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Single isomer trisubstituted olefins bearing alkyl groups

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ABSTRACT

E-β-Chloro-α-iodo-α,β-unsaturated esters were converted to single isomer trisubstituted olefins bearing alkyl substituents by using and alkyl-Suzuki cross coupling. The process was highly selective, and the products in all cases were isolated as single isomers. Mechanistic investigations indicated that this process transfers a hydrogen from water to the α-position of the substrate, and then an alkyl group is introduced to the β-position of the intermediate template while replacing a chloride.

1. Introduction

The stereocontrolled synthesis of trisibstituted olefins remains a significant challenge in organic synthesis. Carbon–carbon coupling strategies, such as the Wittig,[1] Horner–Wadsworth–Emmons,[2] or metathesis reactions[3] often produce mixtures of isomers that can be difficult to separate. Indirect methods such as the carbometallation of alkynes,[4,5] or cross couplings with olefin templates[6] can successfully overcome the stereochemical problems, but may introduce issues of a regiochemical nature. While these methods have been utilized to achieve selectivity in the production of trisubstituted olefins, methods that are able to introduce alkyl substituents onto the double bond are relatively uncommon.

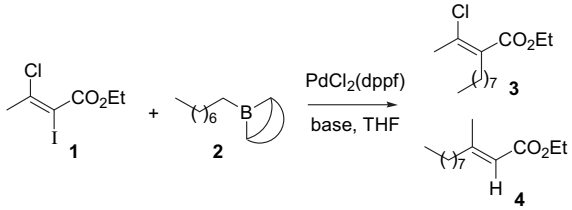
We recently described an efficient synthesis of trisubstituted olefins from *E*-β-chloro-α-iodo-α,β-unsaturated ester templates and organoboronic acids.[7] This method utilized very small ligands in mild reaction conditions, and reliably produced the products as single isomers. The boronic acids used in this study were invariably aromatic or sp^2 hybridized, and while useful, this technology would benefit if alkyl substituted groups could also be employed. In this paper we describe the development of a method for the preparation of trisubstututed olefins from *E*-β-chloro-α-iodo-α,β-unsaturated ester templates that allows for the introduction of alkyl substituents. This method is simple and, more importantly, provides the products as single isomers.

2. Results and discussion

As shown in Table 1, treatment of template **1** with 9-octyl-BBN **2**[8] at room temperature in the presence of $PdCl_2$(dppf) using K_3PO_4 as a base gave no reaction. Heating the mixture to reflux again returned the starting material, along with a small amount of **3**. To try to improve the cross coupling, a small amount of H_2O was introduced,[9] however this modification was unfruitful. When the hydrated form of K_3PO_4 was instead employed as the base, the production of a small amount of the trisubstituted olefin **4** resulted.

Because of difficulties encountered during the separation of the product from the non-polar substrate when 9-octyl-BBN was used

Table 1
Attempts to prepare a tetrasubstituted olefin from *E*-β-chloro-α-iodo-α,β-unsaturated esters and alkyl boranes



Entry[a]	Base	Temperature °C	Product (yield)
1	K_3PO_4	25	NR
2	K_3PO_4	66	**3**: trace
3	K_3PO_4+H_2O	66	**3**: trace
4	$K_3PO_4 \cdot H_2O$	66	**4**: 27%

[a] Conditions: 0.05 equiv of $PdCl_2$(dppf), 3.0 equiv of base, 3.0 equiv of 1-(9-borabicyclo[3.3.1]nonana-9-yl)-hexane, THF (0.09 M), 18 h.

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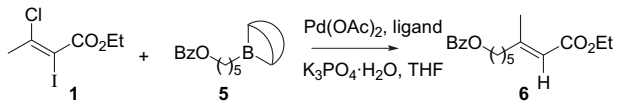
as the coupling partner, the reaction was optimized using a more polar coupling partner **5**. An initial experiment, run at room temperature for 18 h produced only an 8% yield of the trisubstituted olefin product **6** using dppf as a ligand. Although the yield was disappointingly low, the reaction proceeded at room temperature and gave the compound as a single isomer (Table 2, entry 1). Other bridged diaryl phosphine ligands were tried, that resulted in improved yields of the trisubstituted olefin **6** (entries 2–6).

Table 2
Effect of the ligand used on the formation of trisubstituted olefins from *E*-β-chloro-α-iodo-α,β-unsaturated esters and alkyl boranes

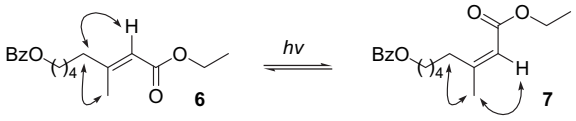


Entry[a]	Ligand	Yield[b] (%)
1	dppf	8
2	dppm	3
3	dppp	0
4	dppb	21
5	Xantphos	36
6	Diphos	31
7	PPh_3	39
8	$PMe_3 \cdot HBF_4$	6
9	$PEt_3 \cdot HBF_4$	60
10	$PtBu_2Me \cdot HBF_4$	79
11	PCy_3	61
12	Davephos	60
13	*S*-phos	86

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of ligand, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09 M), 23 °C, 18 h.
[b] Isolated yield; products were obtained as single isomers.

When PPh_3 was used as a ligand, no improvement in yield was noted. The use of trialkyl phosphine ligands produced significant improvements in the yield of the process (entries 9–10). This study suggested that employing hindered ligands could be an effective way to effect the transformation of *E*-β-chloro-α-iodo-α,β-unsaturated esters, such as **1**, into the corresponding trisubstituted olefins, such as **6**. Toward this end, the use of the biaryl ligands Davephos and *S*-phos was explored (entries 12 and 13). *S*-Phos proved to be the best ligand for this transformation, giving trisubstituted olefin **6** in 86% isolated yield from the reaction between template **1** and borane **5**.

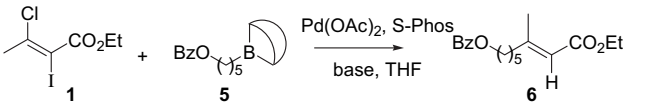
The stereochemistry of each product was confirmed using NOE interactions. As shown in Scheme 1, the key reaction product **6** displayed a strong NOE interaction between the γ-methyl and the CH_2 group of the added alkyl substituent, as well as an enhancement between the first alkyl methylene and the olefinic hydrogen. The *E*-olefin product **6** was isomerized to the *Z*-product **7** using brief photolysis. Product **7** displayed an NOE enhancement between the methyl group and the olefin hydrogen, while no interaction was seen between the alkyl methylene group and the olefin. These NOE interactions were consistent with the assignment of an *E*-configuration to the original cross coupled product **6**. The regiochemistry of product **6** was established by the magnitude of the coupling constant between the olefinic hydrogen and the methyl group (1.2 Hz). In product **4** the coupling constant associated with the olefinic hydrogen and the methyl group was also small (0.8 Hz).[10]



Scheme 1. Determination of the stereochemistry of product **6**.

A survey of bases was then conducted to try to improve the yield of the process. As shown in Table 3, the use of K_3PO_4 resulted in a recovery of only 3% of the product. Adding H_2O to the reaction mixture restored some reactivity, but the reaction was not as efficient as that using $K_3PO_4 \cdot H_2O$ as the base. Other bases were tried, in each case a matching amount of water was included in the medium.[11]

Table 3
Effect of the base used on the formation of trisubstituted olefins from *E*-β-chloro-α-iodo-α,β-unsaturated esters and alkyl boranes



Entry[a]	Base	Yield[b] (%)
1	$K_3PO_4 \cdot H_2O$	86
2	K_3PO_4	3
3	$K_3PO_4 + H_2O$	52
4	$K_2HPO_4 + H_2O$	11
5	$KH_2PO_4 + H_2O$	5
6	$K_2CO_3 + H_2O$	65
7	$CsCO_3 + H_2O$	78
8	$Et_3N + H_2O$	0
9	$Et^iPr_2N + H_2O$	0
10	DABCO + H_2O	0

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of *S*-phos, 3.0 equiv of Base, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09 M), 23 °C, 18 h.
[b] Isolated yield; Products were obtained as single isomers.

In almost all cases, the yield was significantly lowered compared to the reaction using $K_3PO_4 \cdot H_2O$. Two exceptions were K_2CO_3 and $CsCO_3$ (entries 6 and 7), however the hydrate of K_3PO_4 proved to be superior to either of these bases. Finally, the use of amine bases was completely ineffective, as the presence of the product could not be detected in any of these reaction mixtures (entries 8–10).

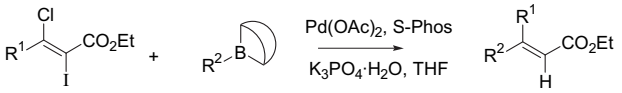
Other boron-containing groups[9] were investigated in the coupling process. In all cases however, no product could be detected when cross coupling was attempted using an alkyl catecholborane,[12] alkyl-pinacol borane,[13] alkyl boronic acid or alkyl BF_3 salt.[14] In each case only starting material was recovered.

Finally we investigated the effect of adding additional water. When using $K_3PO_4 \cdot H_2O$ as the base, a yield of 86% of **6** was obtained by cross coupling template **1** and borane **5**. A reaction in which 3 equiv of water was introduced gave a slightly reduced yield of product (73%). Using ^{i}PrOH as an additive[15] was also explored, but this modification did not produce an improvement in yield (48% yield of **6** was observed).

The scope of the process was explored using a variety of coupling partners (Table 4). A simple methyl substitution at the β position of the *E*-β-chloro-α-iodo-α,β-unsaturated ester template **1** provided an excellent yield when **5** was used as the coupling partner (entry 1). Switching the methyl group on the chloro–iodo template to a hydrogen (entry 2) decreased the yield of the cross coupled product significantly (30%). Interestingly, this compound proved to be the *Z*-isomer, and was the only compound in this study in which the introduced alkyl group and the ester of the original substrate were *syn* to each other. Branched substituents, such as a cyclohexyl group (entry 3) were tolerated in the process and produced a moderate yield of the trisubstituted olefin product **11** (46%).

Substituted alkyl chains were compatible with the reaction conditions as shown in entry 4, in which a TIPS ether was present on the substrate side chain. Treating a variety of terminal alkenes with 9-BBN produced 9-alkyl-9-BBN boranes that were used to

Table 4
Formation of trisubstituted olefins from *E*-β-chloro-α-iodo-α,β-unsaturated esters and alkyl boranes

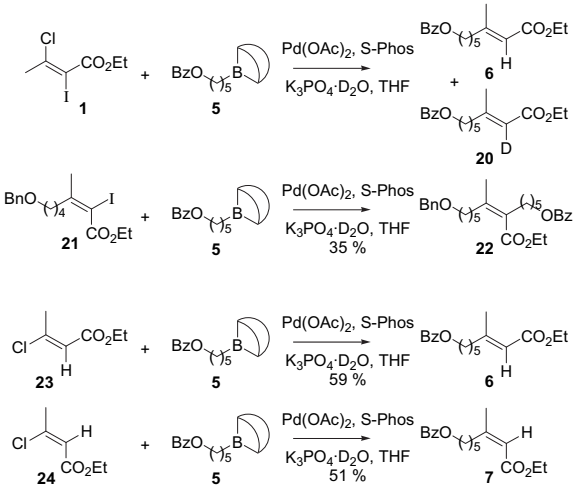


Entry[a]	Substrate	Product[b]	Yield[c] (%)
1	**1**: R^1=CH_3	**6**: R^2=$BzO(CH_2)_5$	86
2[d]	**8**: R^1=H	**9**: R^2=$BzO(CH_2)_5$[e]	30
3	**10**: R^1=C_6H_{12}	**11**: R^2=$BzO(CH_2)_5$	46
4[d]	**12**: R^1=$CH_3(CH_2)_4$	**13**: R^2=$BzO(CH_2)_5$	74
5	**14**: R^1=$TIPSO(CH_2)_4$	**15**: R^2=$BzO(CH_2)_5$	66
6	**1**: R^1=CH_3	**3**: R^2=$CH_3(CH_2)_7$	82
7	**1**: R^1=CH_3	**16**: R^2=$BnO(CH_2)_5$	73
8	**1**: R^1=CH_3	**17**: R^2=$TIPSO(CH_2)_5$	60
9	**1**: R^1=CH_3	**18**: R^2=$BzO(CH_2)_3CHCH_3$	76
10	**1**: R^1=CH_3	**19**: R^2=*c*-C_6H_{11}	0

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of *S*-phos, 3.0 equiv of $K_3PO_4\cdot H_2O$, 3.0 equiv of borane, THF (0.09 M), 23 °C, 18 h.
[b] Products were obtained as single isomers.
[c] Isolated yield.
[d] The methyl ester was used in place of the ethyl ester.
[e] The *Z*-isomer was produced exclusively in this reaction.

cross couple to the *E*-β-chloro-α-iodo-α,β-unsaturated ester template **1** under our optimized conditions. Using a straight alkyl chain such as an octyl group (entry 6) produced the desired product with an excellent yield (82%). Starting with a benzyloxy substituted alkene (entry 7), resulted in a very good yield (73%), similar to that obtained when a benzoyloxy protected alkene was employed as the starting material (entry 2). Using a more bulky triisopropylsilyloxy protected alkene resulted in a slight decrease in the yield of the transformation to 60% (entry 8). Finally, a benzoyloxy protected branched alkene (entry 9) worked beautifully in the process to provide a good yield of the cross coupled material (76%). Unfortunately, the presence of branching at the boronic acid was not tolerated in the reaction, as exemplified by the results of entry 10 in which no product could be constructed.

A series of mechanistic experiments were performed to try to identify the source of hydrogen and stereoselectivity in this process. As shown in Scheme 2, the use of $K_3PO_4\cdot D_2O$ as the base resulted in the observation of deuterated product **20**. This suggested that the olefinic hydrogen in the product was most likely derived from the water present in the reaction medium. Previous experience with *E*-β-chloro-α-iodo-α,β-unsaturated esters[7,16] had shown that initial cross couplings invariably occurred at the iodide position. That this selectivity was operative in the present process



Scheme 2. Mechanistic experiments.

was confirmed by subjecting iodide **21** to the reaction conditions. In this experiment, the trisubstituted product **16** was not detected, instead only the tetrasubstituted product **22** was obtained.

If the hydrogen introduction was indeed the initial step in the process, then cross coupling with chlorides, such as **23** or **24** should lead cleanly to trisubstituted products, such as **6**. When the *trans* chloride **23**[17] was used in a coupling with borane **5**, the trisubstituted product **6** was produced. The use of the corresponding *cis* chloride **24**[17] in a similar reaction led to the formation of isomeric olefin **7**. The results of these experiments were consistent with a sequence in which the hydrogen was introduced onto the template before the alkyl group was transferred. These observations also suggested that the stereochemistry of the final trisubstituted olefins was established during the introduction of the hydrogen onto the chloro–iodo template.

3. Conclusion

A stereoselective and regiospecific cross coupling of alkyl boranes and *E*-β-chloro-α-iodo-α,β-unsaturated ester templates that produces single isomer trisubstituted olefins was developed. This method is convenient, and is a reliable way to selectively prepare stereodefined trisubstituted olefins. The reaction is compatible with a variety of functional groups and proceeds under very mild reaction conditions. Mechanistic experiments are consistent with a process in which the stereochemistry of the product is established during an initial proton transfer. The details of this process are still unclear and will require further investigation to elucidate.

4. Experimental section

4.1. General

Reactions were performed under nitrogen in flame-dried glassware equipped with a magnetic stir bar and a rubber septum. Solvents were freshly distilled prior to use as follows: THF and toluene over sodium/benzophenone; dioxane over calcium hydride. All other reagents were obtained from commercial sources and used without further purification unless otherwise indicated. Reactions were monitored by TLC analysis using aluminum plates precoated with silica gel 60 F_{254}. The plates were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or *p*-anisaldehyde stains. Flash chromatography was carried out on 230–400 mesh silica gel 60. ^1H and ^{13}C NMR spectra were acquired on a Bruker Advance 400 MHz instrument in the specified solvent, reporting chemical shifts downfield from tetramethylsilane. Infrared spectra were acquired from neat films on a sodium chloride cell using a Bomen Michaelson 100 FTIR spectrometer. High resolution mass spectra were obtained using an Analytical Concept spectrometer using either electron impact (EI) or chemical ionization (CI). High resolution mass spectroscopy (HRMS) was performed with an electron beam of 70 eV, or using a double focusing magnetic sector mass spectrometer. Melting points were determined using an Electrothermal Meltemp apparatus and are uncorrected.

4.2. General procedure for the preparation of trisubstituted alkenes from (2*E*)-3-chloro-2-iodo-2-alkenoates. (6*E*)-8-Ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (6)

To an oven dried flask equipped with a Teflon-coated stir bar was added $Pd(OAc)_2$ (6.1 mg, 0.0091 mmol), *S*-phos (7.5 mg, 0.0182 mmol), and $K_3PO_4\cdot H_2O$ (125 mg, 0.546 mmol) under a nitrogen atmosphere. Freshly distilled THF was added (1.0 mL) followed by a solution of (2*E*)-ethyl 3-chloro-2-iodobut-2-enoate **1**[18] (50 mg, 0.182 mmol) in THF (1 mL). To a second oven dried flask

equipped with a Teflon-coated stir bar were added pent-4-enyl benzoate (104 mg, 0.546 mmol) and 9-borabicyclo[3.3.1]nonane (0.5 M solution in THF, 1.10 mL, 0.546 mmol). The resulting mixture was stirred at room temperature for 2 h. This alkyl-9-BBN solution was transferred to the first flask via cannula, and the resulting mixture was stirred for 18 h at room temperature. The solution was then diluted with Et_2O and washed three times with H_2O. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The pure product (48 mg, 86%) was obtained as a yellow oil by flash chromatography (2% EtOAc in hexane): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.03–8.01 (m, 2H), 7.66–7.61 (m, 1H), 7.54–7.49 (m, 2H), 5.68 (q, J=1.2 Hz, 1H), 4.32 (t, J=6.4 Hz, 2H), 4.08 (q, J=7.2 Hz, 2H), 2.22 (td, J=7.6, 1.2 Hz, 2H), 2.15 (d, J=1.2 Hz, 3H), 1.82 (p, J=6.4 Hz, 2H), 1.64–1.47 (m, 4H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.8 (C), 167.7 (C), 134.8 (CH), 132.4 (C), 131.1 (CH), 130.4 (CH), 130.1 (C), 117.4 (CH), 66.4 (CH_2), 60.7 (CH_2), 42.1 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 19.6 (CH_3), 15.6 (CH_3); IR (neat) 1718, 1648 cm^{-1}; MS 304.2 (M^+); HRMS calcd for $C_{18}H_{24}O_4$ 304.1675, found 304.1659.

*4.2.1. (2E)-Ethyl 3-methylundec-2-enoate (**3**).* Prepared from ethyl (2*E*)-3-chloro-2-iodobut-2-enoate **1**[18] (50 mg, 0.182 mmol) using a procedure similar to that described that provided the title compound after purification by flash chromatography (1% EtOAc in hexane) as a colorless oil (34 mg, 82%). ^{1}H NMR (400 MHz, acetone-d_6) δ 5.65 (q, J=1.2 Hz, 1H), 4.09 (q, J=7.2 Hz, 2H), 2.17 (td, J=7.2, 1.2 Hz, 2H), 2.14 (d, J=1.2 Hz, 3H), 1.53–1.26 (m, 12H), 1.22 (t, J=7.2 Hz, 3H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.8 (C), 161.7 (C), 117.2 (CH), 60.7 (CH_2), 42.3 (CH_2), 33.6 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 30.9 (CH_2), 29.2 (CH_2), 24.3 (CH_2), 19.6 (CH_3), 15.6 (CH_3), 15.3 (CH_3); IR (neat) 1637 cm^{-1}; MS 226.2 (M^+); HRMS calcd for $C_{14}H_{26}O_2$ (M^+) 226.1933, found 226.1904.

*4.2.2. (6Z)-8-Methoxy-8-oxooct-6-enyl benzoate (**9**).* Prepared from ethyl (2*E*)-3-chloro-2-iodoacrylate **8**[18] (57 mg, 0.230 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (19.1 mg, 30%). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.04–8.01 (m, 2H), 7.66–7.61 (m, 1H), 7.53–7.49 (m, 2H), 6.36–6.29 (dt, J=11.2, 7.2 Hz, 1H), 5.79 (dt, J=11.2, 1.6 Hz, 1H), 4.32 (t, J=6.4 Hz, 2H), 3.65 (s, 3H), 2.70 (dq, J=7.2, 2.0 Hz, 2H), 1.84–1.77 (m, 2H), 1.56–1.48 (m, 4H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.9 (C), 167.8 (C), 151.9 (CH), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 121.2 (CH), 66.4 (CH_2), 52.1 (CH_3), 30.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 27.2 (CH_2); IR (neat) 1713, 1637 cm^{-1}; MS 245.1 (M^+-OCH_3); HRMS calcd for $C_{15}H_{17}O_3$ (M^+-OCH_3) 245.1178, found 245.1154.

*4.2.3. (6Z)-6-Cyclohexyl-8-ethoxy-8-oxoocto-6-enyl benzoate (**11**).* Prepared from ethyl (2*E*)-3-chloro-3-cyclohexyl-2-iodoacrylate **10**[18] (50 mg, 0.146 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (25 mg, 46%). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.04–8.02 (m, 2H), 7.66–7.61 (m, 1H), 7.53–7.49 (m, 2H), 5.59 (br, 1H), 4.33 (t, J=6.4 Hz, 2H), 4.08 (q, J=7.2 Hz, 2H), 3.68 (m, 1H), 2.22 (t, J=6.4 Hz, 2H), 1.87–1.26 (m, 16H), 1.22 (t, J=6.8 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 169.7 (C), 167.7 (C), 167.6 (C), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 116.2 (CH), 66.4 (CH_2), 60.8 (CH_2), 42.3 (CH), 34.7 (CH_2), 32.7 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 15.6 (CH_3); IR (neat) 1717, 1633 cm^{-1}; MS 327.2 ($M^+-OCH_2CH_3$); HRMS calcd for $C_{21}H_{27}O_3$ ($M^+-OCH_2CH_3$) 327.1955, found 327.1933.

*4.2.4. (6E)-6-(2-Methoxy-2-oxoethylidene)undecyl benzoate (**13**).* Prepared from methyl (2*E*)-3-chloro-2-iodooct-2-enoate **12**[18] (53 mg, 0.168 mmol) using a procedure similar to that described that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (43 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.58–7.53 (m, 1H), 7.46–7.42 (m, 2H), 5.63 (s, 1H), 4.32 (t, J=6.8 Hz, 2H), 3.67 (s, 3H), 2.59 (td, J=7.6, 2.0 Hz, 2H), 2.17 (td, J=7.6, 0.8 Hz, 2H), 1.79 (m, 2H), 1.59–1.41 (m, 8H), 1.35–1.30 (m, 2H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.9 (C), 166.6 (C), 164.8 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 114.8 (CH), 64.8 (CH_2), 50.8 (CH_3), 38.2 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 25.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3); IR (neat) 1712, 1701 cm^{-1}; MS 315.2 (M^+-OCH_3); HRMS calcd for $C_{20}H_{27}O_3$ (M^+-OCH_3) 315.1955, found 315.1953.

*4.2.5. (6E)-6-(2-Ethoxy-2-oxoethylidene)-10-(triisopropylsilyloxy) decyl benzoate (**15**).* Prepared from ethyl (2*E*)-3-chloro-2-iodo-7-(triisipropylsilyloxy)hept-2-enoate **14** (50 mg, 0.103 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (35 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.41 (m, 2H), 5.64 (s, 1H), 4.32 (t, J=6.6 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.69 (t, J=6.0 Hz, 2H), 2.63 (t, J=7.5 Hz, 2H), 2.18 (t, J=6.9 Hz, 2H), 1.79 (m, 2H), 1.58–1.43 (m, 8H), 1.27 (t, J=7.2 Hz, 3H), 1.04 (s, 21H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 163.9 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 115.6 (CH), 64.9 (CH_2), 63.1 (CH_2), 59.5 (CH_2), 38.1 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 28.6 (CH_2), 27.3 (CH_2), 25.8 (CH_2), 24.9 (CH_2), 18.0 (CH_3), 14.3 (CH_3), 11.9 (CH); IR (neat) 1716, 1720 cm^{-1}; MS 475.3 ($M^+-CH(CH_3)_2$); HRMS calcd for $C_{27}H_{43}O_5Si$ ($M^+-CH(CH_3)_2$) 475.2874, found 475.2909.

*4.2.6. (2E)-Ethyl 8-(benzyloxy)-3-methyloct-2-enoate (**16**).* Prepared from ethyl (2*E*)-3-chloro-2-iodobut-2-enoate **1**[18] (50 mg, 0.182 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (39 mg, 73%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.34–7.24 (m, 5H), 5.66 (q, J=1.2 Hz, 1H), 4.48 (s, 2H), 4.09 (q, J=7.2 Hz, 2H), 3.47 (t, J=6.4 Hz, 2H), 2.18 (td, J=7.6, 0.9 Hz, 2H), 2.14 (d, J=1.2 Hz, 3H), 1.66–1.59 (m, 2H), 1.55–1.48 (m, 2H), 1.43–1.36 (m, 2H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.8 (C), 161.6 (C), 141.1 (C), 130.0 (CH), 129.2 (CH), 129.1 (CH), 117.3 (CH), 74.2 (CH_2), 71.7 (CH_2), 60.7 (CH_2), 42.3 (CH_2), 31.3 (CH_2), 28.9 (CH_2). 27.6 (CH_2), 19.6 (CH_3), 15.6 (CH_3); IR (neat) 1634 cm^{-1}; MS 245.2 ($M^+-OCH_2CH_3$); HRMS calcd for $C_{16}H_{21}O_2$ ($M^+-OCH_2CH_3$) 245.1536, found 245.1574.

*4.2.7. (2E)-Ethyl 3-methyl-8-(triisopropylsilyloxy)oct-2-enoate (**17**).* Prepared from ethyl (2*E*)-3-chloro-2-iodobut-2-enoate **1**[18] (50 mg, 0.182 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (34 mg, 60% from ethyl but-2-ynoate). ^{1}H NMR (300 MHz, acetone-d_6) δ 5.66 (s, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.74 (t, J=6.0 Hz, 2H), 2.19 (t, J=7.2 Hz, 2H), 2.14 (d, J=1.2 Hz, 3H), 1.62–1.38 (m, 6H), 1.22 (t, J=7.2 Hz, 3H), 1.09–1.06 (m, 21H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.8 (C), 161.5 (C), 117.3 (CH), 64.9 (CH_2), 60.7 (CH_2), 42.3 (CH_2), 34.5 (CH_2), 28.9 (CH_2), 27.2 (CH_2), 19.6 (CH_3), 19.4 (CH), 15.7 (CH_3), 13.7 (CH_3); IR (neat) 1645 cm^{-1}; MS 313.2 ($M^+-CH(CH_3)_2$); HRMS calcd for $C_{17}H_{33}O_3Si$ (M^+) 313.2193, found 313.2181.

*4.2.8. (5E)-7-Ethoxy-3,5-dimethyl-7-oxohept-5-enyl benzoate (**18**).* Prepared from ethyl (2*E*)-3-chloro-2-iodobut-2-enoate **1**[18] (50 mg, 0.182 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (42 mg, 76%). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.05–8.02 (m, 2H), 7.66–7.61 (m, 1H), 7.54–7.49 (m, 2H), 5.70 (q, J=1.2 Hz, 1H), 4.44–4.34 (m, 2H), 4.09 (q, J=7.2 Hz, 2H), 2.32–2.28 (m, 1H), 2.15 (d, J=1.2 Hz, 3H), 2.09 (dd,

J=1.2, 8.0 Hz, 1H), 1.87–1.79 (m, 1H), 1.65–1.57 (m, 2H), 1.22 (t, J=7.2 Hz, 3H), 0.97 (d, J=6.4 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.7 (C), 167.6 (C), 160.0 (C), 134.8 (CH), 132.4 (C), 131.1 (CH), 130.4 (CH), 118.9 (CH), 64.6 (CH_2), 60.8 (CH_2), 49.9 (CH_2), 37.1 (CH_2), 29.8 (CH), 20.7 (CH_3), 19.5 (CH_3), 15.6 (CH_3); IR (neat) 1645 cm^{-1}; MS 259.1 (M+−OCH_2CH_3); HRMS calcd for $C_{16}H_{19}O_3$ (M^+−OCH_2CH_3) 259.1329, found 259.1359.

*4.2.9. (6E)-7-Deutero-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (**20**).* Prepared from ethyl (2*E*)-3-chloro-2-iodobut-2-enoate **1**[18] (50 mg, 0.182 mmol) and D_2O (10 μL, 0.546 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil. ^{1}H NMR (400 MHz, acetone-d_6) (H/D:1:0.67) δ 8.03–8.01 (m, 2H), 7.66–7.61 (m, 1H), 7.54–7.49 (m, 2H), 5.68 (q, J=1.2 Hz, 0.33H), 4.32 (t, J=6.4 Hz, 2H), 4.08 (q, J=7.2 Hz, 2H), 2.22 (td, J=1.2, 7.6 Hz, 2H), 2.15 (d, J=1.2 Hz, 3H), 1.82 (p, J=6.4 Hz, 2H), 1.64–1.47 (m, 4H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 167.8(C), 167.7 (C), 161.3 (C), 134.7 (CH), 132.4 (C), 131.1 (CH), 130.3 (CH), 117.3 (CH), 66.4 (CH_2), 60.7 (CH_2), 42.1 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 19.5 (CH_3), 15.6 (CH_3); IR (neat) 1713, 1648 cm^{-1}; MS 305.2 (M^+−OCH_2CH_3); HRMS calcd for $C_{16}H_{18}DO_3$ (M^+−OCH_2CH_3) 260.1391, found 260.1374.

*4.2.10. (2E)-Ethyl 7-(benzyloxy)-2-iodo-3-methylhept-2-enoate (**21**).* To an oven dried round bottom flask (100 mL) equipped with a Teflon-coated stir bar were added CuI (0.37 g, 1.93 mmol) and freshly distilled THF (15.0 mL), followed by freshly titrated MeLi (1.0 M solution in Et_2O; 3.84 mL, 3.84 mmol) under a nitrogen atmosphere. The reaction mixture was cooled to −78 °C. A solution of ethyl 7-(benzyloxy)hep-2-ynoate (0.5 g, 1.92 mmol) in THF (5.0 mL) was introduced via cannula and the resulting mixture was stirred at the same temperature for 1 h. Following the addition of I_2 (1.46 g, 5.76 mmol), the reaction mixture was cooled to 0 °C and stirred for an additional 2 h. The reaction was quenched with saturated NH_4Cl, the mixture was extracted twice with Et_2O, then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The pure product (0.52 g, 68%) was obtained after flash chromatography (2% Et_2O in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 4.49 (s, 2H), 4.22 (q, J=7.2 Hz, 2H), 3.47 (t, J=6.0 Hz, 2H), 2.46 (t, J=7.2 Hz, 2H), 2.04 (s, 3H), 1.64–1.57 (m, 4H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.7 (C), 153.9 (C), 138.5 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 72.9 (CH_2), 69.9 (CH_2), 61.8 (CH_2), 36.3 (CH_2), 29.4 (CH_2), 29.1 (CH_3), 24.9 (CH_2), 14.0 (CH_3); IR (neat) 1709 cm^{-1}; MS 402.1 (M^+); HRMS calcd for $C_{17}H_{23}O_3I$ (M^+) 402.0692, found 402.0701.

*4.2.11. (6E)-11-(Benzyloxy)-6-(ethoxycarbonyl)-7-methylundec-6-enyl benzoate (**22**).* Prepared from (2*E*)-ethyl 7-(benzyloxy)-2-iodo-3-methylhept-2-enoate **21** (50 mg, 0.124 mmol) using a procedure similar to that described above that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (18.4 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.02 (m, 2H), 7.58–7.52 (m, 1H), 7.46–7.41 (m, 2H), 7.34–7.27 (m, 5H), 4.49 (s, 2H), 4.31 (t, J=6.6 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 3.47 (t, J=6.3 Hz, 2H), 2.27 (t, J=7.8 Hz, 4H), 1.77 (s, 3H), 1.67–1.39 (m, 10H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.9 (C), 166.6 (C), 144.2 (C), 138.6 (C), 132.8 (CH), 130.5 (C), 129.5 (CH), 128.4 (C), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 72.9 (CH_2), 70.3 (CH_2), 64.9 (CH_2), 59.9 (CH_2), 36.2 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 25.9 (CH_2), 25.0 (CH_2), 19.2 (CH_3), 14.3 (CH_3); IR (neat) 1717, 1698 cm^{-1}; MS 421.2 (M^+−OCH_2CH_3); HRMS calcd for $C_{27}H_{33}O_4$ (M^+−OCH_2CH_3) 421.2373, found 421.2369.

*4.2.12. (E)-Ethyl 3-chloro-2-iodo-7-(triisopropylsilyloxy)hept-2-enoate (**14**).* To an oven dried round bottom flask (100 mL) equipped with a Teflon-coated stir bar was added ethyl 7-(triisopropylsilyloxy) hept-2-ynoate (1.05 g, 3.22 mmol) in 32 mL $ClCH_2CH_2Cl$ followed by BU_4NI (3.6 g, 9.67 mmol). The solution was refluxed for 72 h. When the reaction was judged to be complete by TLC, the solution was cooled and washed twice with 10% aqueous $NaHSO_3$, saturated sodium bicarbonate, and brine. The organic phase was then dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by flash chromatography (1% Et_2O in hexanes) to afford the title compound as a clear oil (0.7 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, J=6.9 Hz, 2H), 3.72 (t, J=6.3 Hz, 2H), 2.72 (t, J=7.2 Hz, 2H), 1.76–1.57 (m, 4H), 1.33 (t, J=7.2 Hz, 2H), 1.07–1.03 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.0 (C), 138.9 (C), 80.3 (C), 62.8 (CH_2), 62.4 (CH_2), 41.4 (CH_2), 31.8 (CH_2), 23.3 (CH_2), 18.1 (CH_3), 13.9 (CH_3), 12.0 (CH_3); IR (neat) 1732 cm^{-1}; MS 445.0 (M^+−$CH(CH_3)_2$); HRMS calcd for $C_{15}H_{27}ClIO_3Si$ (M^+−$CH(CH_3)_2$) 445.0457, found 445.0483.

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Supplementary data

Experimental procedures and product characterization data for the E isomers. ^{1}H and ^{13}C spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.002. These data include MOL files and InChIKeys of the most important compounds described in this article.

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10. Similar analyses were carried out for the other products described in this work.

11. Reactions using the bases listed in entries 4–10 in which no water was added resulted in no reaction
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