CONCISE SYNTHESIS OF (3Z)-DODECEN-12-OLIDE, PHEROMONE COMPONENT OF THE EMERALD ASH BORER

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GRAPHICAL ABSTRACT

Abstract Emerald ash borer (EAB), Agrilus planipennis Fairmaire, is an invasive insect that has killed millions of ash trees in Canada and the USA. (3Z)-Dodecen-12-olide is a known female-produced pheromone of this insect, and a concise, three-step synthesis of a 2:1 blend of (3Z)-dodecen-12-olide and (3E)-dodecen-12-olide starting from commercially available (2-carboxyethyl)triphenylphosphonium bromide and 10-bromo-1-decene is described. The key steps in this synthesis are a lithium-salt-free Wittig reaction and an intramolecular SN2 esterification. Both of these macrocyclic lactones are behaviorally active toward EAB, and the 2:1 blend whose synthesis is described here has the potential to be a detection agent, mating disruptor, or mass trapping agent, which could be used in the control of EAB.

Keywords (3E)-Dodecen-12-olide; (3Z)-dodecen-12-olide; emerald ash borer; mating disruption; pheromone

INTRODUCTION

The emerald ash borer (EAB, Agrilus planipennis Fairmaire) is an invasive palearctic species that has killed millions of ash trees (Fraxinus spp. L.) (Oleaceae) in North America.[1–3] Early detection of EAB infestations is difficult because visual signs appear only after trees have been heavily infested for years.[1,4] Previous work has shown that adult EABs respond to volatiles from girdled ash,[5] ash leaves,[4,6,7] and Manuka and Phoebe oils,[8,9] indicating that plant semiochemicals may provide

Received November 8, 2013.
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a means for monitoring EAB. To this end, our laboratory has been researching the pheromone chemistry of the EAB, in the hope that a synthetic pheromone could be combined with a kairomone (a host-plant-produced semiochemical) as a tool for detection, trapping, or mating disruption. Our starting point was the work of Bartelt and coworkers, who first published the antennally active, predominantly female-produced macrocyclic lactone $1$ ((3$Z$)-dodecen-12-olide, $Z$-lactone, Scheme 1) as a female-produced pheromone of EAB in 2007.$^{[10]}$

Gas chromatography/electroantennographic detection (GC/EAD) studies in our laboratory have shown that the excised antennae of EABs respond to both $1$ and its $E$-isomer, (3$E$)-dodecen-12-olide $2$ ($E$-lactone, Scheme 1). This is a technique wherein the excised head of an insect is affixed to an electrolytic gel, and the eluent from a gas chromatograph column is split and passed through a flame-ionization detector (FID) and over the antennal preparation simultaneously. The electrophysiological responses of the antennae are correlated with the peaks from the FID.$^{[11]}$ To synthesize $1$, we have modified$^{[2]}$ and extensively used a benchmark synthesis first published by Boden in 1993$^{[12]}$ (see Scheme 2). This synthesis gave $1$ in $\sim97\%$ stereochemical purity and $38\%$ yield over eight steps. We have also previously published a synthesis of $2$ (also in $\sim97\%$ stereochemical purity) in $16\%$ yield over six steps.$^{[1]}$ The response of EAB antennae to both isomers of dodecen-12-olide was noticed as a result of $\sim3\%$ of the $E$-isomer $2$ being intrinsic to the synthesis of the $Z$-isomer $1$.$^{[12]}$ Extensive study in our laboratory and in the field has confirmed that $1$ is emitted by female $A.\ planipennis$, confirming the work of Bartelt et al.$^{[10]}$ and also that $1$ was found to increase mean catch of males on green prism sticky traps when combined with the green leaf volatile, (3$Z$)-hexenol (relative to the green leaf volatile alone), when the traps are deployed in the tree canopy.$^{[2]}$ For this reason, $1$ could prove very useful as a mating disruption agent of EAB, provided large quantities could be produced and an efficient method of delivery of $1$ in the field could be devised. The role of $2$ in EAB semiochemistry is less clear, however; our own research has shown that it is not significantly different from $1$ in terms of its attractiveness toward male EAB in trap capture when both are combined with (3$Z$)-hexenol, and in fact, $2$ is more attractive than $1$ toward male EAB in Y-tube olfactometer tests.$^{[2]}$

The Boden synthesis, with several modifications, was used extensively in our laboratory to make small amounts (up to 8 g) of $\sim97\%$ stereochemically pure $1$.

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Scheme 1. (3$Z$)-Dodecen-12-olide $1$ and (3$E$)-dodecen-12-olide $2$. 
The modifications were the addition of a tert-butyl(dimethyl)silyl (TBS) protecting group at the beginning of the synthesis (step a), which greatly improved the yield of the Wittig step (step c). The major advantage of this synthesis is that all the steps are high yielding (between 80 and 100%), and I is obtained in very high stereochemical purity. The major drawback of this synthesis is that it requires eight steps. Also, the last step, which is a Mitsunobu ring closure (g), requires high dilution, uses expensive reagents [DEAD (diethylazodicarboxylate)], and can only be done on a small scale. These only become drawbacks when more than a relatively small amount of I is needed; for an extensive EAB mating disruption study conceived in our laboratory, approximately 20 g of I was needed. Consequently, we relate our efforts in the formalization of a concise, convenient, and user-friendly synthesis of I, which is not as labor intensive as Boden’s synthesis. Our criteria were that the synthesis contain a minimum number of steps, have relatively good yields, and be easy to carry out in the laboratory.

Also, it was felt that the rate-limiting step in Boden’s synthesis of I was the macrocyclization (g). As previously mentioned, an intramolecular macrocyclization poses difficulties as, no matter the method employed, the intermolecular reaction would compete to give a dimer, making high dilution necessary. The Mitsunobu esterification as reported by Justus and Steglich\cite{13} was used by Boden\cite{12} to close
the ring and generate 1 (Scheme 2, step g) and was used successfully by us, albeit on a relatively small scale. We felt that, if possible, a simple, atom-efficient method such as an intramolecular S_N2 reaction would be ideal to close the ring for our purposes. Intermolecular reaction, and hence dilution, would still be an issue; however, we felt that the simplicity of the reaction and the inexpensive reagents for an S_N2 reaction would counter this. Two other routes to form 1 were studied first, however, and are described here.

RESULTS AND DISCUSSION

The use of ring-closing olefin metathesis (RCOM) would seem to be an ideal method for the synthesis of 1 in only 2 steps (Scheme 3). Diene 12 was easily obtained by Steglich esterification\(^{[14]}\) of 3-butenoic acid 11 and 9-decen-1-ol 3 with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). However, under all conditions attempted (CH\(_2\)Cl\(_2\) or tetrahydrofuran [THF] as solvent, temperatures from 0 to 65 °C), and with all catalysts used (see Fig. 1),\(^{[15,16]}\) subjection of 12 to RCOM gave a complicated, inseparable mixture of products in which 1 was only a minor component.

It is possible that the electron-withdrawing carbonyl group in diene 12 is too close to the olefin for Ru-catalyzed RCOM to occur without competing side reactions. It was noted that in all cases studied for this reaction, dimers such as 13 and 14 formed a significant amount (~40%) of the mass balance in the mixture of products. It was our belief that dimerization, trimerization, and oligomerization in general were too energetically favorable in the Ru-catalyzed RCOM of this system, leading to catalyst fouling and excessive side reactions. Insulation of the ester functionality from the alkenes by at least three methylene groups seems necessary for RCOM to proceed successfully.\(^{[17]}\)

As RCOM was impractical for both large-scale and small-scale synthesis of 1, a route that employed the Wittig step as the macrocyclization was attempted.
(unsuccessfully) and is outlined in Scheme 4. The DCC and DMAP coupling of 20 and 3 gave iodide 21 in only 8% yield (most of 3 was converted into 22b). Regardless of the poor yield, ozonolysis of 21 with reductive workup gave 23 in 75% yield. The Wittig salt 24 was presumably formed by refluxing 23 with PPh3 in THF for 10 days (as monitored by thin-layer chromatography, TLC); then the reaction mixture was cooled to −78 °C and NaHMDS (sodium hexamethyldisilylamide) was added. After warming to rt and stirring for 16 h, neither Z-lactone 1 or E-lactone 2 were isolated. Assuming successful formation of 24, only removal of H4 by NaHMDS would give rise to the desired ylide, which in turn could react intramolecularly with the aldehyde.

Scheme 4. (a) DCC, DMAP, CH2Cl2, rt, 8% yield of 21, the major by-product being 22b, whose yield was not determined; (b) (i) O3, Sudan III, CH2Cl2, −78 °C (ii) PPh3, −78 °C–rt, 75%; (c) PPh3, THF, reflux; (d) NaHMDS, −78 °C–rt, one pot; no product 1 was obtained.
and give lactone 1 or 2. There are still two other protons (H\textsubscript{b} and H\textsubscript{c}) in 24 that are acidic enough to be removed by NaHMDS; removal of either of these would not lead to the desired product 1. It is likely that this is, in fact, what occurred.

Although attempts to form the macrocycle via intramolecular Wittig reaction were unsuccessful, attention was still focused on a Wittig reaction to build the backbone of 1. To this end, Wittig salt 25a was prepared from commercially available 3-iodopropionic acid 20 and triphenylphosphine (Scheme 5). This was accomplished by refluxing 20 and PPh\textsubscript{3} in various solvents until TLC showed complete consumption of starting materials (see Table 1). The formation of the Wittig salt 25a was slow, and also, subsequent Wittig reaction in the same pot using NaHMDS as the base and aldehyde 26a proved capricious, sometimes giving poor yield or no product (27a) at all (see Table 1; also see experimental for a general procedure).

However, the commercial availability of (2-carboxyethyl)triphenylphosphonium bromide 25b (Scheme 5) rendered Wittig salt synthesis unnecessary and led to much improved yield and ease of reaction in the Wittig step to give 27a, b, or c. Indeed, the use of 25b has been reported previously in the synthesis of Ferrulactone II\textsuperscript{18} [(S, Z)-dodec-3-en-11-olide, 28, Scheme 5] in a Wittig reaction similar to that employed by us (Scheme 5). As THF gave the best Z-selectivity in the product

\[ \text{Scheme 5. (a) PPh}_3\text{ solvent, reflux (see Table 1); (b) (i) NaHMDS, one pot, 0°C–rt; (ii) 26a, –78°C–rt; see Table 1 for yield and Z/E ratio of product 27a; (c) (i) NaHMDS, THF, 0°C–rt; (ii) 26a, 26b, or 26c, –78°C–rt; 70% yield for 27a, 67% for 27b, 61% for 27c.} \]
when the Wittig salt 25a was synthesized in situ (Table 1, entry 3), this solvent was used in subsequent Wittig reactions with commercially available 25b. For aldehydes 26a, b, and c, yields of 70%, 67%, and 61%, respectively, were obtained for the Wittig reaction using 25b as the Wittig salt, THF as the solvent, and NaHMDS as the base (Scheme 5). A straightforward intramolecular SN2 reaction of 27a using potassium carbonate (K2CO3) as base, potassium iodide (KI) as promoter, and refluxing acetone as solvent yielded a 2:1 mixture of 1:2 in good yield (82%, Scheme 6). A small amount (ca. 10%) of dimer 13 was formed as expected by intermolecular SN2 reaction between two molecules of 27a followed by an intramolecular SN2 reaction of the dimer.

Iodoaldehyde 26b could be used in the Wittig step to give iodoacid 27b (Scheme 5), which cyclized in the same fashion as 27a to a mixture of 1 and 2 in similar yield (72%) and Z/E selectivity (2:1), but without the KI promoter (Scheme 6). Dimer 13 was formed in ca. 10% of the overall yield whether 27a or b was cyclized.

Acetal 27c could also be obtained in a Wittig reaction employing Wittig salt 25b and aldehyde 26c in similar yield (61%) and Z/E (2:1) selectivity to acids 27a and b (Scheme 5). The hydroxyl group of 27c can then be unmasked with hydrochloric acid in wet THF (quantitative yield) to give 10, and the Mitsunobu conditions as reported by Boden et al.,[12] using diisopropylazodicarboxylate

![Diagram](image1)

Scheme 6. (a) K2CO3, KI (only for 27a), acetone, reflux; 82% yield of 1 + 2 for 27a; 72% for 27b.

Table 1. Wittig reaction of 25a (generated in situ from 20 and PPh3 in the specified solvent) with NaHMDS as base and with aldehyde 26a to give bromoacid 27a; see Scheme 5

| Entry | Solvent | Yield (%) of 27a | Z/E ratio | Time required for formation of 25a |
|-------|---------|-----------------|-----------|-----------------------------------|
| 1     | Toluene | 35              | 1:1.6     | 24 h                              |
| 2     | 1,2-DME<sup>a</sup> | 16 | 1:4 | 4 d |
| 3     | THF     | 30              | 1.6:1     | 4 d                               |
| 4     | Benzene | 0               | n/a       | 3 d                               |
| 5     | EtOH<sup>b</sup> | 0 | n/a | 3 d |

<sup>a</sup>See Experimental section for in situ formation of 25a and subsequent Wittig reaction in 1,2-DME.

<sup>b</sup>EtOH was removed in vacuo after formation of 25a was complete, and THF was added as the solvent for the subsequent Wittig reaction.
(DIAD) instead of DEAD, readily forms the lactone as a mixture of Z and E isomers 1 and 2 (84% combined yield) as well as a small amount of the dimer 13 (ca. 5%, Scheme 7).

Aldehydes 26a, b, and c are readily prepared in two steps from commercially available 9-decen-1-ol 3 (see Scheme 8; the yields of 22a, b, and c were 100%, 100%, and 98%, respectively, and the yields for the ozonolysis of 22a into 26a, 22b into 26b, and 22c into 26c were 100%, 92%, and 93%, respectively). The commercial availability of 22a makes 26a obtainable in only one step.

The success of the intramolecular SN2 reaction in the conversion of 27a or b into a mixture of 1 and 2 (82% and 72% yields, respectively) could be due to the fact that the leaving group (bromide or iodide ion) is on an \( sp^3 \) carbon, and the negatively charged carboxylate acts as the nucleophile. This is similar to Mitsunobu conditions in that, under Mitsunobu conditions, the hydroxyl on the terminal \( sp^3 \) carbon of 10 is converted into a leaving group (in the case of the Mitsunobu reaction, triphenylphosphine oxide), and the carboxylic acid on the other terminus of the molecule acts as the nucleophile. This is in contrast to more typical Steglich conditions for

![Scheme 7](image)

**Scheme 7.** (a) HCl, H2O, THF, rt, quantitative; (b) DIAD, PPh3, PhCH3, rt, 84% yield of 1 + 2.

![Scheme 8](image)

**Scheme 8.** (a) CBr4, PPh3, CH2Cl2, 0°C, quantitative; (b) I2, PPh3, imidazole, 1:3 CH2CN–Et2O, rt, quantitative; (c) ethyl vinyl ether, PPTS, CH2Cl2, rt, 98%; (d) (i) O3, Sudan III, CH2Cl2, −78°C, (ii) PPh3, −78°C–rt, quantitative yield for 26a, 92% for 26b, 93% for 26c.
esterification of a hydroxyacid (DCC, DMAP)\[^{13,14}\] in which the carboxyl group is activated, and the hydroxyl on the other end of the molecule acts as the nucleophile.

In conclusion, a user-friendly, concise, three-step synthesis of a 2:1 mixture of Z/E lactones 1 and 2 was developed in an overall yield of 57% from commercially available 25b [(2-carboxyethyl)triphenylphosphonium bromide] and commercially available 10-bromo-1-decene 22a. The key steps in this synthesis are a Wittig reaction to form the 12-carbon backbone of 1 and an intramolecular SN2 reaction to close the ring. The major drawback of this synthesis is that 1 and 2 are synthesized as an inseparable, 2:1 mixture; however, as previously mentioned, 2 has attractiveness comparable to 1 for male EAB, and so the mixture of 1 and 2 could conceivably disrupt EAB mating as effectively as pure 1. Field tests of the efficacy of this mixture for the mating disruption of EAB are pending.

**EXPERIMENTAL**

All nonaqueous reactions were conducted in oven-dried glassware under an argon atmosphere. Air-sensitive reagents were transferred via syringe through rubber septa. Reagents were purchased from commercial suppliers and directly used without further purification. Analytical thin-layer chromatography (TLC) was performed using Whatman TLC plates, precoated with 0.25 mm of UV\(_{254}\) silica gel on aluminum backing. Visualization was done by dipping the TLC plate in potassium permanganate solution, followed by baking on a hot plate. Flash column chromatography was performed using a glass column filled with 230- to 400-mesh Silia Flash F60 silica gel from Silicycle unless otherwise specified. Reagent-grade solvents were used without further purification. All compounds purified by SiO\(_2\) chromatography were greater than 98% pure as determined by GC/MS and/or NMR. Synthetic compounds were characterized by GC/MS on an Agilent 6890 GC and an Agilent 5973 mass selective detector in the electron impact (unit resolution, EI, 70 eV) mode. For all analyses, we employed a temperature program of 70°C for 2 min and then increased the temperature in increments of 10°C/min until the oven temperature reached 220°C, which was then maintained for 25 min. A Zebron ZB-5MS Inferno capillary GC column (Phenomenex, Torrance, CA; 30 m, 0.25 mm id, 0.25-μm film) was used for all analyses. NMR spectroscopy (\(^1\)H and \(^{13}\)C) was carried out on a Varian Unity 400-MHz spectrometer or a Varian Innova 300-MHz spectrometer in CDCl\(_3\), with tetramethylsilane (TMS) as internal standard, with chemical shifts reported in parts per million (ppm) (δ). Infrared (IR) spectra were recorded on a Varian 640-IR FT-IR spectrometer. High-resolution mass spectra (HRMS) were obtained at Dalchem Mass Spectrometry Laboratory in Halifax, NS, Canada.

**Synthesis of 25a**

A round-bottomed flask was charged with iodoacid 20 (5.12 g, 25.6 mmol), 1,2-dimethoxyethane (DME, 60.0 mL), and triphenylphosphine (6.74 g, 25.7 mmol). The reaction mixture was heated at reflux for 4 d. Thin-layer chromatography (TLC) was used to monitor the reaction’s progress. Upon completion, the mixture of Wittig salt 25a in DME was used directly in the subsequent Wittig step to make 27a.
Synthesis of 27a via 25a

Compound 25a (25.6 mmol) in DME was cooled to 0°C, and sodium hexamethyldisilylamine (NaHMDS, 60.0 mL, 1.0 M in THF, 60.0 mmol) was added dropwise over 6 min. The reaction mixture was stirred at 0°C for 30 min, warmed to rt, stirred for 75 min, and then cooled to −78°C. Aldehyde 26a (3.89 g, 17.6 mmol) in THF (2 mL) was added via syringe with rinsing (2 × 2.0 mL THF). The reaction was allowed to warm to rt over 1 h and stirred at rt for 20 h. Saturated aqueous NH₄Cl (100 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 80 mL). The combined organic layers were washed with brine (100 mL) and dried (MgSO₄). Column chromatography on silica gel (80% EtOAc = hexanes as eluent) yielded bromoacid 27a (1:4 Z/E) as a colorless, transparent liquid (730 mg, 2.64 mmol, 15%).

Synthesis of 27a via Commercially Available 25b

A round-bottomed flask was charged with 25b (5.07 g, 12.2 mmol) and THF (60 mL) and cooled to 0°C. NaHMDS (25.0 mL, 1.0 M in THF, 25.0 mmol) was added dropwise over 5 min. The reaction was stirred at 0°C for 1 h, warmed to rt, and stirred for 2 h. After cooling to −78°C, aldehyde 26a (2.63 g, 11.9 mmol) in THF (3.0 mL) was added via syringe with rinsing (2 × 3.0 mL THF). The reaction was allowed to warm to rt over 1 h and then stirred for 17 h. Saturated aqueous NH₄Cl (100 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with brine (100 mL) and dried (MgSO₄). Column chromatography on silica gel (EtOAc as eluent) yielded bromoacid 27a (2:1 Z/E) as a colorless, transparent liquid (2.30 g, 8.30 mmol, 70%). Rf = 0.27 (1:2 EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz): δ 5.59 (m, 2H), 3.44 (t, 2H, J = 6.8 Hz), 3.16 (d, 1.34H, J = 6.2 Hz), 3.10 (d, 0.66H, J = 6.0 Hz), 2.06 (m, 2H), 1.88 (p, 2H, J = 6.9 Hz), 1.32–1.47 (m, 10H), OH proton not seen. ¹³C NMR (CDCl₃, 100 MHz): δ 177.9, 177.8, 135.4, 134.0, 120.8, 120.0, 34.02, 33.99, 32.79, 32.78, 32.4 (two signals), 29.23, 29.21, 29.16, 29.1, 29.00, 28.96, 28.7 (two signals), 28.1 (two signals), 27.3 (two signals). IR (neat, cm⁻¹): 2926 (br, s), 2854 (m), 1700 (s), 1462 (w), 1343 (m), 1292 (w), 1250 (s), 1180 (w), 1089 (w), 1045 (m). HRMS for 27a: Calc. for C₁₂H₁₀₇Ag₁Br₉O₄: 382.9770. Found: 382.9754. Difference: 4.18 ppm.

Ring Closure of 27a

A round-bottomed flask was charged with 27a (1.06 g, 3.83 mmol), acetone (500 mL), K₂CO₃ (640 mg, 4.63 mmol), and KI (1.10 g, 6.63 mmol). The reaction mixture was heated to reflux for 4 d, and then cooled to rt. After ~90% of the solvent was removed in vacuo, H₂O (40 mL) was added, and the mixture was extracted with hexanes (6 × 30 mL). The combined extractions were washed with brine (100 mL) and dried (MgSO₄). Column chromatography with a Buchi 660 fraction collector on silica gel (25 g) with a solvent gradient of 0 to 7% EtOAc/hexanes over 20 min and then removal of the solvent in vacuo yielded lactones 1 and 2 in a 2:1 ratio as an inseparable mixture, and a small amount of the dimer 13 (~10% of the total yield). The mixture of 1 and 2 was a colorless, transparent liquid (619 mg, 3.16 mmol,
82%). $R_f = 0.27$ (1:20 EtOAc/hexanes). For spectral data of 1 and 2, see Refs. 12 and 1, respectively.

**Synthesis of 10**

A round-bottomed flask was charged with 27c (2.14 g, 7.48 mmol), THF (80 mL), and 2 M HCl (aqueous) (5.0 mL). After stirring at rt for 40 min, H$_2$O (20 mL) was added, and the mixture was extracted with diethyl ether (4 × 20 mL). The combined extractions were washed with brine (100 mL) and dried (MgSO$_4$) to give hydroxyacid 10 (1.60 g, 7.48 mmol, 100%) as a white solid. See Refs. 12 and 1 for the spectral data of $Z$-10 and $E$-10, respectively. Compound 10 was used without further purification in the Mitsunobu ring closure reported by Boden et al. in 1993 and Magee et al. in 2013[12,1] to give a 2:1 mixture of 1 and 2 in 84% yield, as well as ~5% of the dimer 13.

**Synthesis of 22a**

A round-bottomed flask was charged with 9-decen-1-ol 3 (10.0 g, 64.1 mmol) and CH$_2$Cl$_2$ (300 mL) and cooled to 0°C. Triphenylphosphine (21.8 g, 83.1 mmol) and CBr$_4$ (27.6 g, 83.2 mmol) were added, and the mixture was allowed to warm to rt over 1 h and stirred for 14 h. Column chromatography on silica gel with hexanes as eluent, and then removal of the solvent in vacuo, yielded bromide 22a (14.0 g, 63.9 mmol, 100%) as a colorless, transparent liquid. Spectral data matched that of the authentic commercially available sample.

**Synthesis of 22b**

A round-bottomed flask was charged with 9-decen-1-ol 3 (5.0 g, 32.1 mmol), diethyl ether (133 mL), CH$_3$CN (67 mL), imidazole (3.27 g, 48.1 mmol), triphenylphosphine (10.1 g, 38.5 mmol), and iodine (13.0 g, 51.3 mmol). The reaction was stirred at rt for 4 h. Then H$_2$O (150 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 60 mL). The combined organic layers were washed with brine (100 mL) and dried (MgSO$_4$). Column chromatography on silica gel with hexanes as eluent and then removal of the solvent in vacuo yielded iodide 22b (8.50 g, 32.0 mmol, 100%) as a colorless, transparent liquid. R$_f$ = 0.66 (hexanes). $^1$H NMR (CDCl$_3$, 300 MHz): δ 5.82 (m, 1H), 4.92–5.05 (m, 2H), 3.20 (t, 2H, $J$ = 7.0 Hz), 2.05 (m, 2H), 1.85 (p, 2H, $J$ = 7.0 Hz), 1.32–1.45 (m, 10H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.9, 114.1, 33.7, 33.5, 30.4, 29.2, 28.9, 28.8, 28.4, 7.1. IR (neat, cm$^{-1}$): 3075 (w), 2924 (s), 2852 (s), 1823 (w), 1640 (m), 1461 (m), 1435 (m), 1267 (w), 1192 (m), 1168 (m). MS (EI, 70 eV) (main peaks): m/z 55 (base peak), 69, 83, 97, 127, 141, 155, 169, 183, 196, 210, 224, 266 (M$^+$). HRMS for 22b: calc. for C$_{10}$H$_{107}$AgI: 372.9577. Found: 372.9571. Difference: 1.61 ppm.

**Synthesis of 22c**

A round-bottomed flask was charged with 9-decen-1-ol 3 (1.76 g, 11.2 mmol), CH$_2$Cl$_2$ (100 mL), ethyl vinyl ether (EVE) (2.0 mL, 20.9 mmol), and pyridinium $p$-toluenesulfonate (276.3 mg, 1.10 mmol). The reaction mixture was stirred at rt
for 16 h, water (50 mL) was added, the layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried (MgSO$_4$). Column chromatography (20% EtOAc/hexanes) yielded 22c (2.50 g, 11.0 mmol, 98%) as a colorless, transparent liquid, R$_f$ = 0.52 (1:9 EtOAc/hexanes). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 5.78 (m, 1H), 5.24 (m, 1H), 4.65 (q, 1H, $J = 5.3$ Hz), 3.33–3.68 (m, 4H), 1.98–2.07 (m, 2H), 1.49–1.60 (m, 2H), 1.25–1.40 (m, 13H), 1.20 (t, 3H, $J = 7.0$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 139.2, 114.2, 99.6, 65.3, 60.7, 33.9, 30.0, 29.51, 29.49, 29.1, 29.0, 26.3, 19.9, 15.4. IR (KBr windows) cm$^{-1}$: 3077 (m), 2976 (s), 2927 (s), 2847 (s), 1641 (s), 1459 (s), 1443 (s), 1380 (s), 1339 (s), 1270 (w), 1153 (br, s). MS (EI) major peaks: 55, 73 (base peak), 83, 97, 183, 213, 227 (M$^+$ /C$_0$). HRMS for 22c: Calc. for C$_{14}$H$_{28}$NaO$_2$: 251.1982. Found: 251.1979. Difference: 1.19 ppm.

**Synthesis of 26a**

A round-bottomed flask was charged with 22a (10.0 g, 45.7 mmol), dichloromethane (200 mL), and Sudan III (50.0 mg) and then cooled to $-78^\circ$C. Ozone was bubbled through until the red color of the Sudan III was discharged. Then, oxygen was bubbled through for 30 min at $-78^\circ$C, triphenylphosphine (12.0 g, 45.7 mmol) was added, and the reaction was allowed to warm to rt over 1 h and then stirred for 14 h at this temperature. The solvent was removed in vacuo. Column chromatography on silica gel with 20% EtOAc/hexanes as eluent, then removal of the solvent in vacuo, yielded bromoaldehyde 26a (10.2 g, 46.1 mmol, 100%) as a colorless, transparent liquid. R$_f$ = 0.27 (1:20 EtOAc/hexanes). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.67 (m, 1H), 3.32 (t, 2H, $J = 6.8$ Hz), 2.34 (td, 2H, $J = 7.3$, 1.8 Hz), 1.77 (p, 2H, $J = 6.7$ Hz), 1.54 (m, 2H), 1.24–1.39 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 202.4, 43.5, 33.7, 32.4, 28.8, 28.7, 28.2, 27.7, 21.6. IR (neat, cm$^{-1}$): 2928 (s), 2854 (s), 2719 (w), 1721 (s), 1462 (m), 1438 (m), 1409 (w), 1390 (w), 1250 (w), 1113 (m), 1027 (w). MS (EI, 70 eV) (main peaks): m/z 55 (base peak), 57, 67, 69, 81, 95, 97, 107, 109, 113, 123, 135, 157, 148, 150, 160, 162, 176, 178, 192, 194, 202, 204, 219 (M$^+$ – 1, $^{79}$Br), 221 (M$^+$ – 1, $^{81}$Br). HRMS for 26a: Calc. for C$_9$H$_7$BrNaO: 243.0355. Found: 243.0346. Difference: 3.70 ppm.

**ACKNOWLEDGMENT**

We thank Matt Brophy for technical assistance.

**FUNDING**

We are grateful to Natural Resources Canada and the Atlantic Innovation Fund (AIF, Atlantic Canada Opportunities Agency) through SERG-I for funding this research. All experiments reported here comply with the laws of Canada.

**SUPPLEMENTAL MATERIAL**

Full experimental details and $^1$H and $^{13}$C NMR spectra for this article can be accessed on the publisher’s website.
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