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A simple method to prepare single isomer tetrasubstituted olefins by successive Suzuki–Miyaura cross-couplings of *E*-β-chloro-α-iodo-α,β-unsaturated esters

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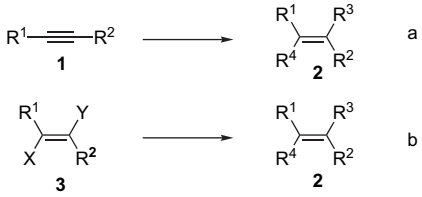
ABSTRACT

A convenient method of synthesizing tetrasubstituted olefins as single isomers is described. *E*-β-Chloro-α-iodo-α,β-unsaturated esters are first converted into the corresponding *E*-β-chloro-α,β-unsaturated esters using Suzuki–Miyaura coupling reactions with arylboronic acids and alkenylboronic acids. These transformations gave complete selectivity, and proceeded with substitution at the more activated α-iodide position. These compounds, isolated as single isomers, were then transformed into tetrasubstituted olefins by Suzuki–Miyaura couplings with arylboronic acids, alkenylboronic acids, and alkyl boranes to afford the corresponding tetrasubstituted olefins as single isomers. During this coupling process, it was discovered that the use of small ligands, such as PMe_3 or PEt_3, was critical for efficient coupling. The stereochemistry and regiochemistry of the products were unequivocally established using NMR methods.

1. Introduction

The efficient regio- and stereodefined synthesis of tetrasubstituted olefins bearing four different carbon-linked appendages presents a significant challenge.[1] The congested nature of the double bond often makes it difficult for reagents to approach each other, reducing the utility of many 'traditional' olefin-producing reactions. The majority of the methods that have been developed to produce tetrasubstituted olefins rely either on the carbometallation of alkynes or on the use of olefin templates in cross-coupling reactions. Alkyne carbometallation is perhaps the most widely used method,[1,2] and because of the convergent nature of the strategy, in principle it provides maximum structural variation (Scheme 1a). Tetrasubstituted double bonds can also be prepared by manipulating a pre-existing olefin template (Scheme 1b).[1,3] Generating the template is often the most difficult aspect of this approach, requiring the installation of directing elements for chemo-, regio-, and stereocontrol. Selectivity issues may arise during the subsequent cross-coupling stages that can lead to the production of isomeric mixtures that may be extremely difficult to resolve.

Many natural products[4] and pharmaceuticals[3b,5,6] contain tetrasubstituted olefins as important structural elements. Tetrasubstituted olefins can also be used as intermediates in asymmetric transformations that generate quaternary centers such as osmylations,[7] epoxidations,[8] and conjugate additions.[9] Compounds containing tetrasubstituted alkenes have been employed as dipeptide mimetics[10] as well as polymerization substrates and catalysts.[11] Material science makes use of these functionalities because of their physical,[12] structural, and electronic properties;[13] and these moieties have often been used to form molecular switches[14] or optical storage devices.[15] All of these applications require preparative chemical transformations that are reliable, simple to perform, and that deliver the products as single isomers.



Scheme 1. General strategies for tetrasubstituted olefin formation.

We have recently developed a mild and versatile method of synthesizing acyclic, single isomer olefins bearing four different carbon-linked substituents.[16] These alkenes were obtained using a differentially halogenated template that was submitted to sequential Sonogashira coupling reactions to produce trans ene–diynes. Herein, we describe the optimization of sequential Suzuki coupling reactions to these templates using arylboronic acids and alkylboranes, a challenging task given the steric demands of the substrates and reagents. An extensive package of tetrasubstituted olefins formed by a simple, regioselective and stereoselective, three-step method is disclosed as well.

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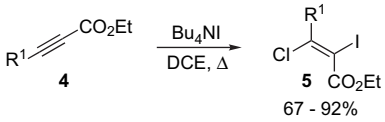
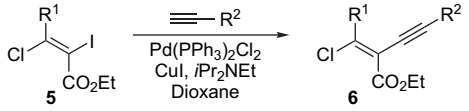
2. Results and discussion

The efficient synthesis of *E*-β-chloro-α-iodo-α,β-unsaturated esters by the exposure of 2-alkynyl esters to Bu_4NI in refluxing dichloroethane represents a versatile entry into tetrasubstituted olefin production.[17] This method gives β-chloro-α-iodo olefin templates such as **5** with complete control of regio- and stereochemistry. This process is directed by the presence of an electron-withdrawing group on the alkyne and provides the starting point for subsequent organometallic coupling reactions that convert the template into a single isomer, all carbon-linked alkene (Scheme 2).



Scheme 2. Generation of single isomer *E*-β-chloro-α-iodo-α,β-unsaturated esters.

The introduction of substituents onto the *E*-β-chloro-α-iodo templates can be done selectively and smoothly. Sonogashira reactions were first explored to obtain intermediate trisubstituted olefins, a task that required some optimization in order to obtain good yields and, importantly, single isomers.[16] Starting with templates **5**, submission to typical Sonogashira conditions produced the desired products **6** that were isolated as single isomers in good yield (Scheme 3).



Scheme 3. Sonagashira coupling of *E*-β-chloro-α-iodo-α,β-unsaturated esters to produce trisubstituted olefin templates.

These results were significant in that they demonstrated that selectivity could be achieved in the cross-coupling of dihalogenated templates such as **5**. Of particular interest was the facile and preferential displacement of the α-iodo substituent. Related templates bearing identical halogens at both the α- and β-position invariably react at the more activated β-position first,[18] a trend reversed in the present series due to the increased reactivity of the iodide relative to the chloride.

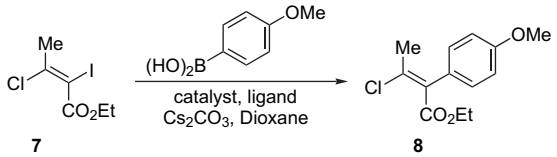
Encouraged by our success with the Sonogashira coupling reaction, efforts were then directed to the development of a Suzuki coupling process[19] in order to introduce a larger variety of nucleophiles at the α-position of substrate **7** (Table 1). The testing of a variety of palladium catalyst precursors suggested that selectivity was possible in this process, however the efficiency of the reaction was very sensitive to the palladium source. The use of $PdCl_2(PPh_3)_2$ (entry 3) gave a moderate improvement in yield compared to the $Pd_2(dba)_3$ that was used originally (entry 1), while the use of $Pd(dppf)Cl_2$ alone resulted in a lower product recovery (entry 2). Using $Pd(OAc)_2$ as a palladium source (entry 4) afforded the highest yield when using P^tBu_3 as the ligand.

Using the best conditions described above as a starting point, an optimization of the reaction solvent was then performed (Table 2). Interestingly, the use of polar solvents such as acetonitrile (entry 1), DMSO (entry 2) or DMF (entry 3) did not lead to any of the desired product. Performing the reaction in other common solvents such as THF, benzene or $CHCl_3$ gave modest amounts of product, but the use of these solvents did not produce any advantages over the dioxane originally used (entries 4–9). A slight but significant increase in the yield of the monosubstituted product **8** was realized when reactions were performed in EtOAc or in toluene (entries 10–12), with toluene giving the best conversion to products.

During these optimization studies, significant amounts of the tetrasubstituted olefin were produced. Because this product was the result of an over-reaction at the β-position, we investigated the possibility of improving the selectivity by lowering the reaction temperature. As shown in Table 3, lowering the temperature of the reaction to 0 °C did not lead to any improvement in reaction selectivity (entry 2). Raising the temperature slightly, however, resulted in a significant increase in the amount of tetrasubstituted product **10** that was formed (entry 3). As there was no advantage in lowering the reaction temperature compared to performing the reactions at room temperature, the more practical conditions were employed for the next set of experiments.

The ligand was found to have a profound impact on reaction efficiency (Table 4). Initial experiments were carried out using $Pd(OAc)_2$ and $P^tBu_3\cdot HBF_4$. These conditions delivered a modest yield of the desired product **9**, together with a small amount of tetrasubstituted adduct **10** (entry 1). Reducing the size of the ligand resulted in the production of significant amounts of the double-coupled material (entries 2–4). Unfortunately, the use of other hindered ligands such as PCy_3 did not improve selectivity, nor did the use of PPh_3 or bidentate ligands such as DPPF (entries 5–7). Use of the biphenyl ligand *S*-PHOS produced a remarkably selective reaction (entry 8), a result that was unequaled by a related ligand

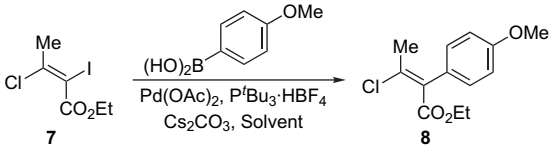
Table 1
Effect of the palladium source in Suzuki coupling reactions at the α-position of **7**



Entry[a]	Catalyst	Ligand	Yield[b] (%)
1	$Pd_2(dba)_3$	$P^tBu_3\cdot HBF_4$	17
2	$Pd(dppf)Cl_2$	—	10
3	$PdCl_2(PPh_3)_2$	$P^tBu_3\cdot HBF_4$	35
4	$Pd(OAc)_2$	$P^tBu_3\cdot HBF_4$	45

[a] Conditions: 0.1 equiv of catalyst, 0.2 equiv of ligand, 4.0 equiv of boronic acid, 4.0 equiv of Cs_2CO_3, and dioxane, 23 °C.
[b] Tetrasubstituted (15–25%) olefin was also obtained in each of these reactions.

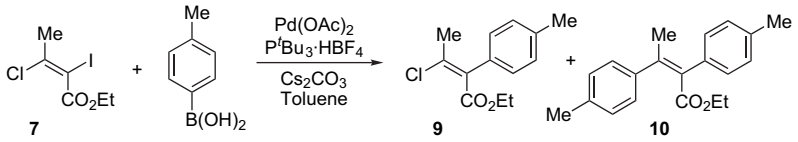
Table 2
Effect of the solvent in the Suzuki coupling reactions of **7**



Entry[a]	Solvent	Yield (%)
1	CH_3CN	NR
2	DMSO	NR
3	DMF	NR
4	CH_2Cl_2	Trace
5	THF	26
6	Benzene	17
7	$CHCl_3$	34
8	Trifluorotoluene	38
9	^{t}BuOMe	35
10	Dioxane	45
11	EtOAc	50
12	Toluene	60

[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of $P^tBu_3\cdot HBF_4$, 4.0 equiv of boronic acid, 4.0 equiv of Cs_2CO_3, and 23 °C.

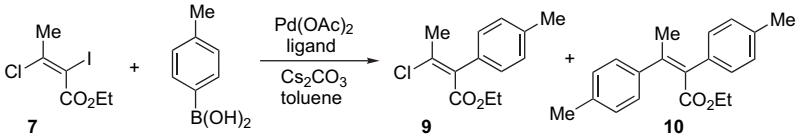
Table 3
Effect of temperature on the efficiency of the Suzuki coupling reaction of **7**



Entry[a]	Temperature (°C)	Yield **9** (%)	Yield **10** (%)
1	23	21	3
2	0	23	2
3	45	18	13

[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of $P^tBu_3 \cdot HBF_4$, 2.0 equiv of boronic acid, 2.0 equiv of Cs_2CO_3, and toluene.

Table 4
Effect of the ligand in the Suzuki coupling of β-chloro-α-iodo-α,β-unsaturated ester **7**



Entry[a]	Ligand	Yield **9**[b] (%)	Yield **10**[b] (%)
1	$P^tBu_3 \cdot HBF_4$	21	3
2	$P^tBuMe_2 \cdot HBF_4$	16	30
3	$PEt_3 \cdot HBF_4$	23	20
4	$PMe_3 \cdot HBF_4$	20	27
5	$PCy_3 \cdot HBF_4$	21	43
6	PPh_3	10	12
7	DPPF	7	19
8	*S*-PHOS	81 (99)	Trace
9	Dave-PHOS	45 (65)	15
10	None	Trace	65 (99)

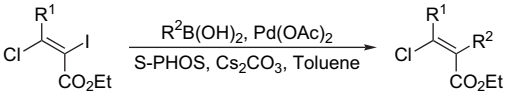
[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of ligand, 2.0 equiv of boronic acid, 2.0 equiv of Cs_2CO_3, toluene, and 23 °C.
[b] Yields in parentheses are corrected for unreacted starting material.

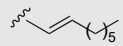
(entry 9). By using ligand-free conditions, clean conversion to the tetrasubstituted olefin product **10** was achieved (entry 10). This result suggested a simple method of carrying out the subsequent conversion of chlorides such as **9** into the ultimately desired single isomer tetrasubstituted products **10**.

The reaction with a variety of substrates and coupling partners was then investigated (Table 5). Selective coupling at the α-position of the β-chloro-α-iodo-substituted substrates was observed for all examples, demonstrating that this position was more activated toward oxidative addition than was the β-position. Coupling with phenylboronic acid resulted in a full conversion of the unsaturated ester **7** to product **11** (entry 2). Substitution on the phenyl ring of the boronic acid gave very good yields with electron-donating groups such as methoxy at the *para*, *meta* and even at the sterically demanding *ortho* position (entries 3–5). An aryl group substituted with fluorine at the *para* position reacted smoothly (entry 6), as did the sterically hindered 1-naphthyl (entry 7) and 2-naphthyl (entry 8) moieties. We were delighted to observe that heterocycles such as thiophene (entry 9) could be added, giving the corresponding trisubstituted product **17**. We further expanded the scope of the reaction to vinyl Suzuki processes, and successfully introduced both a styrenyl substituent and an alkenyl group (entries 10 and 11). The substituent at the β-position of the olefin could be varied to include bulky functions such as a cyclohexyl group (entry 12) or functionalized alkyl chains (entry 13), illustrating that the nature of the R^1 substituent did not significantly impact the reactivity of the template. In all cases the reaction was regioselective and stereoselective, giving single isomers during the process.

With a successful strategy in hand to make the appropriate trisubstituted olefin templates, the synthesis of all carbon tetrasubstituted alkenes bearing four different groups was then explored. Some α-alkynyl-β-chloro substrates such as **6** have previously been subjected to Suzuki coupling conditions to generate a variety of tetrasubstituted alkenes.[16] However, the α-aryl-β-

Table 5
Suzuki coupling of α-iodo-β-chloro-α,β-unsaturated esters with a variety of boronic acids



Entry[a]	Substrate	R^1	R^2	Product	Yield[b] (%)
1	**7**	Me	*p*-MeC_6H_4	**9**	81 (99)
2	**7**	Me	C_6H_5	**11**	100
3	**7**	Me	*p*-$OMeC_6H_4$	**8**	84
4	**7**	Me	*o*-$OMeC_6H_4$	**12**	93
5	**7**	Me	*m*-$OMeC_6H_4$	**13**	65 (98)
6	**7**	Me	*p*-FC_6H_4	**14**	82[c]
7	**7**	Me	1-Naphthyl	**15**	94
8	**7**	Me	2-Naphthyl	**16**	95
9	**7**	Me	2-Thiophenyl	**17**	64 (100)
10	**7**	Me	Styrenyl	**18**	85[d]
11	**7**	Me		**19**	75[d]
12	**20**	Cy	*p*-$OMeC_6H_4$	**21**	79
13	**22**	CH_2OTBS	*p*-$OMeC_6H_4$	**23**	74

[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of *S*-PHOS, 4.0 equiv of boronic acid, 4.0 equiv of Cs_2CO_3, toluene, and 23 °C.
[b] Yields in parentheses are corrected for unreacted starting material.
[c] (*E*)-ethyl 3-(4-fluorophenyl)-but-2-enoate (14%) was also obtained.
[d] Reaction run at 5 °C.

chloro substituted compounds such as **8** were much more crowded than the α-alkynyl-β-chloro substrates **6**, and so we undertook investigations to develop practical conditions to introduce the required aryl substituents. The ligand-free conditions that had previously been found to promote the formation of tetrasubstituted olefins directly from substrate **7** (Table 4, entry 10) were investigated first. Although the use of $Pd(OAc)_2$ alone in dioxane/water had previously given very high conversions of **7** to the tetrasubstituted product **10**, the application of these conditions to the transformation of **8** to **24** was unsuccessful (Table 6, entry 1). Because $Pd(OAc)_2$ alone did not give any of the tetrasubstituted product, the effect of ligand size was investigated as a means of introducing groups at the β-position of chloride-containing substrates such as **8**. As shown, the use of large ligands such as P^tBu_3 or P^tBuMe_2 did not result in the production of significant amounts of tetrasubstituted olefin **24** (entries 2 and 3). The use of PPh_3 was also unfruitful, as all of the starting material was returned unchanged (entry 6). Smaller ligands such as PEt_3 or PMe_3 were, however, very efficient in promoting the cross-coupling, giving an excellent yield of tetrasubstituted olefin **24** as a single stereoisomer (entries 4 and 5). The use of small ligands such as PMe_3 in cross-couplings is unusual, but in the production of congested materials such as **24**, these ligands appear to afford significant advantages.

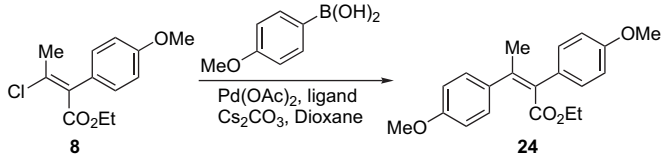
The reaction was compatible with a large variety of functionalities, and substitution at the *para*, *meta*, and even the *ortho* position of the boronic acid component resulted in successful reactions (Table 7, entries 1–3). A simple phenyl group was easily installed, as were aromatic groups substituted with fluorine or methyl at the *para* position (entries 4–6). The reaction could be extended to include alkenyl substituents bearing alkyl or aromatic functionalities (entries 7 and 8), although we were unable to introduce heterocycles such as thiophene (entry 9). Hindered naphthyl groups could be added, but the yield of the process depended on the attachment point to the naphthyl moiety (entries 10 and 11). As before, branched substituents were tolerated at the R^1 position, and substituted alkyl groups could also be present on the olefin template (entries 12 and 13). All of the reactions were stereoselective and all products were isolated as single isomers.

The scope of the functionalities available was further expanded by investigating alkyl-Suzuki coupling reactions on the trisubstituted alkenyl chlorides (Table 8). The use of a typical catalyst and base for this conversion, under anhydrous conditions, was unsuccessful (entry 1). The use of bidentate ligands such as DPPF, DPPM, DPPE, DPPP, or DPPB in THF with K_3PO_4 as a base also met with failure. The biphenyl ligand XANTPHOS was tested, but the use of this material did not result in the formation of a tetrasubstituted olefin. The addition of H_2O to the reaction mixture ultimately led to a successful reaction. Using the hydrated form of K_3PO_4 resulted in the isolation of a small amount of the desired alkyl substituted product **36** (entry 2). The addition of water to the reaction when using anhydrous K_3PO_4 as the base also resulted in the production of this desired material (entry 3). Finally, the use of dioxane, rather than THF as the principal solvent was tested in combination with water. These conditions produced a 64% yield of the alkyl substituted product **36**, rendering the process synthetically useful (entry 4).

These optimized conditions were successfully applied to a number of different substrates and alkyl boranes (Table 9). Simple alkyl chains coupled smoothly to substrates bearing a trimethylsilyl-substituted acetylene (entry 1) as well as to compounds possessing a phenyl terminus on the triple bond (entry 2). Products bearing more polar alkyl chains were easily obtained from different substrates (entries 3 and 4). Aryl substituted olefins obtained by Suzuki couplings at the α-position were also good substrates for this transformation (entries 5 and 6), giving the desired products **40** and **41** in good yields. In these latter reactions, the use of PMe_3 was required in order to achieve efficient coupling. As in all of the other coupling processes developed by our group, the reactions were stereoselective and the products were obtained as single isomers.

The regio- and stereochemistry of all final products were confirmed by NOE methods. This analysis was performed at every stage of the coupling process to confirm the stereochemical and

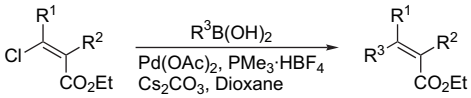
Table 6
Effect of ligand size on the generation of tetrasubstituted olefins

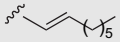


Entry[a]	Ligand	Yield (%)
1	None	NR
2	$P^tBu_3 \cdot HBF_4$	22
3	$P^tBuMe_2 \cdot HBF_4$	NR
4	$PEt_3 \cdot HBF_4$	85
5	$PMe_3 \cdot HBF_4$	99
6	PPh_3	NR

[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of ligand, 2.0 equiv of boronic acid, 2.0 equiv of Cs_2CO_3, dioxane, and 23 °C.

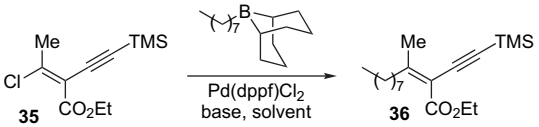
Table 7
Single isomer tetrasubstituted olefins prepared using the Suzuki reaction



Entry[a]	Substrate	R^1	R^2	R^3	Product	Yield[b] (%)
1	**8**	Me	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	**24**	95
2	**8**	Me	*p*-$OMeC_6H_4$	*o*-$OMeC_6H_4$	**25**	91
3	**8**	Me	*p*-$OMeC_6H_4$	*m*-$OMeC_6H_4$	**26**	79
4	**8**	Me	*p*-$OMeC_6H_4$	C_6H_5	**27**	96
5	**8**	Me	*p*-$OMeC_6H_4$	*p*-FC_6H_4	**28**	92
6	**8**	Me	*p*-MeC_6H_4	*p*-MeC_6H_4	**10**	93
7	**8**	Me	*p*-$OMeC_6H_4$	Styrenyl	**29**	85
8	**8**	Me	*p*-$OMeC_6H_4$		**30**	100
9	**8**	Me	*p*-$OMeC_6H_4$	2-Thiophenyl	—	NR
10	**8**	Me	*p*-$OMeC_6H_4$	2-Naphthyl	**31**	92
11	**9**	Me	*p*-MeC_6H_4	1-Naphthyl	**32**	47 (67)
12	**21**	Cy	*p*-$OMeC_6H_4$	C_6H_5	**33**	63 (79)
13	**23**	CH_2OTBS	*p*-$OMeC_6H_4$	C_6H_5	**34**	97

[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of $PMe_3 \cdot HBF_4$, 2.0 equiv of boronic acid, 2.0 equiv of Cs_2CO_3, dioxane, and 23 °C.
[b] Yields in parentheses are corrected for unreacted starting material.

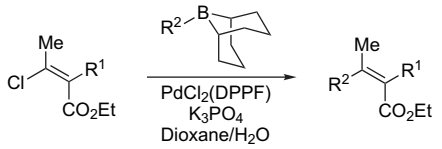
Table 8
Production of tetrasubstituted olefins by alkyl-Suzuki cross-coupling reactions with chloride **35**

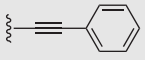
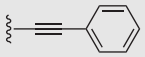


Entry[a]	Base	Solvent	Yield (%)
1	K_3PO_4	THF	NR
2	$K_3PO_4 \cdot H_2O$	THF	19
3	K_3PO_4	THF/H_2O	12
4	K_3PO_4	Dioxane/H_2O	64

[a] Conditions: 0.05 equiv of $Pd(dppf)Cl_2$, 3.0 equiv of alkyl borane, 2.0 equiv of base, and 20 °C.

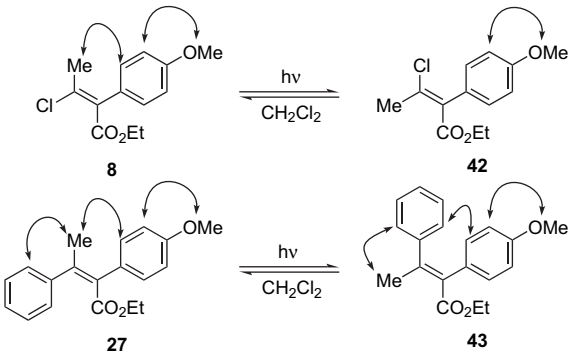
Table 9
Alkyl substituents incorporated via the alkyl-Suzuki reaction into tetrasubstituted olefins



Entry[a]	Substrate	R^1	R^2	Product	Yield (%)
1	**35**	TMS		**36**	64
2	**37**			**38**	48
3	**37**		AcO 	**39**	75
4	**8**[b]	*p*-OMeC$_6$H$_4$	AcO 	**40**	96
5	**8**[b]	*p*-OMeC$_6$H$_4$	BzO 	**41**	76

[a] Conditions: 0.05 equiv of Pd(dppf)Cl$_2$, 3.0 equiv of alkyl borane, 2.0 equiv of K$_3$PO$_4$, and 20 °C.
[b] Conditions: 0.1 equiv of Pd(OAc)$_2$, 0.2 equiv of PMe$_3$·HBF$_4$, 4.0 equiv of alkyl borane, 4.0 equiv of K$_3$PO$_4$, and 20 °C.

regiochemical identity of the materials. In a typical example, a sample of **8** was isomerized by brief photolysis, and the mixture of *E*/*Z* isomers **8** and **42** was then analyzed using NOE networks (Scheme 4). A NOESY spectrum of the pure sample of **8** was separately recorded in order to verify the identity of the initial material. NOE enhancements were observed between the methyl and aromatic group of **8**, indicating a cis-relationship between these substituents. Isomer **42** did not give enhancements between these groups. Instead, NOE interactions were only noted between the aromatic hydrogens and the methoxy group. This network of NOE enhancements was only possible if the stereochemistry of **8** was *Z*, as shown. The other compounds in Table 5 displayed NOE networks consistent with the assigned configurations. This corroborated the stereochemical assignments for the β-chloro alkenyl intermediates such as **8**.



Scheme 4. Stereochemical analysis of α,β-unsaturated esters **8** and **27**.

Similar analyses were performed with the tetrasubstituted products. Thus, a NOESY spectrum of tetrasubstitued olefin **27** was first recorded, that showed interactions between the allylic methyl group and both of the pendant aromatic rings as indicated. Clear NOE interactions between the methyl group of **43** and the neighboring phenyl ring were noted, while the *p*-methoxyphenyl moiety only displayed NOE interactions with the phenyl group. This pattern of interactions was consistent with the *Z* configuration shown for compound **27**. Related compounds in Tables 7 and 9 were treated in a similar manner and gave consistent results, thus corroborating the stereochemical assignments for these materials.

3. Conclusion

A simple, high yielding, and convenient method for the preparation of single isomer tetrasubstituted olefins has been developed. This method utilizes *E*-β-chloro-α-iodo-α,β-unsaturated esters as templates for further cross-coupling reactions. The templates are constructed as single isomers by the exposure of the corresponding alkynyl esters to Bu$_4$NI in refluxing dichloroethane. Once prepared, these templates are readily converted to tetrasubstituted olefins using cross-coupling reactions. By carefully controlling the reaction conditions, Suzuki-type coupling reactions can be done at the α-position selectively, giving *E*-β-chloro-α-aryl-α,β-unsaturated esters as single isomers in excellent yields. The use of these coupling methods gives a facile way to prepare such olefins linked directly to sp^2 hybridized carbons at the position α-to the ester group. Subsequent cross-couplings have been successfully accomplished at the β-position of the template using sp, sp^2- or sp^3-hybridized substituents, giving a wide scope to the process. In the case of the Suzuki process at the β-chloro center, a direct dependence between ligand size and coupling success was observed in which small ligands gave the best conversions and yields of these hindered products. In all cases single isomers were obtained, eliminating the need for a tedious and difficult separation of isomeric products. This technology provides a simple, convenient method of making single isomer tetrasubstituted olefins bearing four different carbon-linked appendages using inexpensive reagents and only a few synthetic steps.

4. Experimental

4.1. General

Reactions were performed under nitrogen in flame-dried glassware equipped with a magnetic stirbar and a rubber septem. 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. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 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 Suzuki cross-coupling reaction of β-chloro-α-iodo-α,β-unsaturated esters. (*Z*)-Ethyl 3-chloro-2-(4-methylphenyl)but-2-enoate (9)

A flame-dried flask charged with Pd(OAc)$_2$ (12.0 mg, 0.018 mmol, 0.1 equiv), *S*-PHOS (14.8 mg, 0.036 mmol, 0.2 equiv), Cs$_2$CO$_3$ (118.3 mg, 0.54 mmol, 2.0 equiv), and *p*-tolylboronic acid (48.9 mg, 0.36 mmol, 2.0 equiv) was purged for 10 min with N$_2$. To

this mixture was added toluene (2.0 mL) and the resulting solution was sparged for 20 min with N_2. To the solution was added (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**7**)[16] (50.0 mg, 0.18 mmol, 1.0 equiv) and the reaction was stirred at room temperature for 16 h. The mixture was partitioned between water and Et_2O. The combined organic extracts were washed with water and brine, and then dried over anhydrous $MgSO_4$. The product was purified by flash chromatography (1% Et_2O in hexanes then 5% Et_2O in hexanes) to give the title product as clear oil (35.2 mg, 81%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.25–7.20 (m, 4H), 4.21 (q, J=7.2 Hz, 2H), 2.34 (s, 3H), 2.15 (s, 3H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.3 (C), 140.1 (C), 135.3 (C), 133.6 (C), 131.1 (CH), 130.3 (CH), 62.7 (CH_2), 24.4 (CH_3), 22.2 (CH_3), 15.3 (CH_3); IR (neat) 1716 cm^{-1}; MS 238.1 (M^+); HRMS calcd for $C_{13}H_{15}ClO_2$ (M^+) 238.0761, found 238.0753.

4.3. (*Z*)-Ethyl 3-chloro-2-phenylbut-2-enoate (11)

Prepared from compound **7** (30 mg, 0.12 mmol) using a procedure similar to that described above for **9** with the following modifications: $Pd(OAc)_2$ (16.2 mg, 0.024 mmol, 0.2 equiv) and *S*-PHOS (19.7 mg, 0.048 mmol, 0.4 equiv). The title product was obtained as a clear oil (30 mg, 100%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.45–7.33 (m, 5H), 4.22 (q, J=7.2 Hz, 2H), 2.15 (s, 3H), 1.25 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.2 (C), 136.5 (C), 135.3 (C), 134.3 (C), 130.5 (CH), 130.4 (CH), 130.2 (CH), 62.8 (CH_2), 24.5 (CH_3), 15.3 (CH_3); IR (neat) 1727 cm^{-1}; MS 224.1 (M^+); HRMS calcd for $C_{12}H_{13}ClO_2$ (M^+) 224.0604, found 224.0587.

4.4. (*Z*)-Ethyl 3-chloro-2-(4-methoxyphenyl)but-2-enoate (8)

Prepared from compound **7** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (39 mg, 84%). ^{1}H NMR (400 MHz, benzene-d_6): δ 7.26 (d, J=9.0 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 4.21 (q, J=7.2 Hz, 2H), 3.82 (s, 3H), 2.15 (s, 3H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, benzene-d_6): δ 167.1 (C), 160.0 (C), 133.6 (C), 132.2 (C), 130.2 (CH), 114.3 (CH), 61.2 (CH_2), 54.7 (CH_3), 23.1 (CH_3), 14.0 (CH_3); IR (neat) 1727 cm^{-1}; MS 254.1 (M^+); HRMS calcd for $C_{13}H_{15}ClO_3$ (M^+) 254.0710, found 254.0702.

4.5. (*Z*)-Ethyl 3-chloro-2-(2-methoxyphenyl)but-2-enoate (12)

Prepared from compound **7** (30 mg, 0.12 mmol) using a procedure similar to that described above for **9** with the following modifications: $Pd(OAc)_2$ (16.2 mg, 0.024 mmol, 0.2 equiv) and *S*-PHOS (19.7 mg, 0.048 mmol, 0.4 equiv). The product was obtained as a clear oil (28.0 mg, 93%); ^{1}H NMR (400 MHz, acetone-d_6): δ 7.33 (ddd, J=8.3, 7.4, 1.7 Hz, 1H), 7.24 (dd, J=7.6,1.7 Hz, 1H), 7.04 (dd, J=8.4, 0.8 Hz, 1H), 6.99 (ddd, J=7.5, 7.5, 1.1 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.81 (s, 3H), 2.07 (s, 3H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, benzene-d_6): δ 167.5 (C), 158.9 (C), 137.2 (C), 132.6 (CH), 131.8 (C), 131.0 (CH), 126.4 (C), 122.2 (CH), 113.2 (CH), 62.2 (CH_2), 56.9 (CH_3), 25.9 (CH_3), 15.4 (CH_3); IR (neat) 1725 cm^{-1}; MS 254.1 (M^+); HRMS calcd for $C_{13}H_{15}ClO_3$ (M^+) 254.0710, found 254.0704.

4.6. (*Z*)-Ethyl 3-chloro-2-(3-methoxyphenyl)but-2-enoate (13)

Prepared from compound **7** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (30.3 mg, 65%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.34 (ddd, J=8.2, 8.2, 0.6 Hz, 1H), 6.95 (ddd, J=8.2, 2.6, 0.9 Hz, 1H), 6.89 (m, 2H), 4.22 (q, J=7.1 Hz, 2H), 3.82 (s, 3H), 2.16 (s, 3H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.1 (C), 161.7 (C), 137.7 (C), 135.1 (C), 134.4 (C), 131.6 (CH), 122.6 (CH), 115.9 (CH), 115.8 (CH), 62.8 (CH_2), 56.6 (CH_3), 24.6 (CH_3), 15.4 (CH_3); IR (neat) 1728 cm^{-1}; MS 254.1 (M^+); HRMS calcd for $C_{13}H_{15}ClO_3$ (M^+) 254.0710, found 254.0717.

4.7. (*Z*)-Ethyl 3-chloro-2-(4-fluorophenyl)but-2-enoate (14)

Prepared from compound **7** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as clear oil (22.0 mg, 82%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.40 (dd, J=8.8, 5.6 Hz, 2H), 7.21 (dd, J=8.8, 8.8 Hz, 2H), 4.22 (q, J=7.2 Hz, 2H), 2.14 (s, 3H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.0 (C), 164.4 (d, J=246.2 Hz, C), 135.0 (C), 134.1 (C), 132.6 (d, J=8.3 Hz, CH), 130.4 (d, J=8.5 Hz, C), 117.4 (d, J=21.8 Hz, CH), 62.9 (CH_2), 24.6 (CH_3), 15.3 (CH_3); IR (neat) 1727 cm^{-1}; MS 242.1 (M^+); HRMS calcd for $C_{12}H_{12}ClFO_2$ (M^+) 242.0510, found 242.0507.

4.8. (*Z*)-Ethyl 3-chloro-2-(naphthalen-1-yl)but-2-enoate (15)

Prepared from compound **7** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (49.9 mg, 94%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.97 (m, 3H), 7.58 (m, 3H), 7.48 (dd, J=7.0, 1.2 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 1.92 (s, 3H), 1.18 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 167.8 (C), 136.9 (C), 135.8 (C), 134.5 (C), 133.3 (C), 133.1 (C), 130.8 (CH), 130.3 (CH), 129.1 (CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 126.9 (CH), 62.8 (CH_2), 25.1 (CH_3), 15.3 (CH_3); IR (neat) 1727 cm^{-1}; MS 274.1 (M^+); HRMS calcd for $C_{16}H_{15}ClO_2$ (M^+) 274.0761, found 274.0770.

4.9. (*Z*)-Ethyl 3-chloro-2-(naphthalen-2-yl)but-2-enoate (16)

Prepared from compound **7** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (50 mg, 95%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.92 (m, 4H), 7.55 (m, 2H), 7.45 (dd, J=8.5, 1.8 Hz, 1H), 4.24 (q, J=7.1 Hz, 2H), 2.21 (s, 3H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 166.4 (C), 133.4 (C), 133.3 (C), 133.0 (C), 133.0 (C), 132.2 (C), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 126.8 (CH), 126.7 (CH), 126.1(CH), 61.0 (CH_2), 22.9 (CH_3), 13.5 (CH_3); IR (neat) 1716 cm^{-1}; MS 274.1 (M^+); HRMS calcd for $C_{16}H_{15}ClO_2$ (M^+) 274.0761, found 274.0758.

4.10. (*E*)-Ethyl 3-chloro-2-(thiophen-2-yl)but-2-enoate (17)

Prepared from compound **7** (50.0 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (27 mg, 64%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.58 (dd, J=4.6, 1.9 Hz, 1H), 7.10 (m, 2H), 4.27 (q, J=7.1 Hz, 2H), 2.34 (s, 3H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 165.9 (C), 134.8 (C), 132.6 (C), 128.4 (CH), 127.5 (C), 127.3 (CH), 127.2 (CH), 61.3 (CH_2), 23.1 (CH_3), 13.5 (CH_3); IR (neat) 1732 cm^{-1}; MS 230.0 (M^+); HRMS calcd for $C_{10}H_{11}ClO_2S$ (M^+) 230.0168, found 230.0169.

4.11. (*Z*)-Ethyl 3-chloro-2-((*E*)-styrenyl)but-2-enoate (18)

A flame-dried flask charged with $Pd(OAc)_2$ (6.1 mg, 0.0091 mmol, 0.1 equiv), *S*-PHOS (7.5 mg, 0.018 mmol, 0.2 equiv), Cs_2CO_3 (89.1 mg, 0.27 mmol, 3.0 equiv), and (*E*)-styrenylboronic acid (27.2 mg, 0.18 mmol, 2.0 equiv) was purged for 10 min with N_2. To this mixture was added toluene (1.0 mL), and the resulting solution was sparged for 20 min with N_2 The mixture was cooled to 0 °C before (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**7**) (25.0 mg, 0.091 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 5 °C for 16 h and then the solution was partitioned between water and Et_2O. The organic extracts were washed with water and

brine, then dried over anhydrous $MgSO_4$. The product was purified by flash chromatography (1% Et_2O in hexanes then 5% Et_2O in hexanes) to give the title product as clear oil (19.4 mg, 85%). ^1H NMR (400 MHz, acetone-d_6): δ 7.55 (m, 2H), 7.32 (m, 3H), 7.10 (d, J=16.2 Hz, 1H), 7.01 (d, J=16.2 Hz, 1H), 4.35 (q, J=7.2 Hz, 2H), 2.40 (s, 3H), 1.35 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.1 (C), 138.5 (C), 135.2 (C), 133.7 (CH), 132.7 (C), 130.6 (CH), 130.1 (CH), 128.6 (CH), 122.9 (CH), 62.8 (CH_2), 23.1 (CH_3), 15.4 (CH_3); IR (neat) 1722, 1624 cm^{-1}; MS 250.1 (M^+); HRMS calcd for $C_{14}H_{15}ClO_2$ (M^+), 250.0761, found 250.0776.

4.12. (2*Z*,3*E*)-Ethyl 2-(1-chloroethylidene)dec-3-enoate (19)

Prepared from compound **7** (25.0 mg, 0.091 mmol, 1.0 equiv) using a procedure similar to that described above for compound **18** that provided the title product as a clear oil (17.7 mg, 75%). ^1H NMR (400 MHz, acetone-d_6): δ 6.28 (ddd, J=15.7, 3.0, 1.5 Hz, 1H), 5.65 (ddd, J=15.7, 14.3, 7.1 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 2.23 (s, 3H), 2.17–2.11 (m, 2H), 1.42–1.36 (m, 2H), 1.32–1.27 (m, 9H), 0.87 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 168.2 (C), 136.8 (CH), 134.9 (C), 130.0 (C), 124.4 (CH), 62.7 (CH_2), 34.7 (CH_2), 33.5 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 24.2 (CH_2), 22.7 (CH_3), 15.5 (CH_3), 15.4 (CH_3). IR (neat) 1733 cm^{-1}; MS 258.2 (M^+); HRMS calcd for $C_{14}H_{23}ClO_2$ (M+) 258.1387, found 258.1383.

4.13. (*Z*)-Ethyl 3-chloro-3-cyclohexyl-2-(4-methoxyphenyl)-acrylate (21)

Prepared from compound **20**[16] (30 mg, 0.088 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (22 mg, 79%). ^1H NMR (500 MHz, acetone-d_6): δ 7.23 (d, J=9.0 Hz, 2H), 6.98 (d, J=9.0 Hz, 2H), 4.19 (q, J=7.5 Hz, 2H), 3.82 (s, 3H), 2.63–2.55 (m, 1H), 1.73–1.57 (m, 2H), 1.62–1.57 (m, 5H), 1.24 (t, J=7.5 Hz, 3H), 1.05–1.20 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 168.6 (C), 161.7 (C), 142.6 (C), 134.0 (C), 131.4 (CH), 128.5 (C), 116.0 (CH), 62.2 (CH_2), 56.6 (CH), 43.6 (CH_3), 32.1 (CH_2), 27.2 (CH_2), 15.4 (CH_3); IR (neat) 1727 cm^{-1}; MS 322.1 (M^+); HRMS calcd for $C_{18}H_{23}ClO_3$ (M^+) 322.1336, found 322.1344.

4.14. (*Z*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-3-chloro-2-(4-methoxyphenyl)but-2-enoate (23)

Prepared from compound **22**[16] (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **9** that provided the title product as a clear oil (35.0 mg, 74%). ^1H NMR (400 MHz, acetone-d_6): δ 7.31 (d, J=8.8 Hz, 2H), 6.99 (d, J=8.8 Hz, 2H), 4.34 (s, 2H), 4.26 (q, J=6.8 Hz, 2H), 3.83 (s, 3H), 1.28 (t, J=7.2 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6): δ 168.2 (C), 162.1 (C), 137.0 (C), 135.1 (C), 131.6 (CH), 127.6 (C), 115.9 (CH), 65.2 (CH_2), 62.9 (CH_2), 56.7 (CH_3), 27.1 (CH_3), 19.8 (C), 15.3 (CH_3), −4.2 (CH_3); IR (neat) 1720 cm^{-1}; MS 327.1 ($M^+-C_4H_9$); HRMS calcd for $C_{15}H_{20}ClO_4Si$ ($M^+-C_4H_9$) 327.0819, found 327.0837.

4.15. General procedure for the generation of tetrasubstituted olefins via Suzuki coupling reaction. (*Z*)-Ethyl 2,3-bis-(4-methoxyphenyl)but-2-enoate (24)

A flame-dried flask charged with $Pd(OAc)_2$ (2.6 mg, 0.0039 mmol, 0.1 equiv), $PMe_3{\cdot}HBF_4$ (1.3 mg, 0.0079 mmol, 0.2 equiv), Cs_2CO_3 (25.6 mg, 0.079 mmol, 2.0 equiv), and *p*-methoxyphenylboronic acid (12.0 mg, 0.079 mmol, 2.0 equiv) was purged with N_2 for 10 min. Dioxane (0.3 mL) was added, and the mixture was sparged with N_2 for 10 min before **8** (10.0 mg, 0.039 mmol, 1.0 equiv) was added as a solution in dioxane (0.5 mL). After 16 h, the reaction mixture was partitioned between Et_2O and H_2O. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography (2% Et_2O in hexanes then 20% Et_2O in hexanes) to give the title product as a clear oil (11.4 mg, 95%). ^1H NMR (400 MHz, acetone-d_6): δ 7.29 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 3.87 (q, J=6.8 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.03 (s, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 171.2 (C), 161.1 (C), 151.0 (C), 142.3 (C), 137.2 (C), 134.2 (C), 132.2 (CH), 131.6 (C), 130.3 (CH), 115.5 (CH), 115.3 (CH), 61.7 (CH_2), 56.5 (CH_3), 56.5 (CH_3), 23.0 (CH_3), 15.1 (CH_3); IR (neat) 1739 cm^{-1}; MS 326.4 (M^+); HRMS calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, found 326.1533.

4.16. (*Z*)-Ethyl 3-(2-methoxyphenyl)-2-(4-methoxyphenyl)-but-2-enoate (25)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **24** that provided the title product as a yellow oil (11.6 mg, 91%). ^1H NMR (400 MHz, acetone-d_6): δ 7.26–7.16 (m, 8H), 3.84 (q, J=7.2 Hz, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 2.03 (s, 3H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.9 (C), 143.1 (C), 142.1 (C), 138.9 (C), 138.9 (C), 136.4 (C), 134.7 (CH), 130.9 (CH), 130.8 (CH), 130.5 (CH), 129.0 (CH), 61.7 (CH_2), 23.0 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 15.0 (CH_3); IR (neat) 1720 cm^{-1}; MS 326.4 (M^+); HRMS calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, found 326.1535.

4.17. (*Z*)-Ethyl 3-(3-methoxyphenyl)-2-(4-methoxyphenyl)-but-2-enoate (26)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **24** that provided the title product as a yellow oil (10.0 mg, 79%). ^1H NMR (400 MHz, acetone-d_6): δ 7.32–7.25 (m, 3H), 7.00–6.96 (m, 2H), 6.91–6.86 (m, 3H), 3.85 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.05 (s, 3H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.9 (C), 161.5 (C), 161.1 (C), 146.5 (C), 142.6 (C), 134.6 (C), 132.2 (C), 131.3 (CH), 131.0 (CH), 121.4 (CH), 115.5 (CH), 114.7 (CH), 61.7 (CH_2), 56.6 (CH_3), 56.5 (CH_3), 22.9 (CH_3), 15.0 (CH_3); IR (neat) 1713 cm^{-1}; MS 326.4 (M^+); HRMS calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, found 326.1531.

4.18. (*Z*)-Ethyl 2-(4-methoxyphenyl)-3-phenylbut-2-enoate (27)

A flame-dried flask charged with $Pd(OAc)_2$ (2.6 mg, 0.0039 mmol, 0.1 equiv), $PMe_3{\cdot}HBF_4$ (1.3 mg, 0.0079 mmol, 0.2 equiv), Cs_2CO_3 (50.8 mg, 0.059 mmol, 4.0 equiv), and phenylboronic acid (19.2 mg, 0.059 mmol, 4.0 equiv) was purged with N_2 for 10 min. Dioxane (0.3 mL) was added, the resulting mixture was sparged with N_2 for 10 min before chloride **8** (10.0 mg, 0.039 mmol, 1.0 equiv) was added as a solution in dioxane (0.5 mL). After 5 h, additional portions of phenylboronic acid (9.6 mg, 0.030 mmol, 2.0 equiv) and Cs_2CO_3 (25.4 mg, 0.030 mmol, 2.0 equiv) were added to the solution. After 16 h, the reaction mixture was partitioned between Et_2O and H_2O. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography (2% Et_2O in hexanes then 20% Et_2O in hexanes) to give the title product as a clear oil (11.1 mg, 96%). ^1H NMR (400 MHz, acetone-d_6): δ 7.38–7.18 (m, 7H), 6.97 (d, J=8.8 Hz, 2H), 3.82 (q, J=7.2 Hz, 2H), 3.82 (s, 3H), 2.05 (s, 3H), 0.82 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.9 (C), 161.1 (C), 145.1 (C), 143.0 (C), 134.7 (C), 132.2 (CH), 131.3 (C), 129.9 (CH), 129.1 (CH), 129.0 (CH), 115.5 (CH), 61.7 (CH_2), 56.5 (CH_3), 23.1 (CH_3), 14.9 (CH_3); IR (neat) 1709 cm^{-1}; HRMS calcd for $C_{19}H_{20}O_3$ (M^+) 296.1412, found 296.1405.

4.19. (*Z*)-Ethyl 3-(4-fluorophenyl)-2-(4-methoxyphenyl)but-2-enoate (28)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (11.3 mg, 92%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.37 (dd, J=8.9, 5.4 Hz, 2H), 7.30 (d, J=8.9 Hz, 2H), 7.14 (dd, J=8.9, 8.9 Hz, 2H), 6.98 (d, J=8.9 Hz, 2H), 3.86 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 2.05 (s, 3H), 0.88 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.8 (C), 164.0 (d, J=244.3 Hz, C), 161.1 (C), 142.0 (C), 141.3 (d, J=3.3 Hz, C), 135.1 (C), 132.2 (CH), 131.2 (C), 130.9 (d, J=8.1 Hz, CH), 116.5 (d, J=21.5 Hz, CH), 115.3 (CH), 61.8 (CH_2), 56.5 (CH_3), 23.2 (CH_3), 15.0 (CH_3); IR (neat) 1715 cm^{-1}; MS 314.1 (M^+); HRMS calcd for $C_{19}H_{19}FO_3$ (M^+) 314.1318, found 314.1318.

4.20. (*Z*)-Ethyl 2,3-di-(4-methylphenyl)but-2-enoate (10)

Prepared from compound **7** (10.0 mg, 0.042 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (11.5 mg, 93%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.01–6.88 (m, 8H), 4.22 (q, J=7.2 Hz, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 171.0 (C), 143.2 (C), 140.9 (C), 138.4 (C), 138.1 (C), 136.4 (C), 133.8 (C), 131.4 (CH), 130.5 (CH), 130.3 (CH), 62.1 (CH_2), 24.3 (CH_3), 22.1 (CH_3), 15.5 (CH_3); IR (neat) 1716 cm^{-1}; MS 294.2 (M^+); HRMS calcd for $C_{20}H_{22}O_2$ (M^+) 294.1620, found 294.1633.

4.21. (2*Z*,4*E*)-Ethyl 2-(4-methoxyphenyl)-3-methyl-5-phenylpenta-2,4-dienoate (29)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (10.7 mg, 85%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.56 (d, J=16.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 2H), 7.38 (dd, J=7.2, 7.2 Hz, 2H), 7.29 (tt, J=6.8, 1.2 Hz, 1H), 7.22 (d, J=8.8 Hz, 2H), 6.96 (d, J=16.8 Hz, 1H), 6.97 (d, J=8.8 Hz, 2H), 4.24 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.97 (s, 3H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.3 (C), 161.0 (C), 139.5 (C), 139.2 (C), 135.6 (C), 133.8 (CH), 132.3 (CH), 131.5 (C), 130.6 (CH), 130.0 (CH), 129.9 (CH), 128.6 (CH), 115.4 (CH), 62.2 (CH_2), 56.5 (CH_3), 17.2 (CH_3), 15.6 (CH_3); IR (neat) 1712 cm^{-1}; MS 322.2 (M^+); HRMS calcd for $C_{21}H_{22}O_3$ (M^+) 322.1569, found 322.1587.

4.22. (2*Z*,4*E*)-Ethyl 2-(4-methoxyphenyl)-3-methylundeca-2,4-dienoate (30)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (12.9 mg, 100%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.16 (d, J=8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 6.70 (dt, J=15.6, 1.6 Hz, 1H), 6.04 (dt, J=15.6, 7.2 Hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 3.81 (s, 3H), 2.19 (ddd, J=7.2, 7.2, 1.6 Hz, 2H), 1.81 (s, 3H), 1.47–1.29 (m, 8H), 1.21 (t, J=7.2 Hz, 3H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.5 (C), 160.9 (C), 139.1 (C), 136.4 (CH), 133.4 (C), 132.3 (CH), 131.6 (C), 131.5 (CH), 115.4 (CH), 62.0 (CH_2), 56.5 (CH_3), 34.9 (CH_2), 33.5 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 24.3 (CH_2), 17.1 (CH_3), 15.5 (CH_3), 15.3 (CH_3); IR (neat) 1713 cm^{-1}; MS 330.2 (M^+); HRMS calcd for $C_{21}H_{30}O_3$ (M^+) 330.2195, found 330.2196.

4.23. (*Z*)-Ethyl 2-(4-methoxyphenyl)-3-(naphthalen-2-yl)-but-2-enoate (31)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (12.4 mg, 92%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.92–7.89 (m, 3H), 7.83 (d, J=1.5 Hz, 1H), 7.54–7.49 (m, 3H), 7.37–7.34 (m, 2H), 7.02–7.00 (m, 2H), 3.84 (s, 3H), 3.79 (q, J=7.2 Hz, 2H), 2.16 (s, 3H), 0.72 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.9 (C), 161.1 (C), 143.0 (C), 142.7 (C), 135.2 (C), 134.6 (C), 132.3 (CH), 131.4 (C), 129.8 (CH), 129.5 (CH), 129.4 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 115.6 (CH), 61.7 (CH_2), 56.6 (CH_3), 23.1 (CH_3), 14.9 (CH_3); IR (neat) 1710 cm^{-1}; MS 346.6 (M^+); HRMS calcd for $C_{23}H_{22}O_3$ (M^+) 346.1569, found 346.1586.

4.24. (*Z*)-Ethyl 2-(4-methylphenyl)-3-(naphthalen-1-yl)-but-2-enoate (32)

Prepared from compound **9** (10.0 mg, 0.042 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (6.4 mg, 47%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.00–7.98 (m, 1H), 7.94–7.92 (m, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.55–7.47 (m, 3H), 7.41 (d, J=8.2 Hz, 2H), 7.34 (dd, J=7.0, 1.2 Hz, 1H), 7.29 (d, J=7.8 Hz, 2H), 3.60–3.50 (m, 2H), 2.39 (s, 3H), 2.13 (s, 3H), 0.40 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.2 (C), 143.9 (C), 143.1 (C), 139.1 (C), 136.0 (C), 135.6 (C), 131.2 (C), 131.2 (CH), 130.8 (CH), 130.1 (CH), 129.1 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.2 (CH), 126.3 (CH), 61.3 (CH_2), 24.3 (CH_3), 22.2 (CH_3), 14.5 (CH_3); IR (neat) 1711 cm^{-1}; MS 330.4 (M^+); HRMS calcd for $C_{23}H_{22}O_2$ (M^+) 330.1620, found 330.1628.

4.25. (*Z*)-Ethyl 3-cyclohexyl-2-(4-methoxyphenyl)-3-phenylacrylate (33)

Prepared from compound **21** (10.0 mg, 0.031 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (7.0 mg, 63%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.36–7.18 (m, 5H), 7.17 (d, J=6.4 Hz, 2H), 6.98 (d, J=8.8 Hz, 2H), 3.84 (s, 3H), 3.68 (q, J=7.2 Hz, 2H), 2.59–2.52 (m, 1H), 1.68–1.60 (m, 3H), 1.52–1.47 (m, 1H), 1.12–1.05 (m, 3H), 0.93–0.85 (m, 3H), 0.72 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 169.7 (C), 140.9 (C), 132.0 (CH), 131.1 (CH), 129.0 (CH), 128.6 (CH), 125.5 (C), 115.5 (C), 61.4 (CH_2), 56.5 (CH_3), 43.4 (CH), 33.0 (CH_2), 27.7 (CH_2), 27.4 (CH_2), 14.9 (CH_3); IR (neat) 1712 cm^{-1}; MS 364.2 (M^+); HRMS calcd for $C_{24}H_{28}O_3$ (M^+) 364.2038, found 364.2063.

4.26. (*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-3-phenylbut-2-enoate (34)

Prepared from compound **23** (10.0 mg, 0.026 mmol) using a procedure similar to that described above for compound **27** that provided the title product as a yellow oil (10.8 mg, 97%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.41 (d, J=8.8 Hz, 2H), 7.37–7.30 (m, 5H), 6.99 (d, J=8.8 Hz, 2H), 4.44 (s, 2H), 3.85 (q, J=7.2 Hz, 2H), 3.84 (s, 3H), 0.84 (t, J=7.2 Hz, 3H), 0.77 (s, 9H), −0.15 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.7 (C), 161.6 (C), 144.0 (C), 144.2 (C), 136.9 (C), 132.2 (CH), 130.3 (CH), 130.0 (C), 129.5 (CH), 129.2 (CH), 115.5 (CH), 65.3 (CH_2), 61.9 (CH_2), 56.6 (CH_3), 27.1 (CH_3), 19.7 (C), 14.9 (CH_3), −4.4 (CH_3); IR (neat) 1720 cm^{-1}; MS 426.2 (M^+); HRMS calcd for $C_{25}H_{34}O_4Si$ (M^+) 426.2226, found 426.2232.

4.27. General procedure for the alkyl-Suzuki coupling reaction of β-chloro-α,β-unsaturated olefins. (*Z*)-Ethyl 3-methyl-2-(phenylethynyl)undec-2-enoate (38)

To a solution of 1-octene (0.05 mL, 0.30 mmol, 3.0 equiv) in THF (1.0 mL) was added 9-borabicyclo[3.3.1]nonane (0.6 mL, 0.30 mmol, 3.0 equiv, 0.5 M in THF) and the mixture was stirred for 0.5 h. A separate flask was charged with $PdCl_2$(DPPF) (3.7 mg, 0.005 mmol, 0.05 equiv) and K_3PO_4 (42.4 mg, 0.20 mmol, 2.0 equiv). To this were added sequentially dioxane (1.0 mL) and

37[16] (25.0 mg, 0.10 mmol, 1.0 equiv). The 9-octyl-9-bora-bicyclo[3.3.1]nonane solution was introduced via canula, H_2O (0.3 mL) was added, and the reaction mixture was stirred for 18 h. The mixture was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by column chromatography on silica gel, eluting with hexanes to 5% EtOAc in hexanes to afford the product as a colorless oil (15.7 mg, 48%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.49–7.37 (m, 5H), 4.22 (q, J=7.2 Hz, 2H), 2.61 (dd, J=9.6, 7.6 Hz, 2H), 2.19 (s, 3H), 1.55–1.50 (m, 2H), 1.33–1.29 (m, 10H), 1.31 (t, J=7.2 Hz, 3H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 166.5 (C), 163.6 (C), 132.9 (CH), 130.4 (CH), 130.1 (CH), 125.4 (C), 114.6 (C), 95.8 (C), 87.8 (C), 62.3 (CH_2), 36.9 (CH_2), 33.6 (CH_2), 31.4 (CH_2), 31.4 (CH_2), 31.1 (CH_2), 30.1 (CH_2), 24.4 (CH_3), 24.3 (CH_2), 15.5 (CH_3), 15.3 (CH_3); IR (neat) 1719 cm^{-1}; MS 326.2 (M^+); HRMS calcd for $C_{22}H_{30}O_2$ (M^+) 326.2246, found 326.2232.

4.28. (*Z*)-Ethyl 3-methyl-2-((trimethylsilyl)ethynyl)undec-2-enoate (36)

Prepared from compound **35** (50.0 mg, 0.20 mmol) using a procedure similar to that described above for compound **38** that provided the title product as a colorless oil (41.3 mg, 64%). ^{1}H NMR (400 MHz, benzene-d_6): δ 4.00 (q, J=7.2 Hz, 2H), 2.58 (dd, J=9.6, 8.0 Hz, 2H), 2.02 (s, 3H), 1.46–1.22 (m, 12H), 0.99 (t, J=7.2 Hz, 3H), 0.89 (t, J=6.8 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6): δ 165.0 (C), 163.7 (C), 113.9 (C), 102.5 (C), 99.4 (C), 60.6 (CH_2), 35.6 (CH_2), 32.2 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 28.7 (CH_2), 23.5 (CH_3), 23.0 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 0.1 (CH_3); IR (neat) 1721 cm^{-1}; MS 322.2 (M^+); HRMS calcd for $C_{19}H_{34}SiO_2$ (M^+) 322.2328, found 322.2347.

4.29. (*Z*)-Ethyl 8-acetoxy-3-methyl-2-(phenylethynyl)oct-2-enoate (39)

Prepared from compound **37** (800.0 mg, 2.53 mmol) using a procedure similar to that described above for compound **38** that provided the title product as a colorless oil (648.9 mg, 75%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.48–7.46 (m, 2H), 7.39–7.37 (m, 3H), 4.23 (q, J=7.2 Hz, 2H), 4.04 (t, J=6.8 Hz, 2H), 2.63 (dd, J=9.6, 7.6 Hz, 2H), 2.20 (s, 3H), 1.99 (s, 3H), 1.69–1.54 (m, 4H), 1.46–1.38 (m, 2H), 1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 171.9 (C), 166.5 (C), 163.4 (C), 132.9 (CH), 130.4 (CH), 130.1 (CH), 125.4 (C), 114.7 (C), 95.9 (C), 87.7 (C), 65.6 (CH_2), 62.3 (CH_2), 36.8 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 24.4 (CH_3), 21.8 (CH_3), 15.5 (CH_3); IR (neat) 1738, 1718 cm^{-1}; MS 342.2 (M^+); HRMS calcd for $C_{21}H_{26}O_4$ (M^+) 342.1831, found 342.1841.

4.30. (*Z*)-Ethyl 8-acetoxy-2-(4-methoxyphenyl)-3-methyloct-2-enoate (42)

A solution of pent-4-enylacetate (20.3 mg, 0.158 mmol, 4.0 equiv) and 9-borabicyclo[3.3.1]nonane (0.32 mL, 0.158 mmol, 4.0 equiv, 0.5 M in THF) was stirred for 2 h. A separate flask was charged with $Pd(OAc)_2$ (2.6 mg, 0.004 mmol, 0.1 equiv), $PMe_3\cdot HBF_4$ (1.3 mg, 0.0079 mmol, 0.2 equiv), and Cs_2CO_3 (51.1 mg, 0.158 mmol, 4.0 equiv). To this was added sequentially dioxane (0.7 mL) and **8** (10.0 mg, 0.039 mmol, 1.0 equiv). The reaction was sparged for 20 min. The 9-octyl-9-bora-bicyclo[3.3.1]nonane solution was introduced via canula, H_2O (2.8 μL) was added, and the reaction mixture was stirred for 18 h. The mixture was partitioned between ether and H_2O and the aqueous layer was extracted with ether (3×20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography (hexanes then 1% ether in hexanes) to afford the product as a colorless oil (13.1 mg, 96%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.14–7.10 (m, 2H), 6.92–6.89 (m, 2H), 4.11 (q, J=7.1 Hz, 2H), 4.05 (t, J=6.7 Hz, 2H), 3.80 (s, 3H), 2.40–2.36 (m, 2H), 2.00 (s, 3H), 1.69 (s, 3H), 1.67–1.57 (m, 4H), 1.47–1.40 (m, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 172.0 (C), 170.3 (C), 160.7 (C), 146.1 (C), 132.2 (CH), 115.3 (CH), 65.7 (CH_2), 61.7 (CH_2), 56.5 (CH_3), 37.5 (CH_2), 29.6 (CH_2), 27.6 (CH_2), 21.8 (CH_3), 21.3 (CH_3), 15.5 (CH_3); IR (neat) 1713 cm^{-1}; MS 348.2 (M+); HRMS calcd for $C_{20}H_{28}O_5$ (M^+) 348.1937, found 348.1950.

4.31. (*Z*)-8-Ethoxy-7-(4-methoxyphenyl)-6-methyl-8-oxooct-6-enyl benzoate (41)

Prepared from compound **8** (10.0 mg, 0.039 mmol) using a procedure similar to that described above for compound **40** that provided the title product as a yellow oil (12.0 mg, 76%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.06–8.03 (m, 2H), 7.67–7.62 (m, 1H), 7.54–7.50 (m, 2H), 7.13–7.10 (m, 2H), 6.93–6.87 (m, 2H), 4.35 (t, J=6.6 Hz, 2H), 4.11 (q, J=7.1 Hz, 2H), 3.80 (s, 3H), 2.44–2.40 (m, 2H), 1.84 (quint, J=6.6 Hz, 2H), 1.69 (s, 3H), 1.71–1.63 (m, 2H), 1.60–1.53 (m, 2H), 1.17 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.3 (C), 146.0 (C), 134.8 (C), 132.5 (C), 132.2 (CH), 131.1 (CH), 130.4 (CH), 113.4 (CH), 66.4 (CH_2), 61.7 (CH_2), 56.4 (CH_3), 37.5 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 27.7 (CH_2), 21.2 (CH_3), 15.5 (CH_3); IR (neat) 1711 cm^{-1}; MS 410.2 (M^+); HRMS calcd for $C_{25}H_{30}O_5$ (M^+) 410.2093, found 410.2113.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.004.

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