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Tetrahedron
Tetrahedron 61 (2005) 7807–7813

Indium (III) mediated Markovnikov addition of malonates and β-ketoesters to terminal alkynes and the formation of Knoevenagel condensation products

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Received 28 March 2005; revised 17 May 2005; accepted 18 May 2005

Available online 22 June 2005

Abstract—The indium(III) triflate mediated addition of active methylene compounds to terminal alkynes has been expanded to use malonates and low boiling terminal alkynes to form the Markovnikov addition products. Indium(III) chloride and indium(III) bromide were also found to be efficient catalysts. Knoevenagel condensation products were isolated when reactions involved a simple malonate or β-ketoester.

1. Introduction

Developing environmentally friendly, or green and atom efficient processes is becoming more and more important in modern organic chemistry.[1] Indium(III) salts, such as indium(III) triflate and indium(III) chloride, are efficient green Lewis acids[2] and have become the focus of attention in several organic reactions.[3] A particularly powerful application of this Lewis acid in the preparation of terminal olefins was recently reported by Nakamura and co-workers.[4] The indium triflate (0.5–5%) promoted addition of β-ketoester and 1,3-diketone to terminal alkynes described therein attracted our attention. Compounds **1** and **2** (Fig. 1) are important intermediates in Pfizer's drug research and development program, and we envisioned that these molecules could be accessed through intermediates **3** and **4**, products of an indium(III) promoted addition employing malonates as the active methylene species.

Moreover, terminal olefins comprise one of the most important classes of compounds vis a vis functional group transformation, giving alcohols, amines, aldehydes carboxylic acid derivatives, ethers and epoxides as products of various catalytic reactions.[5] The recent revolution in olefin metathesis and ring-closing metathesis (RCM) led by Grubbs,[6] Schrock,[7] Hoveyda[8] and others[9] also raises the question of our ability to prepare densely functionalized olefins using metal catalysis. Although the classic Wittig olefination[10] or Horner–Emmons reaction[11] has been used frequently to prepare terminal olefins, the Wittig reaction suffers from the generation of a notorious side-product, phosphine oxide. Indeed developing a green, simple and efficient method to prepare functionalized, terminal olefins, reducing our dependence on the Wittig reaction is extremely significant.

2. Results and discussion

There were several issues to address at the beginning of our study. First, could malonate be one of the starting materials? Secondly, could low boiling alkynes, such as 1-pentyne (bp 39–41 °C) and 1-hexyne (bp 71–72 °C) be employed under neat conditions involving temperatures of 100–140 °C? Finally, although it was reported that other Lewis acids are not efficient and only indium triflate works well,[4] would

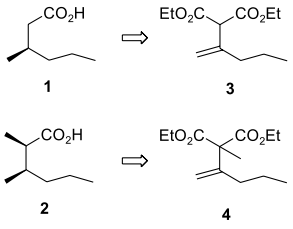

Figure 1. Some useful compounds potentially from the reaction of malonate and 1-alkynes mediated by indium(III).

Keywords: Indium (III); Active methylene; Alkyne; Markovnikov; Knoevenagel.
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doi:10.1016/j.tet.2005.05.065

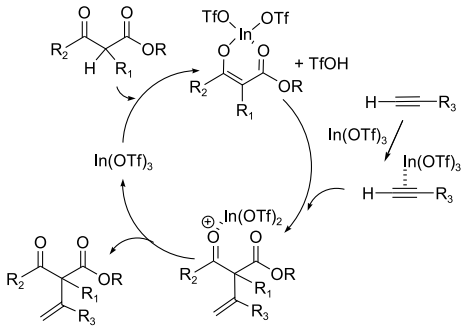
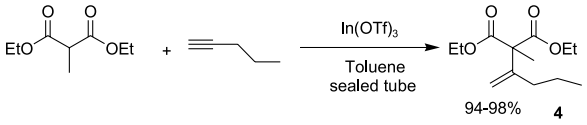


Figure 2. Possible mechanism of In(III) mediated addition of β-ketoester to terminal alkyne.

other indium salts be effective? Furthermore, by what mechanism does the reaction proceed? In light of some related reports using allylindiums in the allylation of unactivated alkynes[12] and an indium(III) catalyst in the Friedel–Crafts alkenylation of arenes using alkynes,[13] as well as indium triflate as an alkyne activator to catalyze a double addition of heterocyclic arenes to alkyne,[13] we believe the mechanistic rationale proposed by Nakamura[4] might be incomplete. Since other Lewis acids that favored the formation of the enolate anion[14] did not promote this reaction, we therefore postulate that activation of alkyne is required in order for the reaction to proceed (Fig. 2).[15]

The low boiling point of 1-pentyne and the desired reaction temperature of 100–140 °C necessitated performing the reaction in a sealed tube. Employing Nakamura's conditions, a neat mixture of nearly stoichiometric amounts of 1-pentyne and diethyl methylmalonate and 5% $In(OTf)_3$ was heated to 100–140 °C for 10 h (Scheme 1). Surprisingly, it gave only a low yield of desired product, as well as at least two other significant side-products. We also



Scheme 1. Addition of malonate to low boiling alkyne.

observed that as the heating continued, the reaction became self-heating causing the temperature to rise quickly in a very short time. This is a potential safety concern for large scale application.

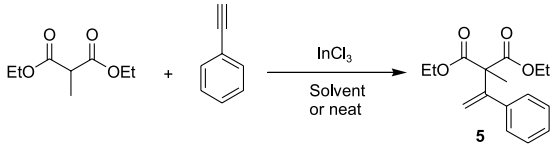
Thus, we decided to dilute the neat mixture with a high boiling, non-polar solvent, such as toluene. The reaction proceeded very well under these conditions. On 20 mmol scale the desired product was isolated in 98% yield. A 1.2 mole scale reaction afforded product in 98% yield, isolated by simple vacuum distillation. This reaction proceeded without the previously described exotherm.

A solvent screen (Table 1) revealed *o*-xylene (bp 143–145 °C) to be an ideal solvent in which to run the reaction at higher temperature with excellent yield when phenylacetylene was the reactant. Indeed, neat conditions also provided the desired product in excellent yield on this scale. Addition of an amine base such as *N*-methylmorpholine, reported to promote formation of the enolate,[16] had a deleterious effect.

A screen of various Lewis acids was then conducted using the reaction between phenylacetylene and diethyl methylmalonate as the model. The study (Table 2) revealed that other indium(III) salts could promote the reaction as efficiently as $In(OTf)_3$. However, the unique nature of indium was once again illustrated by the lack of reactivity exhibited by other Lewis acids.

We then turned our attention to other alkynes (Table 3). Unlike phenylacetylene, 3-phenyl-1-propyne and 4-phenyl-1-butyne gave products **8** and **9** in 58 and 54% yield. If activation of the alkyne by $In(OTf)_3$ occurs, it will form the carbocation intermediate suggested by Shirakawa.[13] The phenyl group is much better at stabilizing the cation than an alkyl group. Since this is a highly regioselective reaction, giving the Markovnikov addition product (branched product) even under the high temperature/sealed tube conditions, it strongly suggests that electronic effects are much more important than steric effects in governing the regiochemistry. Otherwise one might expect the reaction

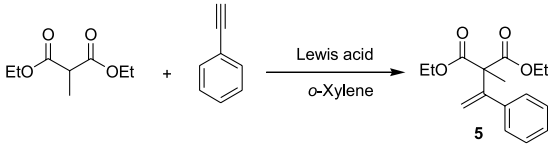
Table 1. Solvent screen using $InCl_3$[a]



Entry	Solvent	Temperature (°C)	Additive[b]	Conversion (%)[c]	
				4 h	20 h
1	*o*-Xylene	135	—	35	94
2	*o*-Xylene	135	NMM	0	1
3	Toluene	110	—	2	53
4	Toluene	110	NMM	0	0
5	Dioxane	100	—	0	0
6	Neat	140	—	61	98
7	Neat	140	NMM	7	34

[a] Reaction conditions: 1 equiv (2.0 mmol) of diethyl methylmalonate, 1.2 equiv of phenylacetylene, 0.02 equiv of $InCl_3$, neat or with desired solvent, 20 h at desired temperature.
[b] 0.10 equiv *N*-methylmorpholine (NMM).
[c] Amount of product relative to malonate. Determined by HPLC analysis of reaction mixture after desired reaction time.

Table 2. Lewis acid screen[a]



Entry	Catalyst	Yield (%)[b]
1	$La(OTf)_3$	Trace
2	$Mg(OTf)_2$	ND[c]
3	$Sc(OTf)_3$	Trace
4	$Sn(OTf)_2$	8
5	$Zn(OTf)_2$	ND
6	$Yb(OTf)_3$	ND
7	$InCl_3$	88
8	$InBr_3$	92
9	$In(OAc)_3$	ND
10	InF_3	ND

[a] Reaction conditions: 1 equiv (10 mmol) of diethyl methylmalonate, 1.2 equiv of phenylacetylene, 0.05 equiv of desired Lewis acid, *o*-xylene, 16 h at 125–130 °C. The reaction time was not optimized.
[b] Isolated yield after purification by silica gel chromatography. Products estimated to be >95% pure by ^{1}H NMR and elemental analysis.
[c] ND=not detected.

would provide the anti-Markovnikov addition product (linear product).

The classic Knoevenagel reaction is the condensation of an aldehyde or ketone with an activated methylene compound in the presence of ammonia or amine.[17] Recently, it was reported that the reaction is catalyzed by Lewis acid.[18] The Knoevenagel acceptors are versatile intermediates for Michael addition,[19] Diels–Alder reaction[20] and Pinner reaction.[21] When an unsubstituted malonate was used in this indium(III) mediated reaction, a mixture of conjugated and unconjugated products was formed (Table 4). In some cases, only the Knoevenagel condensation products or alkylidenemalonates were observed. When a β-ketoester was used, it also afforded a mixture of conjugated and unconjugated products, which was inconsistent with Nakamura's study.[4] It is generally accepted that the Knoevenagel condensation between ketones and malonate is often unachievable by using conventional methodology.[22] Thus, this indium (III) mediated highly regioselective Markovnikov addition of malonates and other activated methylene compounds to terminal alkynes, giving high yield of Knoevenagel condensation products, provides an alternative approach.

3. Conclusion

In summary, the indium triflate mediated addition of activated methylene compounds to terminal alkynes has been expanded to use malonates and low boiling terminal alkynes to form Markovnikov addition products. Other indium(III) salts, such as indium chloride and indium bromide were also found to be efficient catalysts. When an unsubstituted malonate or β-ketoester was used, Knoevenagel condensation product was formed. Further investigations, including extension of the use of this reaction will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out under nitrogen atmosphere unless otherwise noted. All solvents and reagents used were from commercial sources and no further purification was performed. Reactions were monitored by mass spectrometry (MS) on a Micromass Platform LC and by thin-layer chromatography on 0.25 mm E. Merck silica gel 60 plates (F254) using UV light and aqueous potassium permanganate–sodium bicarbonate as visualizing agents. E. Merck silica gel 60 (0.040–0.063 mm and 0.063–0.200 mm particle sizes) was used for column chromatography. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a Varian UNITY INOVA AS400. Chemical shifts are reported as delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for deuteriochloroform. Coupling constants (J) are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz on a Varian UNITY Plus INOVA 400. Chemical shifts are reported as delta (δ) units in parts per million (ppm) relative to the center line of the triplet at 77.3 ppm for deuteriochloroform. Elemental analyses were performed out-of-house by Quantitative Technologies Inc.

4.2. General procedure for indium(III) mediated Markovnikov addition of diethyl methylmalonate to phenylacetylene (Table 1). Compound 5

Diethyl methylmalonate (0.348 g, 2.00 mmol) was combined with phenylacetylene (0.245 g, 2.40 mmol, 1.20 equiv) and $InCl_3$ (9 mg, 0.04 mmol, 0.02 equiv), with or without *N*-methylmorpholine (20 mg, 0.20 mmol, 0.10 equiv), in the desired solvent (10 mL), or in the absence of solvent, and heated at a few degrees below reflux for 20 h. Relative amounts of product and malonate starting material in the reaction mixtures were determined by HPLC analysis.

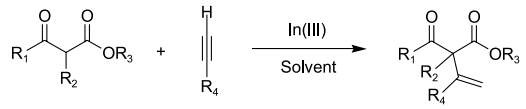
4.3. General procedure for metal mediated Markovnikov addition of diethyl methylmalonate to phenylacetylene (Table 2). Compound 5

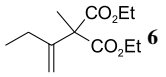
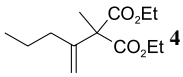
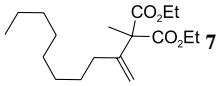
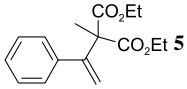
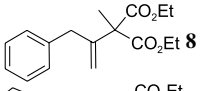
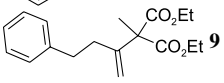
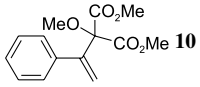
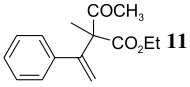
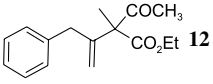
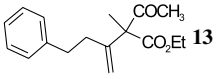
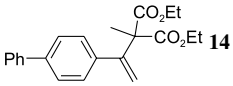
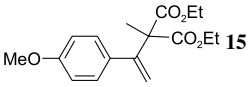
Diethyl methylmalonate (1.74 g, 10.0 mmol) was combined with phenylacetylene (1.23 g, 12.0 mmol, 1.20 equiv) and the desired Lewis acid catalyst (0.50 mmol, 0.05 equiv) in *o*-xylene (10 mL) and stirred at 125–130 °C for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/heptane).

4.4. General procedure for indium(III) mediated Markovnikov addition of malonates and β-ketoesters to terminal alkynes (reagents with bp <130 °C). Compounds 4, 6, 17 and 19

The desired malonate or β-ketoester (10.0 mmol) was combined with the desired alkyne (12.0 mmol, 1.2 equiv) and the desired indium (III) catalyst (0.05–0.20 mmol, 0.005–0.02 equiv) in toluene or *o*-xylene (10 mL) and heated at 140 °C in a sealed tube for 10–20 h. The reaction

Table 3. Addition of different 1-alkynes to branched malonates and β-ketoesters[a]



Entry	Product	Catalyst/Rxn temperature (°C)	Yield (%)[b]
1	 **6**	$In(OTf)_3$/110	95
2	 **4**	$In(OTf)_3$/110[c]	98
3	 **7**	$InCl_3$/130	58
4	 **5**	$In(OTf)_3$/110 $InCl_3$/130 $InBr_3$/130	84 88 92
5	 **8**	$InCl_3$/130 $InBr_3$/130	58 30
6	 **9**	$InCl_3$/130 $InBr_3$/130	54 35
7	 **10**	$InCl_3$/140	81
8	 **11**	$InCl_3$/130	82
9	 **12**	$InCl_3$/130	50
10	 **13**	$InCl_3$/130	41
11	 **14**	$InCl_3$/130	96
12	 **15**	$InCl_3$/130	43

[a] Reaction conditions: 1 equiv (10–20 mmol) of malonate or β-ketoester, 1.2–1.5 equiv of desired alkyne, 0.005–0.05 equiv of desired indium(III) salt, *o*-xylene or toluene, 10–24 h at 110–140 °C. The reaction time was not optimized.
[b] Isolated yield after purification by silica gel chromatography. Products estimated to be >95% pure by ^{1}H NMR and elemental analysis.
[c] Reaction repeated on 0.6 and 1.2 mol scales with identical results.

mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/heptane).

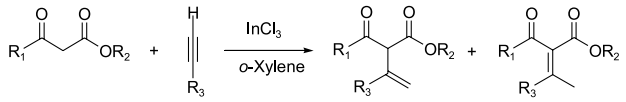
4.4.1. 2-Methyl-2-(1-methylenebutyl)malonic acid diethyl ester (4). ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J=7.3 Hz, 3H), 1.23 (t, J=7.1 Hz, 6H), 1.44–1.53 (m, 2H), 1.56 (s, 3H), 2.01–2.05 (m, 2H), 4.17 (q, J=7.2 Hz, 4H), 4.96–4.98 (m, 1H), 5.02–5.04 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.0, 21.9, 35.1, 60.8, 61.6, 112.2, 147.0, 171.5. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.54; H, 8.82.

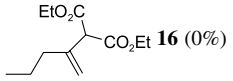
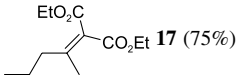
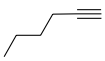
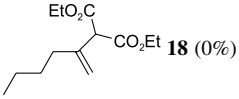
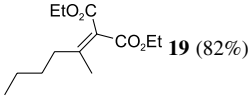
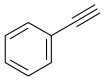
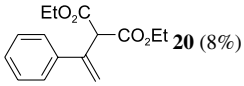
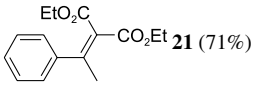
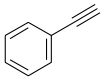
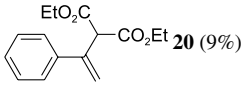
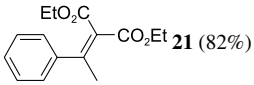
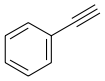
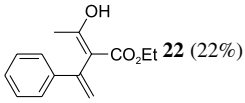
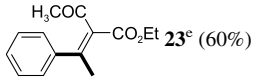
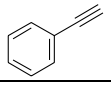
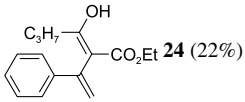
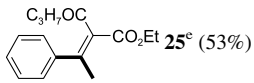
4.4.2. 2-Methyl-2-(1-methylenepropyl)malonic acid diethyl ester (6). ^{1}H NMR ($CDCl_3$): δ 1.08 (t, J=7.5 Hz, 3H), 1.25 (t, J=7.1 Hz, 6H), 1.59 (s, 3H), 2.12 (q, J=7.2 Hz, 2H), 4.19 (q, J=7.1 Hz, 4H), 4.98–5.01 (m, 1H), 5.05–5.07 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 12.9, 14.2, 21.0, 25.7, 60.8, 61.6, 111.6, 148.6, 171.5. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.12; H, 8.36.

4.4.3. 2-(1-Methylbutylidene)malonic acid diethyl ester (17). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J=7.4 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.52 (m, 2H), 2.04 (s, 3H), 2.30 (m, 2H), 4.20 (q, J=7.1 Hz, 2H), 4.21 (q, J=7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.2, 20.8, 21.4, 38.8, 60.9, 61.0, 124.8, 166.0, 158.8, 165.7. Anal. Calcd for $C_{10}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.14; H, 8.75.

4.4.4. 2-(1-Methylpentylidene)malonic acid diethyl ester (19). ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J=7.3 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.33 (m, 2H), 1.47 (m, 2H), 2.05 (s, 3H), 2.33 (m, 2H), 4.21 (q, J=7.1 Hz, 2H),

Table 4. Addition of 1-alkynes to simple malonates or β-ketoesters[a]



Entry	S.m.	Alkyne	Products (%yield)[b]
1			 **16** (0%)  **17** (75%)
2			 **18** (0%)  **19** (82%)
3[c]			 **20** (8%)  **21** (71%)
4[d]			 **20** (9%)  **21** (82%)
5			 **22** (22%)  **23**[e] (60%)
6			 **24** (22%)  **25**[e] (53%)

[a] Reaction conditions: 1 equiv (10 mmol) of malonate or β-ketoester, 1.2–1.5 equiv of desired alkyne, 0.01–0.05 equiv of $InCl_3$, *o*-xylene, 16–20 h at 130–140 °C. The reaction time was not optimized.
[b] Isolated yield after purification by silica gel chromatography. Products estimated to be >95% pure by ^1H NMR and elemental analysis.
[c] Used 1.2 equiv of alkyne. Compounds **20** and **21** isolated as 1:9 mixture.
[d] Used 1.5 equiv of alkyne. Compounds **20** and **21** isolated as 1:9 mixture.
[e] Compounds **23** and **25** isolated as mixtures of *E* and *Z* isomers.

4.22 (q, $J=7.1$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.0, 14.2, 20.9, 22.9, 30.2, 36.7, 60.9, 61.0, 124.6, 159.1, 165.7, 166.0. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.70; H, 8.94.

4.5. General procedure for indium(III) mediated Markovnikov addition of malonates and β-ketoesters to terminal alkynes (reagents with bp >130 °C). Compounds 5, 7–15 and 20–25

The desired malonate or β-ketoester (10.0 mmol) was combined with the desired alkyne (12.0–15.0 mmol, 1.20–1.50 equiv) and the desired indium (III) catalyst (0.10–0.50 mmol, 0.01–0.05 equiv) in toluene or *o*-xylene (10 mL), and heated at 110–140 °C for 16–24 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/heptane).

4.5.1. 2-Methyl-2-(1-phenylvinyl)malonic acid diethyl ester (5). ^1H NMR ($CDCl_3$): δ 1.20 (t, $J=7.1$ Hz, 6H), 1.59 (s, 3H), 4.14–4.21 (m, 4H), 5.34 (d, $J=0.7$ Hz, 2H), 7.23–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.5, 60.3, 61.9, 118.3, 127.6, 128.1, 128.5, 141.0, 148.0, 171.6. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.68; H, 7.29.

4.5.2. 2-Methyl-2-(1-methylenenonyl)malonic acid diethyl ester (7). ^1H NMR ($CDCl_3$): δ 0.87 (t, $J=7.1$ Hz, 3H), 1.21–1.33 (m, 16H), 1.41–1.52 (m, 2H), 1.59 (s, 3H), 2.03–2.10 (m, 2H), 4.19 (q, $J=7.16$ Hz, 4H), 4.98–5.00 (m, 1H), 5.05–5.07 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 14.3, 21.0, 22.9, 28.8, 29.5, 29.8, 32.1, 33.0, 60.8, 61.6, 112.1, 147.3, 171.5. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.21; H, 10.39.

4.5.3. 2-(1-Benzylvinyl)-2-methylmalonic acid diethyl ester (8). ^1H NMR ($CDCl_3$): δ 1.27 (t, $J=7.1$ Hz, 6H), 1.66 (s, 3H), 3.47 (s, 2H), 4.19 (q, $J=7.1$ Hz, 4H), 4.72–4.79 (m, 1H), 5.10–5.16 (m, 1H), 7.15–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.2, 39.7, 60.4, 61.8, 115.9, 126.4, 128.5, 129.8, 139.5, 146.8, 171.4. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.59; H, 7.79.

4.5.4. 2-Methyl-2-(1-methylene-3-phenylpropyl)malonic acid diethyl ester (9). ^1H NMR ($CDCl_3$): δ 1.27 (t, $J=7.1$ Hz, 6H), 1.62 (s, 3H), 2.38–2.46 (m, 2H), 2.78–2.86 (m, 2H), 4.21 (q, $J=7.2$ Hz, 4H), 5.09 (br s, 1H), 5.18 (br s, 1H), 7.14–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.1, 34.9, 35.2, 60.8, 61.7, 112.9, 126.1, 128.6, 128.6, 142.1, 146.6, 171.4. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.34; H, 8.18.

4.5.5. 2-Methoxy-2-(1-phenylvinyl)malonic acid dimethyl ester (10). ^1H NMR ($CDCl_3$): δ 3.49 (s, 3H), 3.73 (s, 6H), 5.52 (s, 1H), 5.76 (s, 1H), 7.28 (m, 3H), 7.42 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 53.1, 54.3, 87.8, 121.6, 127.2, 128.1, 128.4, 138.7, 142.4, 168.2. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 64.01; H, 6.12.

4.5.6. 2-Acetyl-2-methyl-3-phenylbut-3-enoic acid ethyl ester (11). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J=7.1 Hz, 3H), 1.51 (s, 3H), 2.28 (s, 3H), 4.16 (dq, J=7.1 Hz, 0.6, 2H), 5.27 (br s, 1H), 5.42 (br s, 1H), 7.16–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.1, 21.5, 27.6, 61.8, 66.0, 119.0, 127.8, 128.0, 128.3, 140.6, 148.2, 172.0, 205.5. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.03.

4.5.7. 2-Acetyl-3-benzyl-2-methylbut-3-enoic acid ethyl ester (12). ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J=7.2 Hz, 3H), 1.56 (s, 3H), 2.24 (s, 3H), 3.37 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 4.80–4.89 (m, 1H), 5.06–5.14 (m, 1H), 7.16–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.2, 20.2, 27.3, 39.7, 61.7, 66.2, 116.7, 126.6, 128.6, 129.8, 139.0, 147.0, 171.9, 205.4. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.02; H, 7.63.

4.5.8. 2-Acetyl-2-methyl-3-methylene-5-phenylpentanoic acid ethyl ester (13). ^{1}H NMR ($CDCl_3$): δ 1.27 (t, J= 7.2 Hz, 3H), 1.53 (s, 3H), 2.20 (s, 3H), 2.29–2.36 (m, 2H), 2.77–2.84 (m, 2H), 4.21 (q, J=7.2 Hz, 2H), 5.01–5.11 (m, 1H), 5.22–5.28 (m, 1H), 7.13–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.3, 19.9, 27.3, 34.9, 35.0, 61.7, 66.6, 113.9, 126.2, 128.5, 128.6, 141.8, 146.8, 172.0, 205.5. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.76; H, 7.84.

4.5.9. 2-(1-Biphenyl-4-ylvinyl)-2-methylmalonic acid diethyl ester (14). ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J= 7.1 Hz, 6H), 1.65 (s, 1H), 4.17–4.25 (m, 4H), 5.40 (d, J= 15.6 Hz, 2H), 7.35 (m, 1H) 7.32–7.60 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 60.3, 61.9, 118.3, 126.8, 127.2, 127.6, 128.9, 129.0, 140.0, 140.4, 140.9, 147.7, 171.6. Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.63; H, 6.78.

4.5.10. 2-[1-(4-Methoxyphenyl)-vinyl]-2-methylmalonic acid diethyl ester (15). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J= 7.1 Hz, 6H), 1.58 (s, 3H), 3.78 (s, 3H), 4.14–4.22 (m, 4H), 5.28 (d, J=10.0 Hz, 2H), 6.77–6.83 (m, 2H) 7.16–7.22 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.5, 55.4, 60.4, 61.8, 113.4, 117.6, 129.6, 133.3, 147.5, 159.1, 171.7. Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 67.06; H, 7.22.

4.5.11. 2-(1-Phenylvinyl)malonic acid diethyl ester (20). ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J=7.1 Hz, 6H), 4.20 (dq, J= 7.1, 1.7 Hz, 4H), 4.60 (d, J=1.0 Hz, 1H), 4.51 (d, J= 0.7 Hz, 1H), 5.63 (s, 1H), the phenyl protons of **20** not distinguishable from those of **21**. ^{13}C NMR ($CDCl_3$): δ 14.2, 57.4, 62.0, 117.9, 126.4, 126.4, 140.4, 140.9. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.95; H, 6.85. Data from analysis of 1:9 mixture of **20**:**21**.

4.5.12. 2-(1-Phenylethylidene)malonic acid diethyl ester (21). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J=7.1 Hz, 3H), 1.31 (t, J=7.1 Hz, 3H), 2.43 (s, 3H), 3.95 (q, J=7.1 Hz, 2H), 4.28 (q, J=7.1 Hz, 2H), 7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.8, 14.3, 23.0, 61.1, 61.3, 126.8, 128.5, 128.6, 141.8, 155.9, 165.0, 166.4, 168.1. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.95; H, 6.85. Data from analysis of 1:9 mixture of **20**:**21**.

4.5.13. 3-Hydroxy-2-(1-phenylvinyl)but-2-enoic acid ethyl ester (22). ^{1}H NMR ($CDCl_3$): δ 1.01 (t, J=7.1 Hz, 3H), 2.03 (d, J=1.0 Hz, 3H), 4.07 (q, J=7.1 Hz, 2H), 5.16 (d, J=1.7 Hz, 1H), 5.75 (d, J=1.5 Hz, 1H), 7.22–7.41 (m, 5H), 12.99–13.06 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 19.8, 60.6, 103.9, 117.8, 126.1, 127.7, 128.5, 141.0, 142.7, 172.7, 174.3. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.63; H, 6.77.

4.5.14. 2-Acetyl-3-phenylbut-2-enoic acid ethyl ester (23). ^{1}H NMR ($CDCl_3$): δ 0.91 (dt, J=7.1, 1.5 Hz, 1.3H), 1.30 (dt, J=7.1, 1.3 Hz, 1.7H), 1.85 (d, J=1.5 Hz, 1.7H), 2.32 (d, J=1.2 Hz, 1.3H), 2.34 (d, J=1.2 Hz, 1.3H), 2.39 (d, J=1.2 Hz, 1.7H), 3.93 (dq, J=7.1, 1.3 Hz, 0.8H), 4.26 (dq, J=7.1, 1.3 Hz, 1.2H), 7.16–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.7, 14.3, 23.1, 23.3, 30.6, 31.2, 61.2, 61.3, 126.8, 127.5, 128.5, 128.5, 128.9, 129.1, 133.7, 134.4, 141.1, 142.3, 152.4, 154.3, 165.7, 167.4, 198.4, 201.9. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.57; H, 6.93.

4.5.15. 3-Hydroxy-2-(1-phenylvinyl)hex-2-enoic acid ethyl ester (24). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J=7.5 Hz, 3H), 1.01 (t, J=7.2 Hz, 3H), 1.57–1.68 (m, 2H), 2.25–2.33 (m, 2H), 4.07 (q, J=7.1 Hz, 2H), 5.15 (d, J=1.5 Hz, 1H), 5.75 (d, J=1.7 Hz, 1H), 7.21–7.42 (m, 5H) 13.05–13.09 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 14.2, 20.5, 34.9, 60.6, 103.6, 117.6, 126.2, 127.7, 128.4, 141.1, 142.5, 172.9, 177.3. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.90; H, 7.69.

4.5.16. 3-Oxo-2-(1-phenylethylidene)hexanoic acid ethyl ester (25). ^{1}H NMR ($CDCl_3$): δ 0.63 (t, J=7.5 Hz, 1.7H), 0.88–0.99 (m, 2.6H), 1.28 (t, J=7.1 Hz, 1.7H), 1.34 (q, J= 7.1 Hz, 1.2H), 1.69 (q, J=7.1 Hz, 0.8H), 2.06 (t, J=7.2 Hz, 1.2H), 2.26 (s, 1.2H), 2.41 (s, 1.8H), 2.60 (t, J=7.2 Hz, 0.8H), 3.93 (q, J=7.2 Hz, 0.8H), 4.24 (q, J=7.1 Hz, 1.2H), 7.15–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 13.9, 14.3, 17.2, 17.4, 22.9, 23.3, 44.7, 45.7, 61.1, 126.8, 127.7, 128.4, 128.4, 128.7, 128.9, 133.8, 134.2, 141.2, 142.3, 152.0, 153.4, 165.6, 167.0, 201.5, 204.7. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.84; H, 7.83.

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