylidene)acetate (21). Following the general procedure for the cyclization reaction using 1-iodonaphthalene and **17**, **21** was isolated as a colorless oil (37.1 mg, 70%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=0.61$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=$ 2950, 1714, 1625, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, 1H, $J=8.4$ Hz), 7.81 (d, 1H, $J=7.9$ Hz), 7.80 (d, 1H, $J=8.2$ Hz), 7.71 (d, 1H, $J=8.2$ Hz), 7.46 (m, 2H), 7.22 (d, 1H, $J=8.2$ Hz), 6.27 (s, 1H), 3.77 (s, 3H), 3.53 (dd, 1H, $J=16.3$, 5.7 Hz), 2.91 (dd, 1H, $J=15.7$, 4.2 Hz), 2.83 (dd, 1H, $J=16.1$, 10.3 Hz), 2.51 (dd, 1H, $J=15.7$, 10.3 Hz), 2.20–1.95 (m, 1H), 1.16 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 154.5, 138.6, 133.3, 132.8, 130.1, 128.9, 128.5, 126.7, 126.6, 125.2, 125.1, 118.7, 51.1, 39.1, 37.1, 29.8, 21.7; HRMS calcd for $C_{17}H_{22}O_4$ $[M-OC_2H_5]^+$ 266.1306, found 266.1307.

4.2.8. Ethyl (2*E*)-[3-(benzyloxy)-8-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene]acetate (22). Following the general procedure for the cyclization reaction using 2-iodotoluene and **18**, **22** was isolated as a colorless oil (37.0 mg, 58%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=0.53$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2947$, 1711, 1620, 1433, 1361 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–6.96 (m, 8H), 5.97 (s, 1H), 4.59 (q, 2H, $J=11.9$ Hz), 3.87 (quintet, 1H, $J=$ 5.8 Hz), 3.74 (s, 1H), 3.55 (dd, 1H, $J=16.0$, 5.8 Hz), 3.25 (dd, 1H, $J=16.1$, 6.7 Hz), 2.99 (dd, 1H, $J=15.2$, 4.5 Hz), 2.84 (dd, 1H, $J=15.1$, 7.5 Hz), 2.46 (s, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.1, 152.7, 138.6, 137.5, 136.1, 134.8, 130.1, 128.5, 128.4, 127.7, 127.6, 126.6, 126.5, 119.2, 73.3, 70.4, 51.6, 36.9, 35.2, 22.2; HRMS calcd for $C_{21}H_{22}O_3$ $[M]^+$ 322.1562, found 322.1568.

4.2.9. Methyl (2*E*)-(7-chloro-8-methyl-3-phenyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (23). Following the general procedure for the cyclization reaction using 2-chloro-6-iodotoluene and **19**, **23** was isolated as a brown solid (28.5 mg, 44%) along with a mixture of elimination products **24** and **25** (26.5 mg, 33%,) by flash chromatography using 3→5% Et_2O/hexane as eluant. IR (neat) $\nu=$ 3034, 2953, 1714, 1619, 1458, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 7H), 6.95 (d, 1H, $J=$ 8.1 Hz), 5.93 (t, 1H, $J=1.8$ Hz), 3.73 (s, 3H), 3.48 (ddt, 1H, $J=17.1$, 6.9, 1.8 Hz), 3.32 (ddd, 1H, $J=17.1$, 10.5, 1.8 Hz), 3.03–2.75 (m, 3H), 2.53 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 153.8, 144.9, 139.2, 138.1, 134.2, 132.9, 128.9, 128.6, 127.0, 126.5, 126.2, 119.6, 51.2, 40.3, 37.5, 36.7, 19.0; HRMS calcd for $C_{20}H_{19}O_2Cl$ $[M]^+$ 326.1074, found 326.1064.

4.2.10. Ethyl (2*E*)-(4,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (27). Following the general procedure for the cyclization reaction using 2-iodotoluene and **26**, **27** was isolated as a colorless oil (5.51 mg, 12%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=$ 0.63 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2951$,

1715, 1618, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.00 (m, 3H), 5.92 (t, 1H, $J=1.7$ Hz), 4.21 (q, 2H, $J=7.1$ Hz), 3.33–3.22 (m, 1H), 3.14–3.04 (m, 1H), 2.76–2.68 (m, 1H), 2.47 (s, 3H), 2.10–1.82 (m, 2H), 1.31 (t, 3H, $J=7.1$ Hz), 1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.7, 21.8, 27.0, 29.5, 29.9, 33.9, 60.0, 118.4, 123.2, 128.2, 129.7, 134.9, 136.3, 146.2, 155.1, 167.1; HRMS calcd for $C_{16}H_{20}O_2$ $[M]^+$ 244.1468, found 244.1463.

4.2.11. Ethyl (2*E*)-(3-methyl-1,1a,7,7a-tetrahydro-2*H*-cyclopropa[*b*]naphthalen-2-ylidene)acetate (29). Following the general procedure for the cyclization reaction using 2-iodotoluene and **28a**, **29** was isolated as a colorless oil (12.5 mg, 26%) along with hepta-2,4,6-trienoic acid ethyl ester (**31**)[10] (7.61 mg, 25%) by flash chromatography using 10% EtOAc/hexanes as eluant and further purification by flash chromatography using 80% CH_2Cl_2/hexanes. $R_f=0.73$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2979$, 1704, 1613, 1466, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–6.87 (m, 3H), 5.89 (s, 1H), 4.22 (q, 2H, $J=7.1$ Hz), 3.75 (ddd, 1H, $J=8.2$, 8.2, 4.4 Hz), 3.16–2.94 (m, 2H), 2.43 (s, 3H), 1.80–1.66 (m, 1H), 1.32 (t, 3H, $J=7.1$ Hz), 0.92 (ddd, 1H, $J=8.0$, 8.0, 5.0 Hz), 0.43 (q, 1H, 4.9 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.9, 157.9, 136.7, 135.2, 134.2, 130.3, 128.5, 126.5, 117.2, 59.9, 30.7, 21.5, 17.3, 14.7, 14.4, 11.2; HRMS calcd for $C_{16}H_{18}O_2$ $[M]^+$ 242.1309, found 242.1307.

4.2.12. Ethyl (2*Z*)-(2,2,5-trimethyl-9,9a-dihydronaphtho[2,3-*d*][1,3]dioxol-4(3a*H*)-ylidene)acetate (30). Following the general procedure for the cyclization reaction using 2-iodotoluene and **28b**, **30** was isolated as a colorless oil (14.0 mg, 23%) by flash chromatography using 5:35:60 EtOAc/CH_2Cl_2/hexanes as eluant. $R_f=0.30$ on silica gel (5:35:60 EtOAc/CH_2Cl_2:hexanes). IR (neat) $\nu=2985$, 1715, 1646, 1372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–6.87 (m, 3H), 6.34 (d, 1H, $J=7.5$ Hz), 5.99 (s, 1H), 4.80 (dt, 1H, $J=7.3$, 2.6 Hz), 2.94 (dd, 1H, $J=15.4$, 2.3 Hz), 2.59 (dd, 1H, $J=15.3$, 2.9 Hz), 2.43 (s, 3H), 1.35 (s, 3H), 1.33 (t, 3H, $J=7.1$ Hz), 0.93 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.0, 150.3, 136.4, 135.6, 134.8, 129.6, 128.5, 126.5, 122.1, 109.6, 73.6, 72.4, 60.7, 34.0, 26.2, 25.2, 20.2, 14.4; HRMS calcd for $C_{18}H_{22}O_4$ $[M-CH_3]^+$ 287.1287, found 287.1283.

4.2.13. Methyl (2*E*)-(8-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)acetate (35). Following the general procedure for the cyclization reaction using 2-iodotoluene (0.300 mmol scale) and **32**, **35** was isolated as a colorless oil (58.0 mg, 54%) by flash chromatography using 5% EtOAc/hexanes as eluant. $R_f=0.75$ on silica gel (10% EtOAc/hexanes). IR (neat) $\delta=$ 2952, 1727, 1659, 1435, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.15 (s, 1H), 7.05 (brs, 1H), 5.89 (brs, 1H), 3.82 (brs, 3H), 3.76 (brs, 1H), 3.10–2.88 (m, 1H), 2.83–2.65 (m, 2H), 2.32 (s, 3H), 2.20–1.87 (m, 3H), 0.97 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) ν 166.9, 166.8, 161.9, 150.0, 143.5, 136.0, 133.3, 129.0, 127.7, 127.3, 120.0, 118.6, 71.7, 71.4, 71.2, 51.3, 45.3, 39.1, 37.6, 36.4, 35.0, 29.9, 29.1, 26.03, 25.98, 20.4, 18.3, 18.2, 0.2, −4.2, −4.3, −4.4, −4.5; HRMS calcd for $C_{21}H_{32}O_3Si$ $[M]^+$ 360.2125, found 360.2121.

4.2.14. Methyl (2*E*)-[8-(methoxymethoxy)-4-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene]acetate (36). Following the general procedure for the cyclization reaction using 2-iodotoluene (0.300 mmol scale) and **33**, **36** was isolated as a colorless oil (53.0 mg, 61%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=$ 0.31 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2947$, 1715, 1639, 1435, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (brs, 2H), 6.99 (brs, 1H), 5.74 (brs, 1H), 4.70 (brs, 2H), 4.00 (brs, 1H), 3.75 (brs, 3H), 3.37 (brs, 3H), 2.87 (d, 1H, $J=5.1$ Hz), 2.62–1.70 (m, 4H), 2.27 (brs, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 161.9, 161.5, 142.7, 141.6, 135.5, 134.8, 133.4, 129.2, 127.6, 127.1, 118.8, 95.0, 75.5, 72.5, 55.5, 51.3, 41.5, 38.7, 34.6, 32.4, 28.4, 27.1, 20.4; HRMS calcd for $C_{16}H_{18}O_2$ $[M]^+$ 290.1526, found 290.1518.

4.2.15. Methyl (2*E*)-[4-methoxy-8-(methoxymethoxy)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene]acetate (37). Following the general procedure for the cyclization reaction using 2-iodoanisole (0.300 mmol scale) and **33**, **37** was isolated as a colorless oil (54.0 mg, 59%) by flash chromatography using 25% EtOAc/hexanes as eluant. $R_f=$ 0.18 on silica gel (75% CH_2Cl_2/hexanes). IR (neat) $\nu=$ 2947, 1714, 1643, 1578, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, 1H, $J=8.1$ Hz), 6.83 (d, 1H, $J=8.2$ Hz), 6.78 (d, 1H, $J=7.3$ Hz), 5.88 (s, 1H), 4.68 (q, 2H, $J=6.8$ Hz), 3.90–3.84 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.38 (s, 3H), 3.25 (brs, 1H), 2.85 (d, 2H, $J=6.2$ Hz), 2.70 (brs, 1H), 2.05–1.96 (m, 1H), 1.85–1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 157.1, 155.4, 137.1, 131.0, 128.8, 122.4, 120.0, 110.2, 95.0, 74.1, 56.0, 55.5, 51.2, 40.0, 33.0, 27.9; HRMS calcd for $C_{17}H_{22}O_5$ $[M]^+$ 306.1467, found 306.1467.

4.2.16. Methyl (2*E*)-[3-chloro-7-(methoxymethoxy)-4,7-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene]acetate (38). Following the general procedure for the cyclization reaction using 2-chloro-6-iodotoluene and **34**, **38** was isolated as a colorless oil (35.0 mg, 33%) by flash chromatography using 10% EtOAc/hexanes as eluant. $R_f=$ 0.32 on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2936$, 1721, 1640, 1445, 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (brd, 1H, $J=8.0$ Hz), 6.90 (d, 1H, $J=8.0$ Hz), 5.75 (s, 1H), 4.88 (brs, 1H), 4.79 (brs, 1H), 4.55 (brs, 1H), 4.21 (q, 2H, $J=7.0$ Hz), 3.36 (brs, 3H), 3.11 (brt, 1H, $J=$ 13.1 Hz), 2.57 (brs, 1H), 2.29 (s, 3H), 2.20–2.03 (m, 1H), 2.00–1.71 (m, 2H), 1.43 (brs, 3H), 1.32 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 166.3, 154.9, 153.3, 145.3, 139.4, 133.4, 133.1, 132.0, 128.2, 128.2, 127.2, 127.0, 123.2, 91.2, 90.8, 80.1, 60.3, 60.1, 55.4, 41.1, 39.3, 30.6, 29.3, 28.5, 22.4, 17.8, 14.5; HRMS calcd for $C_{19}H_{25}ClO_4$ $[M]^+$ 352.1448, found 352.1441.

4.2.17. Methyl (2*Z*)-[(4*R*)-4-(2-phenylethyl)-4,5-dihydronaphtho[1,2-*d*]oxepin-1(2*H*)-ylidene]acetate (40). Following the general procedure for the cyclization reaction using 1-iodonaphthalene and **39**, **40** was isolated as slightly yellow oil (56.6 mg, 76%) by flash chromatography using 10% Et_2O/hexane as eluant. $[\alpha]_D^{25}$ −45.2 (*c* 1.0, $CHCl_3$); IR (neat) $\nu=3068$, 3027, 2949, 2858, 1711, 1215, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, $J=7.8$ Hz), 7.80 (m, 2H), 7.45 (m, 2H), 7.30–7.12 (m, 6H), 5.96 (t, 1H,

J=2.7 Hz), 5.07 (m, 2H), 3.79 (s, 3H), 3.37 (dd, 1H, J=14.1, 7.5 Hz), 2.66 (m, 3H), 1.67 (m, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 162.5, 141.8, 134.8, 133.2, 132.3, 130.7, 128.5, 128.3, 127.3, 126.6, 125.8, 125.1, 125.0, 118.8, 75.0, 69.2, 51.4, 37.9, 36.3, 32.1; HRMS calcd for $C_{25}H_{24}O_3$ $[M]^+$ 372.1725, found 372.1736.

4.2.18. Methyl (2*Z*)-[(4*R*)-9-methoxy-4-(2-phenylethyl)-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene]acetate (41). Following the general procedure for the cyclization reaction using 2-iodoanisole and **39**, **41** was isolated as a colorless oil (45.0 mg, 64%) by flash chromatography using 10% Et_2O/hexanes as eluant and further purification by flash chromatography using 0→10% acetone/CH_2Cl_2. $[\alpha]_D^{25}$ −76.9 (c 1.0, $CHCl_3$); IR (neat) ν=3027, 2965, 2838, 1710, 1269, 1172, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.14 (m, 6H), 6.88 (d, 1H, J=8.7 Hz), 6.70 (d, 1H, J=8.7 Hz), 6.00 (t, 1H, J=2.4 Hz), 5.08 (dd, 1H, J=18.9, 2.4 Hz), 4.82 (dd, 1H, J=18.9, 2.4 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.01 (dd, 1H, J=14.1, 6.3 Hz), 2.71 (m, 2H), 2.43 (dd, 1H, J=14.1, 3.0 Hz), 1.89 (m, 2H), 1.62 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 158.7, 156.2, 141.9, 137.4, 129.2, 128.5, 128.3, 126.7, 125.8, 121.3, 118.4, 110.2, 75.4, 67.6, 55.6, 51.2, 37.9, 35.4, 32.1; HRMS calcd for $C_{22}H_{24}O_4$ $[M]^+$ 352.1675, found 352.1684.

4.2.19. Ethyl (2*E*)-6-bromo-4-methylhex-2-enoate (8). A solution of carbon tetrabromide (289 mg, 0.870 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) was added dropwise to a 0 °C solution of triphenylphosphine (228 mg, 0.870 mmol, 1.5 equiv) and ethyl (*E*)-6-hydroxy-4-methyl-hex-2-enoate[11] (100 mg, 0.581 mmol, 1 equiv) in CH_2Cl_2 (5 mL). The reaction was stirred at 0 °C for 1 h, diluted with 10% EtOAc/hexanes (20 mL) and filtered through celite. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (118 mg, 87%) as a pale yellow oil. R_f=0.78 on silica gel (25% EtOAc/hexanes). IR (neat) ν=1186, 1272, 1458, 1652, 1715, 2968 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, 3H, J=6.8 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.90 (m, 1H), 2.57 (m, 1H), 3.35 (ABX$_2$, 2H, $\Delta\nu_{AB}$=29.3 Hz, J_{AB}=3.7 Hz, J_{AX}=6.4 Hz, J_{BX}=6.4 Hz), 4.17 (q, 2H, J=7.0 Hz), 5.84 (d, 1H, J=15.7 Hz), 6.89 (dd, 1H, J=15.6, 8.2 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 152.2, 121.3, 60.5, 38.7, 35.2, 31.3, 19.3, 14.4; HRMS calcd for $C_9H_{14}BrO_2$ $[M-H]^+$ 234.0253, found 234.0255.

4.2.20. 5-{[*tert*-Butyl(dimethyl)silyl]oxy}pent-1-en-3-ol (42). A −78 °C solution of oxalyl chloride (3.16 mL, 36.2 mmol, 1.15 equiv) in CH_2Cl_2 (100 mL) was added dropwise to a solution of dimethyl sulfoxide (5.14 mL, 72.5 mmol, 2.3 equiv) in CH_2Cl_2 (30 mL). The mixture was stirred at −78 °C for 15 min. A solution of 3-(*tert*-butyldimethylsilanyloxy)-propan-1-ol[12] (6.00 g, 31.5 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added dropwise and the reaction mixture was stirred for 1 h −78 °C. Triethylamine (12.3 mL, 88.3 mmol, 2.8 equiv) was added dropwise and the reaction mixture was stirred for 15 min at −78 °C then warmed to rt over 2 h. The reaction was quenched with water (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with 1% aqueous HCl, water, 5% aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude aldehyde was dissolved in THF (50 mL) and added dropwise to a −78 °C solution of vinylmagnesium bromide (47.2 mL, 47.2 mmol, 1.0 M in THF, 1.5 equiv). The mixture was stirred for 2 h at −78 °C then warmed to rt. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the aqueous layer was washed with EtOAc (3×). The combined organic extracts were washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (4.20 g, 60%) as a pale yellow oil. R_f=0.46 on silica gel (10% EtOAc/hexanes). IR (neat) ν=3424, 2955, 1472, 1256, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.78 (m, 1H), 5.26 (dt, 1H, J=17.3, 1.5 Hz), 5.08 (dt, 1H, J=10.4, 1.5 Hz), 4.33 (brs, 1H), 3.94–3.72 (m, 2H), 3.34 (d, 1H, J=3.6 Hz), 1.84–1.62 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 140.7, 114.1, 72.4, 68.9, 38.3, 25.9, 18.1, −5.5; HRMS calcd for $C_{11}H_{24}O_2Si$ $[M-C(CH_3)_3]^+$ 159.0836, found 159.0841.

4.2.21. Ethyl (2*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-hydroxyhex-2-enoate (43). To a mixture of **42** (1.00 g, 4.62 mmol, 1 equiv) and methyl acrylate (12.5 mL, 116 mmol, 25 equiv) in CH_2Cl_2 (20 mL) was added Grubbs' 2nd generation catalyst (200 mg, 0.231 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude oil was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.18 g, 89%) as a pale yellow oil. R_f=0.67 on silica gel (10% EtOAc/hexanes). IR (neat) ν=3480, 2955, 1722, 1659, 1471, 1258 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, 1H, J=15.5, 4.1 Hz), 6.10 (dd, 1H, J=15.6, 1.8 Hz), 4.52 (brs, 1H), 4.17 (q, 2H, J=7.1 Hz), 4.00–3.55 (m, 2H), 3.78 (brs, 1H), 1.92–1.61 (m, 2H), 1.27 (t, 3H, J=7.1 Hz), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.9, 150.0, 120.4, 71.1, 60.5, 42.9, 37.5, 26.0, 18.3, 14.4, −5.4; HRMS calcd for $C_{14}H_{28}O_4Si$ $[M-OEt]^+$ 243.1414, found 243.1416.

4.2.22. Ethyl (2*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methoxymethoxy)hex-2-enoate (44). To a 0 °C solution of **43** (500 mg, 1.73 mmol, 1 equiv) in CH_2Cl_2 (7 mL) was added dropwise diisopropylethylamine (910 μL, 5.20 mmol, 3 equiv), then chloromethyl methyl ether (500 μL, 8.67 mmol, 5 equiv) was added dropwise and the resulting mixture was warmed to rt and stirred for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was washed with EtOAc (3×). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (419 mg, 73%) as a pale yellow oil. R_f=0.52 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2954, 1724, 1659, 1472, 1368, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, 1H, J=15.7 Hz), 5.97 (d, 1H, J=15.7 Hz), 4.60 (q, 2H, J=6.7 Hz), 4.37 (q, 1H, J=6.3 Hz), 4.18 (q, 2H, J=7.1 Hz), 3.78–3.56 (m, 2H), 3.35 (s, 3H), 1.88–1.65 (m, 2H), 1.27 (t, 3H, J=7.1 Hz), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 148.2, 121.9, 95.1, 72.6, 60.6, 59.0, 55.8, 38.4, 26.1, 18.4, 14.4, −5.2; HRMS

calcd for $C_{16}H_{32}O_5Si$ $[M-C(CH_3)_3]^+$ 275.1322, found 275.1315.

4.2.23. Ethyl (2*E*)-6-hydroxy-4-(methoxymethoxy)hex-2-enoate (45). To a 0 °C solution of **44** (75.0 mg, 0.225 mmol, 1 equiv) in THF (2 mL) was added hydrogen fluoride–pyridine (70:30) (0.130 mL, 4.50 mmol, 20 equiv). The resulting mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for 1 h. The reaction was diluted with ether (10 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and filtered. Removal of the solvent gave a crude oil (38.1 mg, 78%) that was used without further purification. $R_f=0.13$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=3418$, 2951, 1714, 1659, 1446, 1370, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, 1H, $J=15.7$, 6.3 Hz), 6.02 (dd, 1H, $J=15.7$, 1.3 Hz), 4.64 (q, 2H, $J=6.7$ Hz), 4.46 (dt, 1H, $J=7.1$, 6.0 Hz), 4.21 (q, 2H, $J=7.1$ Hz), 3.86–3.70 (m, 2H), 3.41 (s, 3H), 1.94–1.78 (m, 2H), 1.30 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 147.1, 122.0, 95.0, 73.8, 60.6, 59.2, 55.9, 37.2, 14.2; HRMS calcd for $C_{10}H_{18}O_5$ $[M-OEt]^+$ 173.0813, found 173.0814.

4.2.24. Ethyl (2*E*)-6-bromo-4-(methoxymethoxy)hex-2-enoate (9). A solution of carbon tetrabromide (63.5 mg, 0.191 mmol, 1.1 equiv) in CH_2Cl_2 (500 μL) was added dropwise to a 0 °C solution of triphenylphosphine (50.2 mg, 0.191 mmol, 1.1 equiv) and **45** (38.0 mg, 0.174 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL). The reaction was stirred at 0 °C for 1 h, diluted with 10% EtOAc/hexanes (10 mL) and filtered through celite. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (40.0 mg, 83%) as a pale yellow oil. $R_f=0.71$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2951$, 1723, 1660, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, 1H, $J=15.8$, 6.6 Hz), 6.04 (dd, 1H, $J=15.8$, 0.7 Hz), 4.64 (dd, 2H, $J=18.1$, 6.9 Hz), 4.46 (dt, 1H, $J=7.0$, 5.5 Hz), 4.21 (q, 2H, $J=7.1$ Hz), 3.60–3.42 (m, 2H), 3.40 (s, 3H), 2.24–2.00 (m, 2H), 1.30 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.9, 146.3, 122.9, 94.9, 73.2, 60.6, 55.9, 37.9, 28.9, 14.2; HRMS-ESI calcd for $C_{10}H_{17}O_4NaBr$ $[M]^+$ 303.0202, found 303.0201.

4.2.25. *tert*-Butyl methyl(2-oxotetrahydrofuran-3-yl)-carbamate (46). To a 0 °C solution of 2-(*tert*-butoxycarbonylamino)-γ-butyrolactone[13] (500 mg, 2.50 mmol, 1 equiv) and iodomethane (464 μL, 7.45 mmol, 3 equiv) in DMF (15 mL) was added NaH (130 mg, 3.23 mmol, 60% dispersion in oil, 1.3 equiv). The resulting mixture was warmed to rt and stirred for 18 h. The reaction was diluted with EtOAc (15 mL) and quenched with water (15 mL). The aqueous layer was washed with EtOAc (3×) and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$ and filtered. Removal of the solvent gave a crude white solid (46.0 mg, 87%) that was used without further purification. The product is a mixture of rotamers in a 3:2 ratio. $R_f=0.49$ on silica gel (50% EtOAc/hexanes). IR (neat) $\nu=2977$, 1782, 1694, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major rotamer δ 4.84 (brt, 1H, $J=11.3$ Hz), 4.45 (brt, 1H, $J=9.1$ Hz), 4.23 (ddd, 1H, $J=9.1$, 9.1, 6.9 Hz), 2.87 (brs, 3H), 2.45 (brs, 2H), 1.47 (s, 9H); minor rotamer δ 4.45 (brt, 1H, $J=9.1$ Hz), 4.35 (brt, 1H, $J=9.4$ Hz), 4.23 (ddd, 1H, $J=9.1$, 9.1, 6.9 Hz), 2.95 (brs, 3H), 2.45 (brs, 2H), 1.47 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 174.3, 155.5, 154.4, 81.2, 80.6, 65.3, 57.1, 56.0, 34.0, 32.5, 29.8, 28.2, 26.3, 25.6; HRMS calcd for $C_{10}H_{17}NO_4$ $[M]^+$ 215.1165, found 215.1158.

4.2.26. Ethyl (2*E*)-4-[(*tert*-butoxycarbonyl)(methyl)-amino]-6-hydroxyhex-2-enoate (47). To a −78 °C solution of **46** (2.13 g, 9.89 mmol, 1 equiv) in THF (60 mL) was added diisobutylaluminum hydride (15.0 mL, 15.0 mmol, 1.0 M in hexanes, 1.5 equiv). The resulting mixture was stirred at −78 °C for 1.5 h. To a separate round-bottom flask was added NaH (415 mg, 10.4 mmol, 60% dispersion in oil, 1.05 equiv) and THF (40 mL). Triethyl phosphonoacetate (1.96 mL, 9.89 mmol, 1 equiv) was added dropwise at 0 °C then warmed to rt and stirred for 30 min. The reaction mixture was cooled to −78 °C and the diisobutylaluminum hydride solution of **46** was added via cannula. The resulting mixture was stirred at −78 °C for 10 min then warmed to rt and stirred for 18 h. The reaction was quenched with 10% aqueous HCl (60 mL) and the aqueous layer was washed with ether (3×). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 75% EtOAc/hexanes as eluant to yield the desired product (1.60 g, 56%) as a pale yellow oil. The product is a mixture of rotamers in a 3:1 ratio. $R_f=0.30$ on silica gel (50% EtOAc/hexanes). IR (neat) $\nu=3441$, 2978, 1694, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major rotamer δ 6.90 (dd, 1H, $J=16.1$, 3.5 Hz), 5.99–5.87 (m, 1H), 5.09 (brs, 1H), 4.21 (q, 2H, $J=7.1$ Hz), 3.74–3.38 (m, 2H), 2.67 (brs, 3H), 1.94–1.64 (m, 2H), 1.48 (s, 9H), 1.30 (t, 3H, $J=7.0$ Hz); minor rotamer δ 6.90 (dd, 1H, $J=16.1$, 3.5 Hz), 5.99–5.87 (m, 1H), 4.21 (q, 2H, $J=7.1$ Hz), 3.74–3.38 (m, 2H), 3.33 (brs, 1H), 2.67 (brs, 3H), 1.94–1.64 (m, 2H), 1.46 (s, 9H), 1.30 (t, 3H, $J=7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 146.9, 122.9, 121.2, 81.0, 60.9, 60.7, 58.8, 58.3, 51.6, 33.0, 29.6, 28.6, 28.5, 14.4; HRMS calcd for $C_{10}H_{17}NO_4$ $[M]^+$ 215.1165, found 215.1158.

4.2.27. Ethyl (2*E*)-6-bromo-4-[(*tert*-butoxycarbonyl)-(methyl)amino]hex-2-enoate (10). A solution of carbon tetrabromide (1.63 g, 4.93 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a 0 °C solution of triphenylphosphine (1.29 g, 4.93 mmol, 1.05 equiv) and **47** (1.35 g, 4.70 mmol, 1 equiv) in CH_2Cl_2 (50 mL). The reaction was stirred at 0 °C for 1 h, diluted with 10% EtOAc/hexanes (10 mL) and filtered through celite. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (49.0 mg, 30%) as an orange oil. $R_f=0.56$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2978$, 1694, 1454, 1392, 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, 1H, $J=15.9$, 4.9 Hz), 5.87 (dd, 1H, $J=15.9$, 1.9 Hz), 4.92 (brs, 1H), 4.21 (q, 2H, $J=7.1$ Hz), 3.35 (t, 2H, $J=6.0$ Hz), 2.74 (s, 3H), 2.35–2.15 (m, 2H), 1.48 (s, 9H), 1.30 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.2, 155.8, 145.6, 122.7, 80.6, 60.9, 55.0, 34.3, 29.9, 29.2, 28.5, 14.4; HRMS calcd for $C_{17}H_{22}O_4$ $[M-C(CH_3)_3]^+$ 293.0274, found 293.0262.

4.2.28. Ethyl (2*E*)-4-[(*tert*-butoxycarbonyl)amino]-6-hydroxyhex-2-enoate (48). To a −78 °C solution of 2-(*tert*-butoxycarbonylamino)-γ-butyrolactone[13] (2.00 g, 9.94 mmol, 1 equiv) in THF (60 mL) was added diisobutylaluminum hydride (15.0 mL, 15.0 mmol, 1.0 M in hexanes, 1.5 equiv). The resulting mixture was stirred at −78 °C for 1.5 h. To a separate round-bottom flask was added NaH (41.7 mg, 10.4 mmol, 60% dispersion in oil, 1.05 equiv) and THF (40 mL). Triethyl phosphonoacetate (1.96 mL, 9.89 mmol, 1 equiv) was added dropwise at 0 °C then warmed to rt and stirred for 30 min. The reaction mixture was cooled to −78 °C and the diisobutylaluminum hydride solution was added via cannula. The resulting mixture was stirred at −78 °C for 10 min then warmed to rt and stirred for 18 h. The reaction was quenched with 10% aqueous HCl and the aqueous layer was washed with ether (3×). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 75% EtOAc/hexanes as eluant to yield the desired product (1.68 g, 62%) as an orange oil. R_f=0.34 on silica gel (50% EtOAc/hexanes). IR (neat) ν=3350, 2979, 1698, 1504, 1366, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, 1H, J=15.6, 4.7 Hz), 5.97 (dd, 1H, J=15.9, 1.9 Hz), 5.03 (d, 1H, J=8.5 Hz), 4.56 (brs, 1H), 4.20 (q, J=14.2, 7.1 Hz), 3.71 (t, 2H, J=9.3 Hz), 3.07 (brs, 1H), 2.03–1.52 (m, 2H), 1.45 (s, 9H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.3, 156.2, 147.9, 121.0, 80.3, 60.6, 58.6, 48.5, 37.2, 28.3, 14.2; HRMS-ESI calcd for $C_{14}H_{25}NO_5Na$ $[M]^+$ 310.1648, found 310.1624.

4.2.29. Ethyl (2*E*)-6-bromo-4-[(*tert*-butoxycarbonyl)-amino]hex-2-enoate (11). A solution of carbon tetrabromide (890 mg, 2.69 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a 0 °C solution of triphenylphosphine (700 mg, 2.69 mmol, 1.05 equiv) and **48** (700 mg, 2.56 mmol, 1 equiv) in CH_2Cl_2 (30 mL). The reaction was stirred at 0 °C for 1 h then warmed to rt. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 50% EtOAc/hexanes as eluant to yield the desired product (436 mg, 51%) as an oil. R_f=0.49 on silica gel (25% EtOAc/hexanes). IR (neat) ν=3360, 2980, 1715, 1682, 1520 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, 1H, J=15.7, 5.5 Hz), 5.97 (dd, 1H, J=15.7, 1.2 Hz), 4.59 (brs, 1H), 4.50 (brs, 1H), 4.20 (q, J=7.1 Hz), 3.50–3.27 (m, 2H), 2.24–2.02 (m, 2H), 1.45 (s, 9H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.0, 154.9, 146.5, 121.7, 80.1, 60.6, 50.5, 37.4, 28.6, 28.3, 14.2; HRMS calcd for $C_{13}H_{23}BrNO_4$ $[M-C(CH_3)_3]^+$ 279.0103, found 279.0106.

4.2.30. *tert*-Butyl(dimethyl)[(2-methylpent-4-enyl)oxy]-silane (49). To a 0 °C solution of imidazole (420 mg, 6.11 mmol, 1.15 equiv) and 2-methyl-4-pentenol[14] (536 mg, 5.35 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added *tert*-butyldimethylsilyl chloride (930 mg, 6.16 mmol, 1.15 equiv). The mixture was stirred for 10 min at 0 °C then warmed to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using hexanes yielding the desired product (812 mg, 71%) as a as a pale yellow oil. NMR spectra are identical to its enatiomerically-enriched form previously reported.[15]

4.2.31. Methyl (2*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-5-methylhex-2-enoate (50). To a solution of **58** (300 mg, 1.40 mmol, 1 equiv) and methyl acrylate (3.15 mL, 35.0 mmol, 25 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (59.4 mg, 0.070 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (290 mg, 76%) as a colorless oil. R_f=0.52 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2954, 1729, 1657, 1436, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, 1H, J=15.6, 7.3 Hz), 5.78 (d, 1H, J=15.6 Hz), 3.69 (s, 3H), 3.40 (ABX, 2H, $\Delta\nu_{AB}$=25.2 Hz, J_{AB}=9.9 Hz, J_{AX}=5.5 Hz, J_{BX}=6.4 Hz), 2.33 (m, 1H), 1.98 (m, 1H), 1.75 (octet, 1H, J=6.7 Hz), 0.86 (s, 9H), 0.84 (s, 3H), 0.55 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.1, 148.5, 122.2, 77.5, 77.2, 76.9, 67.6, 51.4, 36.2, 35.5, 26.0, 18.4, 16.5, −5.3; HRMS calcd for $C_{14}H_{28}O_3Si$ $[M-OCH_3]^+$ 241.1631, found 241.1624.

4.2.32. Methyl (2*E*)-6-bromo-5-methylhex-2-enoate (17). To a solution of dibromotriphenylphosphorane (271 mg, 0.649 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL) was added a solution of **50** in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 1 h then diluted with CH_2Cl_2 (5 mL) and quenched with water (2 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% ether/hexanes as eluant to yield the desired product (108 mg, 86%) as a yellow oil. R_f=0.32 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2927, 1725, 1657, 1435, 1272, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (dt, 1H, J=15.5, 7.5 Hz), 5.89 (dt, 1H, J=15.5, 1.3 Hz), 3.73 (s, 3H), 3.35 (d, 2H, J=5.5 Hz), 2.38 (m, 1H), 2.18 (m, 1H), 2.00 (m, 1H), 1.04 (d, 3H, J=6.8 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.9, 146.4, 123.4, 51.7, 40.2, 37.5, 34.8, 18.9; HRMS calcd for $C_8H_{12}BrO_2$ $[M-H]^+$ 220.0098, found 220.0099.

4.2.33. Methyl (2*E*)-6-bromo-5-hydroxyhex-2-enoate (51). To a solution of 1-bromopent-4-en-2-ol[16] (700 mg, 4.24 mmol, 1 equiv) and methyl acrylate (9.88 mL, 106 mmol, 25 equiv) in CH_2Cl_2 (15 mL) was added Grubbs' 2nd generation catalyst (180 mg, 0.212 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (756 g, 80%) as a colorless oil. R_f=0.19 on silica gel (25% EtOAc/hexanes). IR (neat) ν=3444, 2952, 1715, 1652, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, 1H, J=15.6, 7.3 Hz), 5.69 (dt, 1H, J=15.6, 1.5 Hz), 3.99–3.92 (m, 1H), 3.74 (s, 3H), 5.2 (ABX, 2H, $\Delta\nu_{AB}$=45.4 Hz, J_{AB}=10.4, J_{AX}=3.8 Hz, J_{BX}=6.4 Hz), 2.55–2.47 (m, 2H), 2.35 (brs, OH); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 143.9, 124.3, 69.9, 51.8, 39.3, 38.0; HRMS calcd for $C_7H_{11}BrO_3$ $[M]^+$ 222.9966, found 222.9969.

4.2.34. Methyl (2*E*)-5-(benzyloxy)-6-bromohex-2-enoate (18). To a 0 °C solution of **51** (750 mg, 3.36 mmol, 1 equiv)

CH_2Cl_2 (7 mL) and cyclohexane (14 mL) was added benzyl trichloroacetimidate (94.0 μL, 5.04 mmol, 1.5 equiv) and trifluoromethanesulfonic acid (5 μL, 0.504 mmol, 15 mol%). The resulting mixture was stirred at 0 °C for 20 min then warmed to rt and stirred for 1 h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with 3% aqueous NaOH (10 mL). The organic layer was washed with water (3×), dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (71.3 mg, 83%) as a colorless oil. R_f=0.48 on silica gel (25% EtOAc/hexanes). IR (neat) ν= 2590, 1725, 1660, 1435, 1322, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 6.93 (dt, 1H, J= 14.8, 7.3 Hz), 5.94 (dd, 1H, J=15.7, 1.3 Hz), 4.61 (q, 2H, J=37.5, 11.5 Hz), 3.74 (s, 3H), 3.77–3.68 (m, 1H), 3.48–3.38 (m, 2H), 2.68–2.50 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.8, 144.1, 137.8, 129.0, 128.7, 128.2, 128.1, 124.2, 72.1, 51.8, 36.0, 34.0; HRMS-ESI calcd for $C_{14}H_{17}O_3NaBr$ $[M]^+$ 335.0253, found 335.0251.

4.2.35. [1-(Bromomethyl)but-3-enyl]benzene (52). To a 0 °C solution of 2-phenylpent-4-enol[17] (834 mg, 5.14 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added carbon tetrabromide (2.39 g, 7.20 mmol, 1.4 equiv) and triphenylphosphine (3.78 g, 14.4 mmol, 2.8 equiv). The mixture was stirred for 10 min at 0 °C then warmed to rt and stirred overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using hexane as eluant to yield the desired product (724 mg, 63%) as a colorless liquid. IR (neat) ν=3073, 3028, 2918, 2850, 1640, 149, 1451, 1233, 918; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.15 (m, 5H), 5.65 (m, 1H), 5.04 (m, 2H), 3.60 (dd, 2H, J=6.6, 2.7 Hz), 3.06 (m, 1H), 2.65 (m, 1H), 2.46 (m, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 141.7, 135.3, 128.4, 127.6, 127.0, 117.1, 47.3, 38.3, 38.0; HRMS calcd for $C_{11}H_{13}Br$ $[M]^+$ 224.0201, found 224.0210.

4.2.36. Methyl (2*E*)-6-bromo-5-phenylhex-2-enoate (19). To a solution of **52** (479 mg, 2.13 mmol, 1 equiv) and methyl acrylate (4.80 mL, 53.3 mmol, 25 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (93.0 mg, 0.110 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (381 mg, 63%) as a slightly pink oil. IR (neat) ν=3076, 3030, 2950, 2854, 1726, 1658, 1433, 1275, 1207; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 5H), 6.80 (m, 1H), 5.83 (dt, 1H, J=15.6, 1.2 Hz), 3.67 (s, 3H), 3.57 (m, 2H), 3.13 (m, 1H), 2.84 (m, 1H), 2.60 (m, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.5, 145.6, 140.7, 128.7, 127.5, 127.4, 123.1, 51.4, 46.7, 37.6, 36.4; HRMS calcd for $C_{11}H_{13}Br$ $[M-OMe]^+$ 251.0072, found 251.0077.

4.2.37. 4-Bromopentan-1-ol (53). To a mixture of 4-bromopentyl acetate[18] (2.00 g, 9.57 mmol, 1 equiv) in MeOH (70 mL) was added K_2CO_3 (1.45 g, 10.5 mmol, 1.1 equiv). The reaction was stirred at rt for 2 h then quenched with saturated aqueous NH_4Cl (70 mL). The aqueous layer was washed with EtOAc (3×) and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. Removal of the solvent gave a crude brown oil (1.40 g, 87%) that was used without further purification. NMR spectra match the previously reported data.[19]

4.2.38. Ethyl (2*E*)-6-bromohept-2-enoate (26). To a −78 °C solution of oxalyl chloride (402 μL, 10.5 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL) was added a solution of dimethyl sulfoxide (654 μL, 9.22 mmol, 2.2 equiv) in CH_2Cl_2 (15 mL). The mixture was stirred at −78 °C for 30 min. A solution of **53** (700 mg, 4.19 mmol, 1 equiv) in CH_2Cl_2 (45 mL) was then added dropwise and the reaction mixture was stirred at −78 °C for 15 min. Triethylamine (2.92 mL, 9.22 mmol, 5 equiv) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of (carbethoxymethylene)-triphenylphosphorane (2.92 g, 8.38 mmol, 2 equiv) in CH_2Cl_2 (45 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with water, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (716 mg, 73%) as an orange oil. R_f=0.70 on silica gel (10% EtOAc/hexanes). IR (neat) ν= 2982, 1721, 1656, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, 1H, J=15.5, 6.9 Hz), 5.86 (dt, 1H, J=17.1, 1.5 Hz), 4.17 (q, 2H, J=7.1 Hz), 4.13–4.02 (m, 1H), 2.52–2.27 (m, 2H), 2.05–1.83 (m, 2H), 1.72 (d, 3H, J=6.7 Hz), 1.28 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 147.1, 122.5, 60.6, 50.6, 39.5, 30.8, 26.9, 14.8; HRMS calcd for $C_9H_{15}BrO_2$ $[M-H]^+$ 234.0264, found 234.0255.

4.2.39. [2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)cyclopropyl]methanol (54). Diethylzinc (1.10 mL, 10.7 mmol, 2 equiv) and diiodomethane (865 μL, 10.7 mmol, 2 equiv) were added dropwise to a solution of (2*Z*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}but-2-en-1-ol[20] (1.00 g, 5.37 mmol, 1 equiv) in ether (100 mL). The reaction was stirred at rt for 24 h then quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was washed with ether (3×) and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (700 mg, 60%) as a colorless oil. R_f=0.64 on silica gel (25% EtOAc/hexanes). IR (neat) ν=3484, 2956, 1472, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (dd, 1H, J=11.5, 5.3 Hz), 3.95 (ddd, 1H, J=11.8, 5.6 Hz), 3.34–3.16 (m, 2H), 1.44–1.30 (m, 1H), 1.30–1.15 (m, 1H), 0.91 (s, 9H), 0.82–0.69 (m, 1H), 0.19 (q, 1H, J=5.3 Hz), 0.11 (d, 6H, J=5.3 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 63.9, 63.1, 25.8, 18.2, 17.3, 8.4, −5.3, −5.6; HRMS calcd for $C_{11}H_{24}O_2Si$ $[M]^+$ 217.1612, found 217.1623.

4.2.40. Ethyl (2*E*)-3-[2-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)cyclopropyl]acrylate (55). To a −78 °C solution of oxalyl chloride (440 μL, 5.07 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL) was added a solution of dimethyl sulfoxide (720 μL, 10.0 mmol, 2.2 equiv) in CH_2Cl_2 (15 mL). The

mixture was stirred at −78 °C for 30 min. A solution of **54** (1.00 g, 4.61 mmol, 1 equiv) in CH_2Cl_2 (45 mL) was then added dropwise and the reaction mixture was stirred at −78 °C for 15 min. Triethylamine (3.21 mL, 23.0 mmol, 5 equiv) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of (carbethoxymethylene)triphenylphosphorane (3.21 g, 9.22 mmol, 2 equiv) in CH_2Cl_2 (45 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with water, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.21 g, 92%) as an orange oil. R_f=0.61 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2955, 1718, 1645, 1472, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, 1H, J=15.4, 10.2 Hz), 5.92 (d, 1H, J=15.4 Hz), 4.17 (q, 2H, J=7.1 Hz), 3.83 (dd, 1H, J=11.3, 5.8 Hz), 3.59 (dd, 1H, J=11.3, 7.4 Hz), 1.75–1.67 (m, 1H), 1.56–1.47 (m, 1H), 1.27 (t, 3H, J=7.1 Hz), 1.17–1.09 (m, 1H), 0.89 (s, 9H), 0.71 (q, 2H, J=5.2 Hz), 0.05 (d, 6H, J=2.7 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.7, 150.1, 120.6, 62.8, 60.2, 26.1, 23.5, 19.5, 18.5, 14.6, 13.1, −5.1; HRMS calcd for $C_{15}H_{28}O_3Si$ $[M-C(CH_3)_3]^+$ 227.1106, found 227.1103.

4.2.41. 3 Ethyl (2*E*)-3-[2-(bromomethyl)cyclopropyl]-acrylate (28a). To a solution of dibromotriphenylphosphorane (2.24 mg, 5.06 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added a solution of **55** in CH_2Cl_2 (7 mL). The mixture was stirred at rt for 1 h then diluted with CH_2Cl_2 (25 mL) and quenched with water (15 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (904 mg, 92%) as a yellow oil. R_f=0.63 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2981, 1713, 1646, 1311, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, 1H, J=15.4, 9.9 Hz), 5.99 (d, 1H, J=15.4 Hz), 4.19 (q, 2H, J=7.1 Hz), 3.56 (dd, 1H, J=10.4, 7.7 Hz), 3.39 (dd, 1H, J=10.4, 8.2 Hz), 1.96–1.74 (m, 2H), 1.38–1.31 (m, 1H), 1.29 (t, 3H, J=7.1 Hz), 0.78 (q, 1H, J=5.8 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 147.2, 122.2, 60.5, 34.0, 23.8, 22.6, 17.2, 14.5; HRMS calcd for $C_9H_{13}BrO_2$ $[M]^+$ 232.0092, found 232.0099.

4.2.42. Ethyl (2*E*)-3-[3-(bromomethyl)oxiran-2-yl]acrylate (56). To a solution of 3-chloroperoxybenzoic acid (4.32 g, 18.0 mmol, 70% active, 3 equiv) in CH_2Cl_2 (30 mL) was added to a solution of ethyl (2*E*,4*E*)-6-bromohexa-2,4-dienoate[21] (1.28 g, 5.84 mmol, 1 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (1.34, 92%) as a colorless oil. R_f=0.28 on silica gel (10% EtOAc/hexanes). IR (neat) ν=2983, 1714, 1368, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, 1H, J=15.6, 7.0 Hz), 6.16 (d, 1H, J=15.8 Hz), 4.20 (q, 2H, J=7.1 Hz), 3.49–3.36 (m, 3H), 3.24 (ddd, 1H, J=5.6, 5.6, 1.8 Hz), 1.29 (t, 3H, 7.0 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.3, 142.4, 125.1, 61.1, 59.9, 58.2, 31.5, 14.7; HRMS calcd for $C_9H_{15}BrO_3$ $[M]^+$ 234.9965, found 234.9969.

4.2.43. Ethyl (2*E*)-6-bromo-4,5-dihydroxyhex-2-enoate (57). To a solution of **56** (100 mg, 4.25 mmol, 1 equiv) in THF (2 mL) was added 0.75 M aqueous H_2SO_4 (3.12 mL, 2.34 mmol, 5.5 equiv). The mixture was stirred at rt for 24 h then neutralized to pH 7 with 1.0 M aqueous $NaHCO_3$.The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product that was purified by flash chromatography using 50% EtOAc/hexanes as eluant to yield the desired product (76.9 mg, 71%) as a colorless oil. R_f=0.31 on silica gel (50% EtOAc/hexanes). IR (neat) ν=3427, 2981, 1698, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (dd, 1H, J=15.6, 4.8 Hz), 6.16 (d, 1H, J=15.8 Hz), 4.50 (t, 1H, J=3.6 Hz), 4.21 (q, 2H, J=7.1 Hz), 3.90 (dt, 2H, J=11.2, 4.8 Hz), 3.60–3.49 (m, 2H), 3.2 (brs, 2H), 1.30 (t, 3H, 7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 145.0, 122.9, 73.4, 72.3, 60.9, 35.4, 14.2; HRMS-ESI calcd for $C_{10}H_{18}O_4Br$ $[M]^+$ 253.0069, found 253.0061.

4.2.44. Ethyl (2*E*)-3-[5-(bromomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]acrylate (28b). To a solution of **57** (780 mg, 3.08 mmol, 1 equiv) in acetone (20 mL) was added iodine (160 mg, 0.616 mmol, 20 mol%). The reaction mixture was stirred at rt for 3 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The volatiles were evaporated and the resulting mixture was diluted with CH_2Cl_2 (25 mL). Saturated aqueous $Na_2S_2O_3$ (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (750 mg, 83%) as a colorless oil. R_f=0.64 on silica gel (25% EtOAc/hexanes). IR (neat) ν=2986, 1716, 1661, 1382 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dd, 1H, J=15.5, 5.5 Hz), 6.17 (dd, 1H, J=15.5, 1.0 Hz), 4.84 (t, 1H, 6.2 Hz), 4.51 (q, 1H, J=6.6 Hz), 4.22 (q, 2H, J=7.0 Hz), 3.27 (ABX, 2H, $\Delta\nu_{AB}$=28.1 Hz, J_{AB}=10.4 Hz, J_{AX}=6.7 Hz, J_{BX}=7.0 Hz), 1.53 (s, 3H), 1.40 (s, 3H), 1.30 (t, 1H, J=7.0 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 165.7, 141.0, 123.8, 109.9, 78.0, 76.6, 60.7, 30.1, 27.9, 25.4, 14.2; HRMS calcd for $C_{11}H_{17}BrO_4$ $[M-CH_3]^+$ 277.0073, found 277.0075.

4.2.45. {[1-(Bromomethyl)pent-4-enyl]oxy}(*tert*-butyl)dimethylsilane (58). To a 0 °C solution of 1-bromohex-5-en-2-ol[22] (1 g, 5.58 mmol, 1 equiv) in CH_2Cl_2 (35 mL) was added 2,6-lutidine (980 mg, 8.38 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.54 mL, 6.70 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for 2 h. The reaction was quenched with water (35 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic

layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.40 g, 88%) as a pale yellow oil. $R_f=0.91$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2956, 1642, 1472, 1256\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, 1H, $J=17.0$, 10.1, 6.5, 6.5 Hz), 5.07–4.94 (m, 2H), 3.85 (quintet, 1H, $J=$ 5.8 Hz), 3.38–3.27 (m, 2H), 2.16–2.06 (m, 2H), 1.82–1.55 (m, 2H), 0.90 (s, 9H), 0.08 (d, 6H, $J=6.0$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 138.4, 115.0, 71.5, 37.8, 34.9, 29.3, 26.0, 18.3, −4.2; HRMS calcd for $C_{12}H_{25}BrOSi$ $[M-C(CH_3)_3]^+$ 235.0156, found 235.0154.

4.2.46. Methyl (2*E*)-7-bromo-6-{[*tert*-butyl(dimethyl)-silyl]oxy}hept-2-enoate (32). To a solution of **58** (1.00 g, 3.42 mmol, 1 equiv) and methyl acrylate (7.71 mL, 85.6 mmol, 25 equiv) in CH_2Cl_2 (12 mL) was added Grubbs' 2nd generation catalyst (145 mg, 0.171 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (770 mg, 64%) as a pale orange oil. $R_f=0.79$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=2952$, 1732, 1435, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, 1H, $J=17.0$, 10.2, 6.5, 6.5 Hz), 5.07–4.94 (m, 2H), 3.85 (quintet, 1H, $J=5.8$ Hz), 3.39–3.26 (m, 2H), 2.22–2.00 (m, 2H), 1.82–1.53 (m, 2H), 0.90 (s, 9H), 0.08 (d, 6H, $J=6.0$ Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.2, 148.9, 121.4, 71.2, 51.7, 37.1, 33.8, 27.6, 25.9, 18.2, −4.3; HRMS calcd for $C_{14}H_{27}BrO_3Si$ $[M-CH_3]^+$ 335.0671, found 335.0678.

4.2.47. 6-Bromo-5-(methoxymethoxy)hex-1-ene (59). To a 0 °C solution of 1-bromohex-5-en-2-ol[22] (2.00 mL, 11.2 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added dropwise diisopropylethylamine (5.84 mL, 33.5 mmol, 3 equiv). Chloromethyl methyl ether (3.21 mL. 55.9 mmol, 5 equiv) was added dropwise and then the reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (2.12 g, 85%) as a colorless oil. $R_f=0.57$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=2947$, 1641, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dddd, 1H, $J=17.0$, 6.6, 3.5, 3.5 Hz), 5.08–4.93 (m, 2H), 4.69 (AB, 2H, $J=7.1$ Hz), 3.78–3.65 (m, 1H), 3.50–3.43 (m, 2H), 3.40 (s, 3H), 2.23–2.02 (m, 2H), 1.80–1.65 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 137.9, 115.4, 96.4, 76.4, 56.1, 36.0, 32.7, 29.4; HRMS calcd for $C_8H_{15}BrO_2$ $[M-OCH_3]^+$ 189.9988, found 189.9993.

4.2.48. Methyl (2*E*)-7-bromo-6-(methoxymethoxy)hept-2-enoate (33). To a solution of **59** (1.50 g, 6.72 mmol, 1 equiv) and methyl acrylate (15.1 mL, 168 mmol, 25 equiv) in CH_2Cl_2 (25 mL) was added Grubbs' 2nd generation catalyst (285 mg, 0.336 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (1.48 g, 78%) as a colorless oil. $R_f=0.25$ on silica gel (10% EtOAc/hexanes). IR (neat) $\nu=$ 2950, 1722, 1658, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dt, 1H, $J=15.5$, 6.9 Hz), 5.87 (d, 1H, $J=15.7$ Hz), 4.74 (AB, 1H, $J=7.0$ Hz), 4.68 (AB, 1H, $J=7.0$ Hz), 3.73 (s, 3H), 3.80–3.65 (m, 1H), 3.47 (d, 2H, $J=5.0$ Hz), 3.41 (s, 3H), 2.33 (septet, 2H, $J=8.2$ Hz), 3.80–3.65 (m, 1H), 2.28–1.79 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 167.1, 148.4, 121.7, 96.6, 76.4, 56.1, 51.6, 35.4, 32.0, 27.9; HRMS calcd for $C_{10}H_{17}BrO_4$ $[M-OCH_3]^+$ 249.0121, found 249.0126.

4.2.49. 5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylpentane-1,3-diol (60). A solution of *tert*-butyldimethylsilyl chloride (4.68 g, 31.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a solution of 3-methyl-1,3,5-pentanetriol (5.00 g, 37.3 mmol, 1.2 equiv) and triethylamine (5.19 mL, 37.3 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL). The mixture was stirred at rt overnight then quenched with water (25 mL). The aqueous layer was separated and extracted with EtOAc (3×). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using 50% EtOAc/hexanes as eluant to yield the desired product (3.73 g, 50%) as a pale yellow oil. $R_f=0.50$ on silica gel (50% EtOAc/hexanes). IR (neat) $\nu=3382$, 2929, 1470, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (brs, 1H), 4.02–3.77 (m, 4H), 3.61 (brs, 1H), 1.98–1.77 (m, 2H), 1.70–1.54 (m, 2H), 1.30 (s, 3H), 0.90 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 74.6, 60.7, 59.8, 42.5, 41.7, 26.6, 26.0, 18.2, −5.5; HRMS calcd for $C_{12}H_{28}O_3Si$ $[M]^+$ 249.1871, found 249.1885.

4.2.50. Ethyl (2*E*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-5-hydroxy-5-methylhept-2-enoate (61). To a −78 °C solution of oxayl chloride (579 μL, 6.64 mmol, 1.1 equiv) in CH_2Cl_2 (35 mL) was added a solution of dimethyl sulfoxide (943 μL, 13.3 mmol, 2.2 equiv) in CH_2Cl_2 (20 mL). The mixture was stirred at −78 °C for 30 min. A solution of **60** (1.50 g, 6.04 mmol, 1 equiv) in CH_2Cl_2 (60 mL) was then added dropwise and the reaction mixture was stirred at −78 °C for 15 min. Triethylamine (4.21 mL, 30.2 mmol, 5 equiv) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min then warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of (carbethoxymethylene)triphenylphosphorane (4.21 g, 12.1 mmol, 2 equiv) in CH_2Cl_2 (60 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min and warmed to rt and stirred for 24 h. The reaction was quenched with water (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (1.14 g, 60%) as a colorless oil. $R_f=0.55$ on silica gel (25% EtOAc/hexanes). IR (neat) $\nu=3500, 2931, 1722, 1652, 1472\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (dt, 1H, $J=15.4$, 7.7 Hz), 5.87 (d, 1H, $J=15.7$ Hz), 4.19 (q, 2H, $J=4.4$ Hz), 3.95–3.87 (m, 2H), 2.42 (d, 2H, $J=7.7$ Hz), 1.83–1.60 (m, 2H), 1.29 (t, 3H, $J=7.1$ Hz), 1.24 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.5, 145.2, 124.2,

72.8, 60.8, 60.4, 45.5, 41.1, 27.0, 26.0, 18.2, 14.5, −5.5; HRMS calcd for $C_{16}H_{22}O_4Si$ $[M-OH]^+$ 299.2037, found 299.2042.

4.2.51. Ethyl (2*E*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-5-(methoxymethoxy)-5-methylhept-2-enoate (62). To a 0 °C solution of **61** (336 mg, 1.06 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added dropwise diisopropylethylamine (555 μL, 3.18 mmol, 3 equiv). Chloromethyl methyl ether (306 μL, 5.31 mmol, 5 equiv) was added dropwise and then the reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product that was purified by flash chromatography using 10% EtOAc/hexanes as eluant to yield the desired product (300 g, 79%) as a colorless oil. R_f=0.85 on silica gel (10% EtOAc/hexanes). IR (neat) ν= 2954, 1723, 1656, 1467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (ddd, 1H, J=15.7, 7.7, 7.7 Hz), 5.83 (ddd, 1H, J= 16.8, 1.1, 1.1 Hz), 4.71 (AB, 1H, J=7.0 Hz), 4.68 (AB, 1H, J=7.7 Hz), 4.17 (q, 2H, J=7.1 Hz), 3.71 (ddd, 2H, J=7.1, 7.1, 1.1 Hz), 3.35 (s, 3H), 2.44 (dd, 2H, J=7.4, 1.1 Hz), 1.78 (ddd, 2H, J=6.7, 6.7, 2.2 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.23 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.5, 145.2, 124.1, 91.0, 77.3, 60.4, 59.1, 55.6, 43.2, 42.2, 26.1, 24.4, 18.4, 14.4, −5.2; HRMS calcd for $C_{18}H_{36}O_5Si$ $[M-CH_3]^+$ 229.1436, found 229.1439.

4.2.52. Ethyl (2*E*)-7-hydroxy-5-(methoxymethoxy)-5-methylhept-2-enoate (63). To a 0 °C solution of **62** (920 mg, 2.55 mmol, 1 equiv) in THF (20 mL) was added hydrogen fluoride–pyridine (70:30) (1.40 mL, 51.0 mmol, 20 equiv). The resulting mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for 2 h. The reaction was diluted with ether (60 mL) and quenched with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product that was purified by flash chromatography using 25% EtOAc/hexanes as eluant to yield the desired product (511 mg, 81%) as a colorless oil. R_f=0.15 on silica gel (25% EtOAc/hexanes). IR (neat) ν= 3440, 2980, 1714, 1652, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (ddd, 1H, J=15.4, 7.7, 7.7 Hz), 5.87 (ddd, 1H, J=15.6, 1.1, 1.1 Hz), 4.78 (AB, 1H, J=7.4 Hz), 4.73 (AB, 1H, J=7.7 Hz), 4.19 (q, 2H, J=7.1 Hz), 3.80 (m, 2H), 3.39 (s, 3H), 2.59 (brs, 1H), 2.52 (d, 2H, J=7.7 Hz), 1.95–1.65 (m, 2H), 1.32 (s, 3H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.4, 144.2, 124.6, 91.1, 78.9, 60.5, 59.2, 55.9, 42.9, 41.6, 23.9, 14.4; HRMS calcd for $C_{12}H_{22}O_5$ $[M-OH]^+$ 345.2101, found 345.2097.

4.2.53. Ethyl (2*E*)-7-bromo-5-(methoxymethoxy)-5-methylhept-2-enoate (34). A solution of carbon tetrabromide (722 mg, 2.18 mmol, 1.05 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a 0 °C solution of triphenylphosphine (571 mg, 2.18 mmol, 1.05 equiv) and **63** (512 mg, 2.07 mmol, 1 equiv) in CH_2Cl_2 (20 mL). The reaction was stirred at 0 °C for 1 h then warmed to rt. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 20% EtOAc/hexanes as eluant to yield the desired product (272 mg, 45%) as a colorless oil. R_f=0.65 on silica gel (25% EtOAc/hexanes). IR (neat) ν= 2980, 1714, 1656, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (ddd, 1H, J=15.6, 7.6, 7.6 Hz), 5.88 (ddd, 1H, J= 15.4, 1.1, 1.1 Hz), 4.71 (s, 2H), 4.20 (q, 2H, J=7.1 Hz), 3.48–3.40 (m, 2H), 3.38 (s, 3H), 2.52–2.36 (m, 2H), 2.23–2.00 (m, 2H), 1.30 (t, 3H, J=7.1 Hz), 1.26 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 166.2, 143.6, 124.6, 91.1, 78.8, 60.4, 55.7, 43.6, 42.7, 27.4, 23.5, 14.3; HRMS calcd for $C_{12}H_{21}BrO_5$ $[M]^+$ 309.0709, found 309.0701.

4.2.54. Ethyl (2*R*)-2-(allyloxy)-4-phenylbutanoate (64). To a suspension/solution of ethyl (*R*)-(−)-2-hydroxy-4-phenylbutyrate (2.01 g, 9.65 mmol, 1 equiv) and silver(I) oxide (6.70 g, 29.0 mmol, 3 equiv), $MgSO_4$ (289 mg, 2.40 mmol, 25 mol%) in Et_2O (40 mL) was added allyl bromide (2.51 mL, 29.0 mmol, 3 equiv). The reaction mixture was stirred at rt for 3 days protected from the light. Celite was then added and the mixture was filtrated through Celite and washed with Et_2O. Evaporation of the solvent gave the crude product which was purified by flash chromatography using 10% Et_2O/hexane as the eluant to give the desired product (1.19 g, 49%) as a colorless liquid. $[\alpha]_D^{25}$ +35.8 (*c* 1.1, $CHCl_3$); IR (neat) ν=3027, 2982, 2932, 2865, 1746, 1178, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.14 (m, 5H), 5.92 (m, 1H), 5.25 (m, 2H), 4.18 (m, 3H), 3.88 (m, 2H), 2.75 (m, 1H), 2.06 (q, 2H, J=8.4 Hz), 1.26 (t, 3H, J=7.2 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 172.6, 141.0, 134.0, 128.3, 128.2, 125.8, 117.5, 77.1, 71.3, 60.6, 34.4, 31.2, 14.1; HRMS calcd for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412, found 248.1423.

4.2.55. [(3*R*)-3-(Allyloxy)-4-bromobutyl]benzene (65). To a 0 °C suspension of lithium aluminum hydride (199 mg, 5.25 mmol, 1.1 equiv) in Et_2O (5 mL) was added slowly a solution **64** (1.19 g, 4.77 mmol, 1 equiv) in Et_2O (5 mL). The resulting mixture was warmed to rt and stirred for 6 h. Water (5 mL) was then carefully added at 0 °C followed by 10% aqueous KOH (7.5 mL) at rt and finally water (10 mL). The mixture was extracted with Et_2O (4×) and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude alcohol was then dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Carbon tetrabromide (2.37 g, 7.16 mmol, 1.5 equiv) and triphenylphosphine (1.88 g, 7.16 mmol, 1.5 equiv) were then added and the reaction mixture was stirred for 15 min before warming to rt overnight. The mixture was diluted with Et_2O (20 mL) was added and the resulting suspension was filtrated through celite and concentrated. The crude product was purified by flash chromatography using 2→5% Et_2O/hexane as eluant to provide the desired product (1.03 g, 80% over 2 steps) as a colorless liquid. $[\alpha]_D^{25}$ +18.1 (*c* 0.95, $CHCl_3$); IR (neat) ν= 3027, 2926, 2859, 1495, 1454, 1080, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 5.95 (m, 1H), 5.31 (dq, 1H, J=17.1, 1.5 Hz), 5.20 (dd, 1H, J=10.5, 1.5 Hz), 4.14 (ddt, 1H, J=12.5, 6.0, 0.9 Hz), 4.00 (ddt, 1H, J=12.5, 6.0, 0.9 Hz), 3.55–3.39 (m, 3H), 2.72 (m, 2H), 1.97 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 141.4, 134.5, 128.3, 128.2, 125.8, 117.2, 77.1, 70.7, 34.8, 34.6, 31.2; HRMS calcd for $C_{13}H_{17}OBr$ $[M]^+$ 268.0463, found 268.0468.

4.2.56. Methyl (2*E*)-4-{[(1*R*)-1-(bromomethyl)-3-phenylpropyl]oxy}but-2-enoate (39). To a mixture of **65** (342 mg,

1.27 mmol, 1 equiv) and methyl acrylate (2.83 mL, 31.7 mmol, 25 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (53.9 mg, 0.0635 mmol, 5 mol%). The mixture was stirred at rt overnight. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using 15% Et_2O/hexane as eluant to yield the desired product (306 mg, 74%) as an amber oil. $[\alpha]_D^{25}$ +26.9 (*c* 0.96, $CHCl_3$); IR (neat) ν=3034, 2950, 2865, 1725, 1665, 1304, 1279, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$-*d*) δ 7.32–7.24 (m, 2H), 7.22–7.15 (m, 3H), 6.97 (dt, 1H, *J*=15.9, 4.2 Hz), 6.15 (dt, 1H, *J*=15.9, 1.8 Hz), 4.30 (ddd, 1H, *J*=15.9, 4.2, 1.8 Hz), 4.12 (ddd, 1H, *J*=15.9, 4.2, 1.8 Hz), 3.75 (s, 3H), 3.50 (m, 1H), 3.42 (d, 2H, *J*=5.1 Hz), 2.72 (m, 2H), 1.97 (m, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$-*d*) δ 166.6, 144.1, 141.1, 128.4, 128.3, 126.0, 120.9, 78.1, 68.2, 51.5, 34.7, 34.3, 31.2; HRMS calcd for $C_{15}H_{19}O_3Br$ $[M]^+$ 326.0518, found 326.0525.

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