Direct organocatalytic Wittig/Hetero-Diels-Alder reactions in one-pot: synthesis of highly-substituted tetrahydropyranones

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Dedicated to Prof. Dr. J. S. Yadav in appreciation of his outstanding contributions to synthetic organic chemistry

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Abstract
A practical and environmentally friendly organocatalytic one-pot strategy designed to furnish the hetero-Diels-Alder products was shown to be effective in the preparation of disubstituted tetrahydropyranones in a highly selective manner. (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine catalyzed an asymmetric assembly reaction involving a hetero-Diels-Alder reaction between alkylidene- and arylidene-acetones generated *in situ* from Wittig reactions with diethyl ketomalonate to furnish the substituted tetrahydropyranones in moderate to very good yields with moderate enantioselectivity.

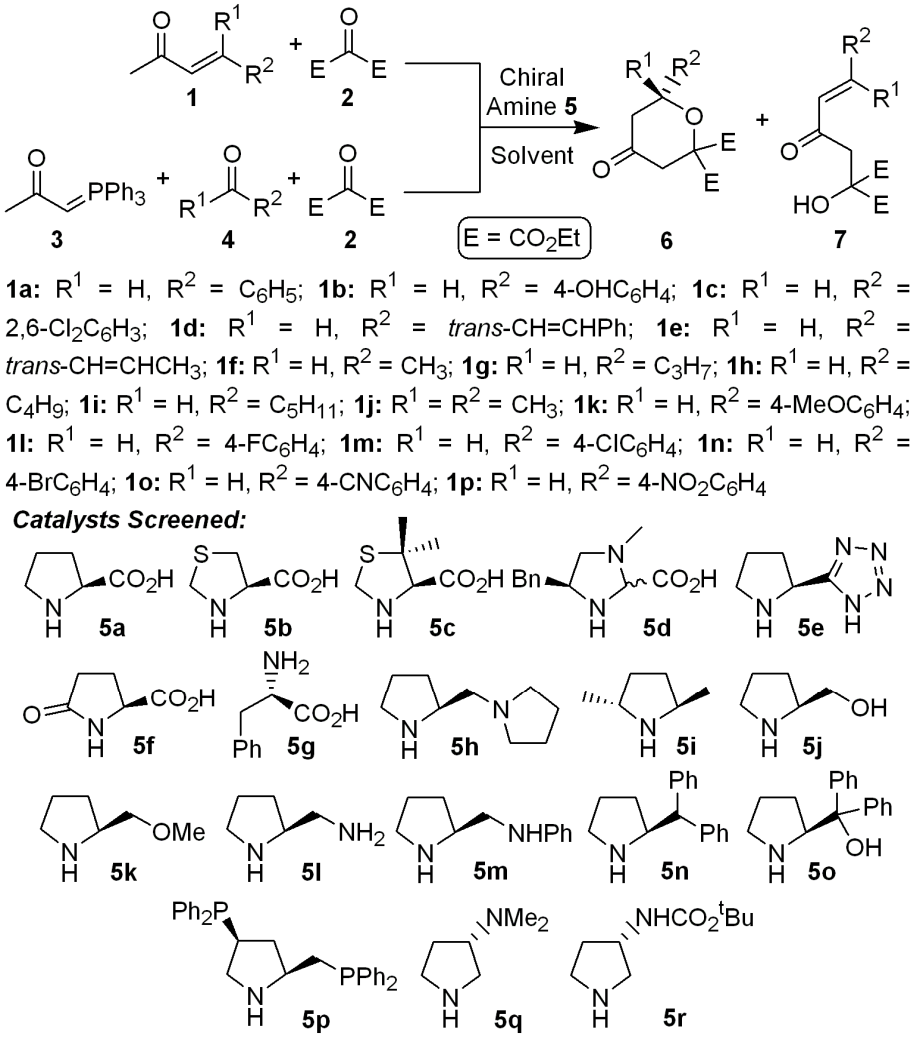
Keywords: Amino acids; diethyl ketomalonate; hetero-Diels-Alder reactions; multi-component reactions; organocatalysis

Introduction

Cycloaddition reactions between carbonyl compounds as the heterodienophiles and homo-dienes provide for the preparation of numerous six-membered oxygen-containing heterocycles that are frequently encountered structural motifs in biologically active natural products.[1-3] The extraordinary range of applications of enantio-pure hetero-Diels-Alder (HDA) adducts has stimulated the search for efficient chiral catalysts for cycloadditions between dienes and carbonyl dienophiles. Many catalysts, including chiral aluminium, boron, titanium, chromium, europium, or ytterbium complexes, can accelerate the reaction of unactivated aldehydes with activated dienes to generate high yields with excellent stereochemical control.[4-7]

Recently metal-free, small chiral organic molecules have emerged as an exciting class of biomimetic catalysts for the generation of enviromentally-friendly asymmetric reactions.[8-10] Rawal *et al*. recently demonstrated that small organic molecules, such as TADDOL

(tetraaryl-1,3-dioxolane-4,5-dimethanol), could catalyze the enantioselective HDA reaction of activated dienes with aldehydes through hydrogen bonding.[11-13] Also, Jørgensen and Juhl developed the enantioselective inverse-electron-demand HDA reaction with an enamine generated *in situ* from an aldehyde and chiral amine with enones under organocatalysis.[14-18] As part of our program to engineer novel asymmetric assembly reactions that proceed in environmentally-sound conditions under amine-catalysis,[8,19-27] we sought to extend the use of chiral organo-amines as catalysts for asymmetric HDA reactions.



Scheme 1. Direct organocatalytic asymmetric Wittig/hetero-Diels-Alder reactions in one pot.

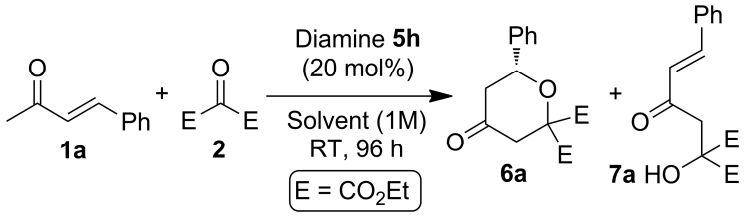
In contrast to cycloadditions involving aldehydes as the heterodienophiles, the Diels-Alder reactions of ketones are still a challenge to chemists. Ketones are less reactive than aldehydes due to both steric and electronic constraints. The challenge herein is to develop a metal-free, small organic molecule-catalyzed, enantioselective HDA reaction of ketones with *in situ* generated conjugated dienes as this reaction will have wide utility in organic chemistry. In this article, we demonstrate the two- and three-component HDA reaction of *in situ* generated Barbas dienamines (2-amino-1,3-butadienes) **10** from enones **1** (generated from Wittig reaction of aldehydes **4** with 1-(triphenylphosphanylidene)propan-2-one **3**) and

chiral organo-amines **5** with activated ketone **2** as heterodienophile to furnish chiral disubstituted tetrahydropyranones **6** in good yields with moderate enantioselectivity as shown in Scheme 1. These HDA products **6** have direct application in the total synthesis of anti-osteoporotic and antibiotic natural products.[28-30]

Results and Discussion

The reaction of benzylideneacetone **1a** and diethyl ketomalonate **2** with a catalytic amount of (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **5h** in MeOH at ambient temperature for 17 h furnished the HDA product **6a** and the aldol product **7a** at a 7:1 ratio respectively, in 99% yield but with only 3% enantiomeric excess (*ee*) of **6a** (Table 1, entry 1).

Table 1. Effect of solvent on direct organocatalytic HDA reactions of **1a** and **2**[a]



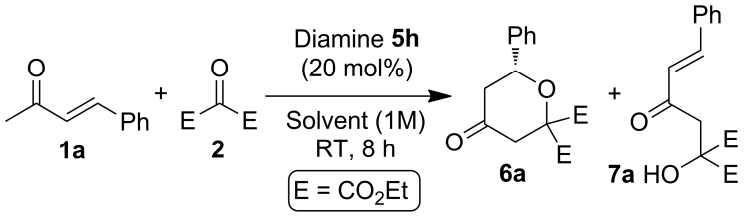
Entry	Solvent	Yield (%)[b]	Ratio (**6a**/**7a**)[c]	ee (%)[d]
1[e]	MeOH	99	7:1	3
2	DMSO	31	2:1	3
3	DMF	63	2.4:1	1
4	[bmim]BF_4	31	3:1	8
5	$CHCl_3$	75	2:1	1
6	CH_2Cl_2	80	1.9:1	2
7	CH_3CN	38	2.5:1	3
8	THF	81	1:1	6
9	CCl_4	37	1.4:1	2
10	$ClCH_2CH_2Cl$	62	3:1	0
11	1,4-Dioxane	6	1:1	14
12	**$CH_3C_6H_5$**	**63**	**1.86:1**	**22**

[a] Reactions were carried out in solvent (1 mL) with 0.5 mmol of **2** and 1.0 mmol of **1a** in the presence of 20 mol% of catalyst. [b] Yield refers to the column-purified product.[c] Ratio determined by ^{1}H NMR analysis. [d] Ee determined by CSP-HPLC analysis.[e] Reaction time was 17 h.

In the asymmetric HDA reaction of enone **1a** and diethyl ketomalonate **2** catalyzed by diamine **5h**, we found that the solvent had a significant effect on reaction path, yields, and *ee*'s of **6a** and **7a** (Tables 1 and 2). The HDA reaction catalyzed by diamine **5h** produced products **6a** and **7a** with an excellent ratio of **6a** to **7a** and excellent yields, but poor *ee*'s in protic solvents (Table 1, entry 1; Table 2, entries 2-6) and with poor chemoselectivity, good yields, and moderate *ee*s in aprotic polar/nonpolar solvents (Table 1, entries 2-12). The same

reaction in the ionic liquid, [bmim]BF_4 provided **6a** in 31% yield, albeit with low *ee* of 8% (Table 1, entry 4). More of the undesired aldol product **7a** was formed in aprotic solvents compared to protic solvents as shown in Tables 1 and 2.

Table 2: Effect of protic solvents on the direct diamine **5h** catalyzed HDA reactions of **1a** and **2**[a]



Entry	Solvent	Yield (%)[b]	Ratio (**6a/7a**)[c]	ee (%)[d]
1[e]	**THF**	**6**	**1:1.5**	**-**
2	MeOH	82	7.6:1	3
3	EtOH	69	9:1	6
4	*n*-PrOH	63	10.7:1	5
5	*i*-PrOH	30	9:1	12
6	***n*-BuOH**	**66**	**12.8:1**	**2**
7	*sec*-BuOH	5	1:99	-
8	*tert*-BuOH	5	1:99	-

[a] Reactions were carried out in solvent (1 mL) with 0.5 mmol of **2** and 1.0 mmol of **1a** in the presence of 20 mol% of catalyst. [b] Yield refers to the column-purified product.[c] Ratio determined by ^{1}H NMR analysis. [d] Ee determined by CSP-HPLC analysis.[e] Reaction time was 17 h.

Next we probed the structure and reactivity relationships among a family of 18 pyrrolidine-based catalysts by monitoring the reaction conversions and *ee* values of the HDA reaction of **1a** and **2** in toluene (Table 3). The amino acid L-proline **5a** catalyzed the HDA reaction to produce **6a** and **7a** in 45% conversion and 13% *ee* with 1:1.4 ratio of **6a** to **7a** after 5 days (Table 3, entry 1). L-Thiaproline **5b** also catalyzed the HDA reaction to produce **6a** and **7a** in 20% conversion and 40% *ee* with 1:2 ratio of **6a** to **7a** after 5 days (Table 2, entry 2). Among the catalysts screened, (*S*)-2-diphenylmethylpyrrolidine **5n** proved to be the most efficient catalyst with respect to *ee*, providing **6a** in 49% *ee* but conversion (30%) and ratio of **6a** to **7a** were poor (Table 3, entry 14). Notable improvement in the enantioselectivity of the reaction was found in L-thiaproline- and (*S*)-2-diphenylmethyl-pyrrolidine-catalyzed HDA reactions.

Table 3. Effect of catalyst on the direct amine **5** catalyzed HDA reactions of **1a** and **2**[a]

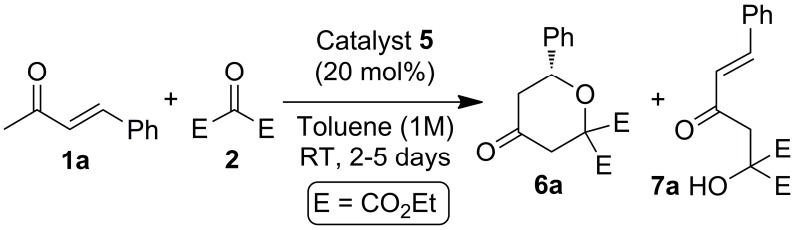
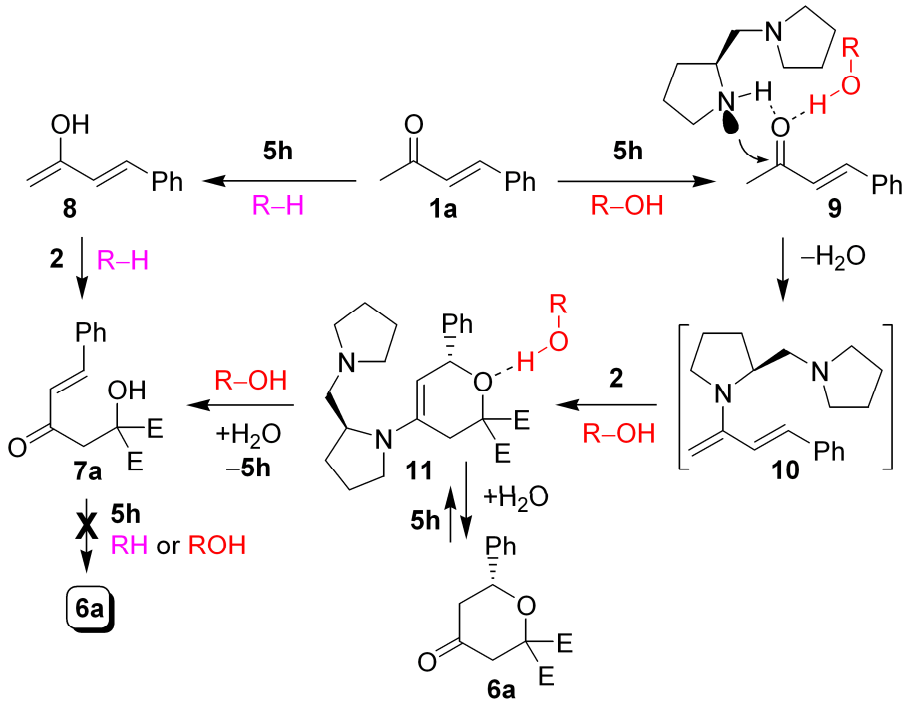


Table 3 (continued)

Entry	Catalyst	Conversion (%)[b]	Ratio (**6a**/**7a**)[c]	ee (%)[d]
1[e]	**5a**	45	1:1.4	13
2	**5b**	**20**	**1:2**	**40**
3	**5c**	<10	-	-
4	**5d**	15	1:19	-
5	**5e**	40	1:1	15
6	**5f**	60	1:19	-
7	**5g**	20	1:19	-
8[f]	**5h**	65	5:1	5
9	**5i**	30	1:9	-
10	**5j**	60	2:1	8
11	**5k**	60	3:1	8
12	**5l**	75	5:1	15
13	**5m**	<10	-	-
14	**5n**	**30**	**1:3**	**49**
15	**5o**	10	1:9	-
16	**5p**	<10	-	-
17	**5q**	30	1:5	7
18	**5r**	75	5:1	3

[a] Reactions were carried out in toluene (1 mL) with 0.5 mmol of **2** and 1.0 mmol of **1a** in the presence of 20 mol% of catalyst **5** at RT for 2-5 days. [b] Conversion based on the ratio of **1a** to **6a** and **7a**, determined by ^{1}H NMR analysis. [c] Ratio determined by ^{1}H NMR analysis. [d] Ee determined by CSP-HPLC analysis. [e] Solvent was MeOH. [f] Additive CF_3CO_2H (30 mol%) was used.

The proposed mechanism for synthesis of chemoselective tetrahydropyranone **6a** and aldol product **7a** through the reaction of enone **1a** and ketone **2** is illustrated in Scheme 2. Chiral (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **5h** or L-proline **5a** presumably catalyze the *in situ* generation of 2-amino-1,3-butadiene **10** or 2-hydroxy-1,3-butadiene **8** from enone **1a**. Subsequent [4+2]-cycloaddition of **10** with ketone **2** furnishes the enamine **11**, which immediately undergoes hydrolysis to furnish HDA product **6a** or to aldol product **7a** *via* retro-Michael reaction under protic solvent conditions. Alternatively, 2-hydroxy-1,3-butadiene **8** reacts with ketone **2** to furnish aldol product **7a**, which does not undergo intramolecular oxy-Michael addition to form **6a** under these conditions. Interconversion of products **6a** and **7a** was confirmed by controlled experiments as shown in Scheme 3 (see Supporting Information). Formation of 2-hydroxy-1,3-butadiene **8**, responsible for the generation of aldol byproduct **7a** (see Scheme 3), is more favorable in aprotic nonpolar solvents under general acid/base-catalysis.



Scheme 2. Proposed reaction mechanism.

We further explored the scope of the (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **5h** catalyzed hetero-Diels-Alder reactions of various 4-substituted 3-buten-2-ones **1a-k** with ketone **2** (Table 4). Even though the enantioselectivities were poor, chiral amine **5h** was used as catalyst to study the chemoselective generation of chemically diverse tetrahydropyranones (chiral amine **5h** is cheaper compared to racemic amine **5h**).[28-30] Interestingly, amine **5h** catalyzed the HDA reaction of arylidene acetones **1a-d** with **2** to furnish the products **6** and **7** in a reasonable ratio as shown in Table 4, entries 1-4. The same reaction with alkylideneacetones **1f-j** furnished the chemoselective HDA products **6f-j** in very good yields (Table 4, entries 6-10); these compounds have direct application in total synthesis of bio-active natural products.

Table 4. Direct amine **5h** catalyzed HDA reactions of different enones **1a-k** with diethyl ketomalonate **2**[a]

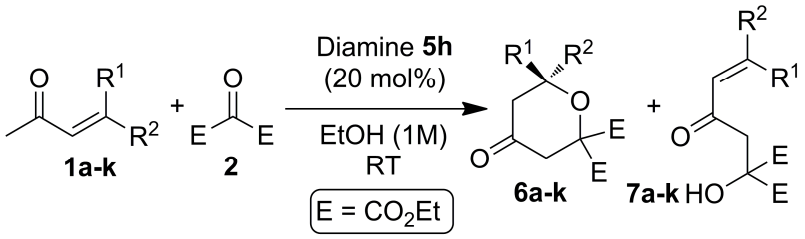


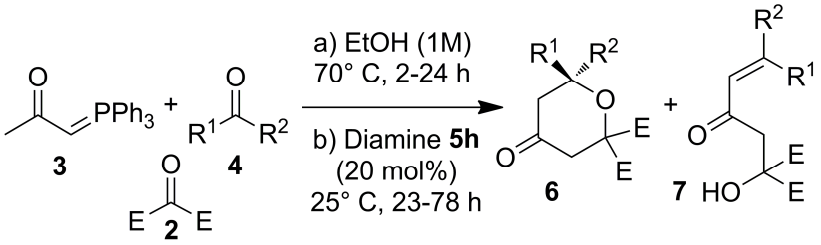
Table 4 (continued)

Entry	Enone	Time (h)	Yield (%)[b]	Ratio(**6**/**7**)[c]
1	**1a**	12	**6a,7a**(75)	9:1
2	**1b**	68	**6b,7b**(65)	1:4
3	**1c**	68	**6c,7c**(60)	2.2:1
4	**1d**	78	**6d,7d**(65)	1:6.5
5	**1e**	72	**6e,7e**(45)	1:2
6	**1f**	78	**6f**(>99)	99:1
7	**1g**	78	**6g**(>99)	99:1
8	**1h**	78	**6h**(92)	99:1
9	**1i**	78	**6i**(83)	99:1
10	**1j**	120	**6j**(85)	99:1
11	**1k**	72	**6k,7k**(54)	1:2

[a] See Supporting Information. [b] Yield refers to the column-purified product. [c] Ratio determined by ^{1}H NMR analysis.

We also evaluated the amine **5h**-catalyzed three-component Wittig/HDA reaction of phosphorane **3**, aldehyde **4**, and ketone **2** to furnish the tetrahydropyranes **6** in good yields as shown in Table 5. Aliphatic aldehyde **4h** did not provide good yields (entry 2), but aromatic aldehydes **4a**, **4l-p** gave good yields of tandem Wittig/HDA products **6** and aldol products **7** (Table 5, entries 1, 3-7).

Table 5. Direct amine **5h** catalyzed three-component Wittig/HDA reactions of **2**, **3**, and **4**[a]



Entry	aldehyde	Time (h)	Yield (%)[b]	Ratio(**6**/**7**)[c]
1	**4a**	2/23	**6a,7a**(85)	9:1
2	**4h**	24/75	**6h**(20)	99:1
3	**4l**	24/72	**6l,7l**(97)	2.4:1
4	**4m**	24/72	**6m,7m**(91)	1:1
5	**4n**	24/72	**6n,7n**(80)	3.3:1
6	**4o**	24/75	**6o,7o**(52)	1.6:1
7	**4p**	4/65	**6p,7p**(60)	2.7:1

[a] See Supporting Information. [b] Yield refers to the column-purified product. [c] Ratio determined by ^{1}H NMR analysis

Conclusions

In summary, we have developed methods for the asymmetric HDA and three-component Wittig/HDA reactions to produce substituted tetrahydropyranes **6** under amine-catalysis. The one-pot reaction proceeds in good yield with diamine **5h** as the catalyst. Furthermore, we have demonstrated that the *in situ* generated 2-hydroxy-1,3-butadienes **8** *via* general acid/base-catalysis with chiral amines **5h-r** and amino acids **5a-g** undergo aldol addition with **2** to yield **7**. Further work is in progress to improve the *ee* of the reaction and utilize these novel HDA products in natural product synthesis.

Experimental Section

General. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses. The coupling constants *J* are given in Hz. Column chromatography was performed using Acme silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LCMS mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Materials. All solvents and commercially available chemicals were used as received.

General experimental procedures for the organocatalytic reactions

Chiral amine or amino acid-catalyzed asymmetric hetero-Diels-Alder reactions

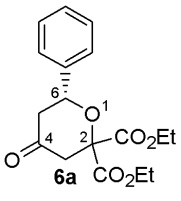
In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the enone **1** and 1.0 mL of solvent, catalyst amine **5** (20 mol%) was added and the reaction mixture was stirred at ambient temperature for 5 minutes. To the reaction mixture 0.5 mmol of diethyl ketomalonate **2** was added and stirred at ambient temperature for the time indicated in Tables 1, 2, 3 and 4. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure hetero-Diels-Alder **6** and aldol **7** products were obtained by flash column chromatography (silica gel; hexane/ethyl acetate mixture).

(*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine (5h) catalyzed Wittig/hetero-Diels-Alder reactions in one-pot

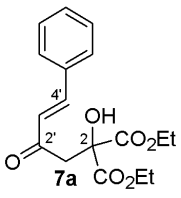
In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the phosphorane **3** and 1.0 mL of EtOH, 0.6 mmol of the aldehyde **4** was added and the reaction

mixture was stirred at 70° C for the time indicated in Table 5. To the reaction mixture catalyst amine **5h** (20 mol-%) was added and the reaction mixture was stirred at ambient temperature for 5 minutes. Then 0.3 mmol of diethylketomalonate **2** was added and stirred at ambient temperature for the time indicated in Table 5. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure tandem Wittig/hetero-Diels-Alder **6** and Wittig/aldol **7** products were obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate). All new compounds were characterized on the basis of IR, ^{1}H and ^{13}C NMR and analytical data (see Supporting Information).

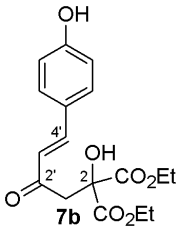
(6*R*)-4-Oxo-6-phenyltetrahydropyran-2,2-dicarboxylic acid diethyl ester (6a). Purified by column chromatography using EtOAc/hexane and isolated as oil. The *ee* was determined by chiral-phase HPLC using a Daicel Chiralcell OD-H column (hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 220 nm), t_R = 10.71 min (minor), t_R = 13.02 min (major); IR (neat): ν_{max} 2984, 1743 (C=O, O-C=O), 1608, 1452, 1369, 1224, 1070, 858, 760, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40-7.23 (5H, m, Ph-*H*), 4.90 (1H, dd, *J* = 9.2, 5.2 Hz), 4.27 (4H, br q, *J* = 7.2 Hz, 2 × OC*H*$_2$CH$_3$), 3.15 (1H, d, *J* = 15.6 Hz), 2.80 (1H, d, *J* = 15.6 Hz), 2.63 (2H, m), 1.264 (3H, t, *J* = 7.2 Hz), 1.259 (3H, t, *J* = 7.2 Hz) [2 × OCH$_2$C*H*$_3$]; ^{13}C NMR ($CDCl_3$, DEPT) δ 202.2 (C, C=O), 167.5 (C, O=C-O), 167.0 (C, O=C-O), 139.3 (C), 128.6 (2 × CH), 128.4 (CH), 125.9 (2 × CH), 82.2 (C, C-2), 75.6 (CH, C-6), 62.6 (2 × CH$_2$, O*C*H$_2$CH$_3$), 47.9 (CH$_2$), 44.2 (CH$_2$), 13.96 (CH$_3$), 13.90 (CH$_3$) [2 × O*C*H$_2$CH$_3$]; HRMS (ESI-TOF): *m/z* 321.1331 (M + H$^+$), calcd for $C_{17}H_{20}O_6H^+$ 321.1333.



2-Hydroxy-2-(2-oxo-4-phenylbut-3-enyl)malonic acid diethyl ester (7a). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3473 (O-H), 2984, 1739 (C=O, O-C=O), 1693, 1665 (C=C), 1611, 1281, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 16.4 Hz, olefinic-β-*H*), 7.50 (1H, m), 7.37 (4H, m), 6.70 (1H, d, *J* = 16.4 Hz, olefinic-α-*H*), 4.27 (4H, q, *J* = 7.2 Hz, 2 × OC*H*$_2$CH$_3$), 3.80 (1H, dd, *J* = 3.6, 2.0 Hz, O-*H*), 3.51 (2H, s, CH$_2$), 1.26 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 196.2 (C, C=O), 169.5 (2 × C, O=C-O), 144.1 (CH), 134.0 (C), 130.8 (CH), 128.9 (2 × CH), 128.4 (2 × CH), 125.7 (CH), 76.8 (C, C-OH), 62.70 (2 × CH$_2$, O*C*H$_2$CH$_3$), 44.9 (CH$_2$), 13.9 (2 × CH$_3$, OCH$_2$*C*H$_3$); HRMS (ESI-TOF): *m/z* 321.1330 (M + H$^+$), calcd for $C_{17}H_{20}O_6H^+$ 321.1333.

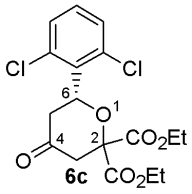


2-Hydroxy-2-[4-(4-hydroxyphenyl)-2-oxobut-3-enyl]malonic acid diethyl ester (7b). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3420 (O-H), 2986, 1747 (C=O, O-C=O), 1647, 1601, 1516, 1445, 1369, 1234, 856, 820, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (1H, d, *J* = 16.4 Hz, olefinic-β-*H*), 7.39 (2H, d, *J* = 8.4 Hz, Ph-*H*), 7.23 (1H, br s, Ar-O*H*), 6.87 (2H, d, *J* = 8.4 Hz, Ph-*H*), 6.54 (1H, d, *J* = 16.0 Hz, olefinic-α-*H*), 4.51 (1H, br s, O-*H*), 4.30 (4H, br q , *J* = 6.8 Hz, 2 × OC*H*$_2$CH$_3$), 3.51 (2H, s, CH$_2$), 1.29 (6H, br t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 196.7 (C, C=O), 169.6 (2 × C, O=C-O), 159.1 (C, C-OH), 144.7 (CH, olefinic-β-*C*H), 130.5 (2 × CH), 126.1 (C), 122.9 (CH, olefinic-α-*C*H), 116.1 (2 × CH), 77.1 (C, C-2), 62.8 (2 ×



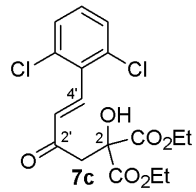
CH_2, OCH_2CH_3), 44.7 (CH_2), 13.9 (2 × CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 359.1115 (M + Na^+), calcd for $C_{17}H_{20}O_7Na^+$ 359.1107; LRMS: *m/z* 337.10 (M + 1), calcd for $C_{17}H_{20}O_7$ 336.1209.

6-(2,6-Dichlorophenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6c).



Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2984, 2926, 1699 (C=O, O-C=O), 1558, 1458, 858, 771, 636 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-7.30 (3H, m, Ph-*H*), 5.78 (1H, dd, *J* = 12.0, 4.0 Hz, C_6-H), 4.29 (4H, q, *J* = 7.2 Hz, 2 × O$CH_2$$CH_3$), 3.33 (1H, dd, *J* = 15.6, 12.0 Hz), 3.17 (1H, br d, *J* = 16.4 Hz), 2.89 (1H, d, *J* = 15.2 Hz), 2.50 (1H, ddd, *J* = 15.6, 10.0, 2.0 Hz), 1.29 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 201.6 (C, C=O), 169.4 (C, O=C-O), 166.5 (C, O=C-O), 135.2 (C, C-Cl), 135.1 (C, C-Cl), 132.7 (C, C-7), 130.1 (2 × CH, Ph-*CH*), 128.8 (CH, Ph-*CH*), 82.3 (C, C-2), 72.4 (CH, C-6), 62.8 (CH_2), 62.6 (CH_2) [2 × OCH_2CH_3]; 44.3 (CH_2), 42.4 (CH_2), 14.0 (CH_3, OCH_2CH_3), 13.9 (CH_3, OCH_2CH_3); LRMS: *m/z* 389.10 (M + 1), calcd for $C_{17}H_{18}Cl_2O_6$ 388.0480; HRMS (ESI-TOF): *m/z* 411.0389 (M + Na^+), calcd for $C_{17}H_{18}Cl_2O_6Na^+$ 411.0378.

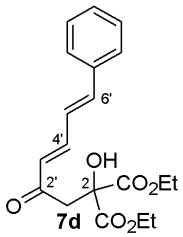
2-[4-(2,6-Dichlorophenyl)-2-oxobut-3-enyl]-2-hydroxymalonic acid diethyl ester (7c).



Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3503 (O-H), 2984, 2926, 1699 (C=O, O-C=O), 1558, 1458, 858, 771, 636 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (1H, d, *J* = 16.4 Hz, olefinic-β-*H*), 7.22-7.17 (3H, m, Ph-*H*), 6.87 (1H, d, *J* = 16.4 Hz, olefinic-α-*H*), 4.30 (4H, q, *J* = 7.2 Hz, 2 × O$CH_2$$CH_3$), 3.56 (2H, s, CH_2), 1.29 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 195.8 (C, C=O), 167.6 (2 × C, O=C-O), 137.2 (CH, olefinic-β-CH), 133.4 (CH, olefinic-α-CH), 131.6 (2 × C), 129.6 (2 × CH), 127.8 (CH), 77.2 (C, C-OH), 62.8 (2 × CH_2, OCH_2CH_3), 45.5 (CH_2), 13.9 (2 × CH_3, OCH_2CH_3); LRMS: *m/z* 389.10 (M + 1), calcd for $C_{17}H_{18}Cl_2O_6$ 388.0480; HRMS (ESI-TOF): *m/z* 411.0389 (M + Na^+), calcd for $C_{17}H_{18}Cl_2O_6Na^+$ 411.0378.

4-Oxo-6-styryltetrahydropyran-2,2-dicarboxylic acid diethyl ester (6d). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2982, 1742 (C=O, O-C=O), 1618 (C=C), 1450, 1365, 1282, 1232, 1014, 858, 750, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40-7.26 (5H, m, Ph-*H*), 6.65 (1H, d, *J* = 16.0 Hz), 6.29 (1H, dd, *J* = 16.0, 6.4 Hz), 4.57 (1H, dd, *J* = 14.4, 6.4 Hz, C_6-H), 4.30 (4H, q, *J* = 7.2 Hz, 2 × O$CH_2$$CH_3$), 3.12 (1H, d, *J* = 15.6 Hz), 2.77 (1H, d, *J* = 15.6 Hz), 2.57 (2H, br d, *J* = 8.0 Hz), 1.30 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.0 (C, C=O), 167.5 (C, O=C-O), 167.0 (C, O=C-O), 135.7 (C), 132.8 (CH), 128.6 (2 × CH, Ph-*CH*), 128.2 (CH), 126.8 (CH), 126.7 (2 × CH, Ph-*CH*), 82.0 (C, C-2), 74.7 (CH, C-6), 62.7 (2 × CH_2, OCH_2CH_3), 46.2 (CH_2), 44.3 (CH_2), 13.9 (2 × CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 369.1328 (M + Na^+), calcd for $C_{19}H_{22}O_6Na^+$ 369.1314.

2-Hydroxy-2-(2-oxo-6-phenylhexa-3,5-dienyl)malonic acid diethyl ester (7d). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3474 (O-H), 2982, 1742 (C=O, O-C=O), 1660 (O=C-C=C), 1618 (C=C), 1450, 1365, 1282, 1232, 1014, 858, 750, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, d, *J* = 6.8 Hz, Ph-*H*), 7.41-7.32 (4H, m, Ph-*H*, olefinic-*H*), 6.99



(1H, d, *J* = 15.2 Hz, $C_{6'}$-*H*), 6.88 (1H, dd, *J* = 15.6, 10.8 Hz, olefinic-*H*), 6.27 (1H, d, *J* = 15.6 Hz , olefinic-*H*)**,** 4.29 (4H, q, *J* = 7.2 Hz, 2 × OCH_2CH_3), 3.47 (2H, s, CH_2), 1.29 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 196.2 (C, C=O), 169.5 (2 × C, O=C-O), 144.1 (CH, C-6′), 142.3 (CH, C-5′), 135.7 (C, C-7′), 129.3 (CH, C-4′), 128.9 (CH, C-3′), 128.8 (2 × CH, Ph-*CH*), 127.3 (2 × CH, Ph-*CH*)**,** 126.2 (CH, Ph-*CH*), 76.8 (C, *C*-OH), 62.6 (2 × CH_2, OCH_2CH_3), 44.7 (CH_2), 13.8 (2 × CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 369.1328 (M + Na^+), calcd for $C_{19}H_{22}O_6Na^+$ 369.1314.

4-Oxo-6-propenyltetrahydropyran-2,2-dicarboxylic acid diethyl ester (6e). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2984, 2932, 1744 (C=O, O-C=O), 1634 (C=C), 1595, 1447, 1369, 1287, 1233, 1136, 1097, 1020, 860, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.82-5.75 (1H, m), 5.60 (1H, br dd, *J* = 15.6, 6.8 Hz) [olefinic-*H*]; 4.53-4.40 (1H, m, C_6-*H*), 4.31 (4H, m, 2 × OCH_2CH_3), 3.08 (1H, d, *J* = 15.2 Hz), 2.69 (1H, d, *J* = 15.2 Hz), 2.45 (2H, d, *J* = 7.2 Hz), 1.72 (3H, d, *J* = 6.4 Hz, CH=CHC*H*$_3$), 1.30 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.4 (C, C=O), 168.3 (2 × C, O=C-O), 130.2 (CH), 129.1 (CH) [C*H*=C*H*CH_3]; 90.0 (C, C-2), 74.8 (CH, C-6), 62.6 (2 × CH_2, OCH_2CH_3), 46.2 (CH_2), 44.1 (CH_2), 17.7 (CH_3, CH=CH*C*H_3), 13.84 (2 × CH_3, OCH_2CH_3); LRMS: *m/z* 285.10 (M + 1), calcd for $C_{14}H_{20}O_6$ 284.1260.

2-Hydroxy-2-(2-oxohepta-3,5-dienyl)malonic acid diethyl ester (7e). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3460 (O-H), 2984, 2932, 1744 (C=O, O-C=O), 1634 (C=C), 1595, 1447, 1369, 1287, 1233, 1136, 1097, 1020, 860, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, dd, *J* = 15.2, 9.2 Hz), 6.22 (2H, m), 6.05 (1H, d, *J* = 15.6 Hz, olefinic-H), 4.31 (4H, m, 2 × OCH_2CH_3), 3.41 (2H, s, CH_2), 1.88 (3H, d, *J* = 6.4 Hz, CH=CHC*H*$_3$), 1.31 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 196.7 (C, C=O), 169.5 (2 × C, O=C-O), 144.6 (CH), 141.7 (CH), 130.1 (CH), 127.1 (CH), 76.9 (C, *C*-OH), 63.4 (2 × CH_2, OCH_2CH_3), 44.5 (CH_2), 18.8 (CH_3, CH=CH*C*H_3), 13.9 (2 × CH_3, OCH_2CH_3); LRMS: *m/z* 285.10 (M + 1), calcd for $C_{14}H_{20}O_6$ 284.1260.

6-Methyl-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6f). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2982, 2936, 1744 (C=O, O-C=O), 1628, 1449, 1385, 1277, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.33-4.26 (4H, br q, *J* = 6.8 Hz, 2 × OCH_2CH_3), 3.99 (1H, m, C_6-H), 3.06 (1H, d, *J* = 16 Hz), 2.64 (1H, d, *J* = 15.2 Hz), 2.43 (1H, br d, *J* = 15.6 Hz), 2.32 (1H, dd, *J* = 15.2, 11.6 Hz), 1.42 (3H, d, *J* = 6 Hz, C_6-C*H*$_3$), 1.30-1.27 (6H, br t, *J* = 6.8 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.5 (C, C=O), 167.5 (C, O-C=O), 167.0 (C, O-C=O), 82.0 (C, C-2), 70.3 (CH, C-6), 62.4 (CH_2, OCH_2CH_3), 62.3 (CH_2, OCH_2CH_3), 47.6 (CH_2), 43.9 (CH_2), 21.7 (CH_3), 13.8 (CH_3, OCH_2CH_3), 13.9 (CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 281.0988 (M + Na^+), calcd for $C_{12}H_{18}O_6Na^+$ 281.1001.

4-Oxo-6-propyltetrahydropyran-2,2-dicarboxylic acid diethyl ester (6g). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2963, 2880, 1746 (C=O, O-C=O), 1632, 1468, 1223, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.32-4.23 (4H, m, 2 × OCH_2CH_3), 3.80 (1H, m, C_6-H), 3.08 (1H, d, *J* = 15.6 Hz), 2.63 (1H, d, *J* = 15.2 Hz), 2.41 (1H, br d, *J* = 16

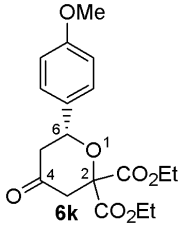
Hz), 2.31 (1H, dd, *J* = 15.2, 11.2 Hz), 1.79 (1H, dd, *J* = 18, 9.2 Hz), 1.60-1.38 (3H, m), 1.28 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3), 0.94 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.5 (C, C=O), 167.5 (C, O-C=O), 167.0 (C, O-C=O), 81.4 (C, C-2), 73.5 (CH, C-6), 62.15 (CH_2, OCH_2CH_3), 62.13 (CH_2, OCH_2CH_3), 46.1 (CH_2), 44.0 (CH_2), 37.7 (CH_2), 18.0 (CH_2), 13.73 (CH_3), 13.70 (CH_3, OCH_2CH_3), 13.4 (CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 309.1319 (M + Na^+), calcd for $C_{14}H_{22}O_6Na^+$ 309.1314; LCMS: *m/z* 287.35 (M + 1), calcd for $C_{14}H_{22}O_6$ 286.1416.

6-Butyl-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6h). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2959, 1745 (C=O, O-C=O), 1628, 1468, 1369, 1215, 1120, 1068, 854, 783, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.26 (4H, m, 2 × OCH_2CH_3), 3.79 (1H, m, C_6-H), 3.08 (1H, d, *J* = 15.6 Hz), 2.64 (1H, d, *J* = 15.2 Hz), 2.42 (1H, br d, *J* = 14 Hz), 2.31 (1H, dd, *J* = 15.2, 11.6 Hz), 1.80 (1H, m), 1.60-1.40 (2H, m), 1.39-1.31 (3H, m), 1.28 (6H, br t, *J* = 6.8 Hz, 2 × OCH_2CH_3), 0.91 (3H, t, *J* = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.9 (C, C=O), 167.7 (C, O-C=O), 167.2 (C, O-C=O), 82.1 (C, C-2), 74.1 (CH, C-6), 62.40 (CH_2, OCH_2CH_3), 62.39 (CH_2, OCH_2CH_3), 46.3 (CH_2), 44.3 (CH_2), 35.6 (CH_2), 27.1 (CH_2), 22.3 (CH_2), 13.97 (CH_3), 13.92 (CH_3, OCH_2CH_3), 13.90 (CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 323.1481 (M + Na^+), calcd for $C_{15}H_{24}O_6Na^+$ 323.1471; LCMS: *m/z* 301.40 (M + 1), calcd for $C_{15}H_{24}O_6$ 300.1573.

4-Oxo-6-pentyltetrahydropyran-2,2-dicarboxylic acid diethyl ester (6i). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2957, 1744 (C=O, O-C=O), 1624, 1466, 1369, 1279, 1213, 1067, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.29-4.26 (4H, br q, *J* = 6.8 Hz, 2 × OCH_2CH_3), 3.80-3.78 (1H, m, C_6-*H*), 3.08 (1H, d, *J* = 15.6 Hz), 2.63 (1H, d, *J* = 15.6 Hz), 2.42 (1H, br d, *J* = 14 Hz), 2.30 (1H, dd, *J* = 15.2, 11.2 Hz), 1.78 (1H, m), 1.60-1.49 (2H, m), 1.30-1.27 (11H, m), 0.89 (3H, t, *J* = 6.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.9 (C, C=O), 167.7 (C, O-C=O), 167.2 (C, O-C=O), 82.0 (C, C-2), 74.0 (CH, C-6), 62.4 (CH_2, OCH_2CH_3), 62.3 (CH_2, OCH_2CH_3), 46.3 (CH_2), 44.3 (CH_2), 35.8 (CH_2), 31.4 (CH_2), 24.6 (CH_2), 22.4 (CH_2), 13.94 (CH_3), 13.93 (CH_3, OCH_2CH_3), 13.89 (CH_3, OCH_2CH_3); HRMS (ESI-TOF): *m/z* 337.1625 (M + Na^+), calcd for $C_{16}H_{26}O_6Na^+$ 337.1627.

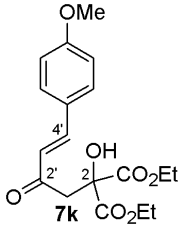
6,6-Dimethyl-4-oxo-tetrahydropyran-2,2-dicarboxylic acid diethyl ester (6j). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2982, 1742 (C=O, O-C=O), 1622, 1467, 1369, 1215, 1066, 945, 860, 791 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.26-4.20 (4H, br q, *J* = 7.2 Hz, 2 × OCH_2CH_3), 2.94 (2H, s), 2.46 (2H, s), 1.34 (6H, br s, 2 × CH_3), 1.25 (6H, br t, *J* = 6.8 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 203.4 (C, C=O), 168.9 (2 × C, O-C=O), 80.2 (C, C-2), 77.3 (C, C-6), 62.4 (2 × CH_2, OCH_2CH_3), 50.9 (CH_2), 42.3 (CH_2), 29.3 (2 × CH_3, C_6-CH_3), 13.8 (2 × CH_3, 2 × OCH_2CH_3); HRMS (ESI-TOF): *m/z* 295.1153 (M + Na^+), calcd for $C_{13}H_{20}O_6Na^+$ 295.1158.

6-(4-Methoxyphenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6k).



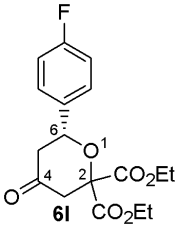
Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2986, 1747 (C=O, O-C=O), 1601, 1514, 1468, 1371, 1246, 1028, 858, 833, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 8.4 Hz) [Ph-*H*]; 4.90 (1H, dd, *J* = 10.4, 4.4 Hz, C_6-H), 4.35-4.27 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.81 (3H, s, OC*H*$_3$), 3.17 (1H, d, *J* = 16.0 Hz), 2.84 (1H, d, *J* = 16.0 Hz), 2.68 (2H, m), 1.32 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 202.6 (C, C=O), 167.7 (C, O=C-O), 167.1 (C, O=C-O), 159.7 (C, *C*-OMe), 130.0 (C), 127.4 (2 × CH, Ph-*C*H), 114.4 (2 × CH, Ph-*C*H), 82.1 (C, C-2), 75.3 (CH, C-6), 63.4 (CH$_2$, O*C*H$_2$CH$_3$), 63.3 (CH$_2$, O*C*H$_2$CH$_3$), 55.4 (CH$_3$, O*C*H$_3$), 47.7 (CH$_2$), 44.8 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: *m/z* 351.15 (M + 1), calcd for $C_{18}H_{22}O_7$ 351.3631.

2-Hydroxy-2-[4-(4-methoxyphenyl)-2-oxobut-3-enyl]malonic acid diethyl ester (7k).



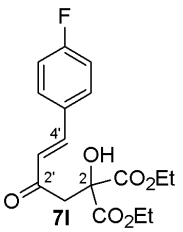
Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3464 (O-H), 2986, 1747 (C=O, O-C=O), 1601, 1514, 1468, 1371, 1246, 1028, 858, 833, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 16.0 Hz, olefinic-β-H), 7.50 (2H, d, *J* = 8.8 Hz), 6.92 (2H, d, *J* = 8.8 Hz) [Ph-*H*]; 6.61 (1H, d, *J* = 15.6 Hz, olefinic-α-H), 4.38-4.26 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.85 (3H, s, OCH$_3$), 3.51 (2H, s, CH$_2$), 1.30 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 196.3 (C, C=O), 169.6 (2 × C, O=C-O), 161.9 (C, *C*-OCH$_3$), 144.0 (CH, olefinic-β-CH), 130.2 (2 × CH, Ph-*C*H), 126.7 (C), 123.5 (CH, olefinic-α-*C*H), 114.4 (2 × CH, Ph-*C*H), 62.6 (2 × CH$_2$, O*C*H$_2$CH$_3$), 55.4 (CH$_3$, O*C*H$_3$), 44.8 (CH$_2$), 13.9 (2 × CH$_3$, OCH$_2$*C*H$_3$); LRMS: *m/z* 351.15 (M + 1), calcd for $C_{18}H_{22}O_7$ 351.3631.

6-(4-Fluorophenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6l).



Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2926, 1747 (C=O, O-C=O), 1603 (C=C), 1508, 1364, 1190, 1082, 849, 779, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42-7.39 (2H, dd, *J* = 8.4, 5.2 Hz), 7.07 (2H, t, *J* = 8.8 Hz) [Ph-*H*]; 4.95 (1H, dd, *J* = 9.6, 4.8 Hz, C_6-H), 4.31-4.28 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.18 (1H, d, *J* = 15.2 Hz), 2.85 (1H, d, *J* = 15.2 Hz), 2.66-2.63 (2H, m), 1.29 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 201.9 (C, C=O), 169.5 (C, O=C-O), 166.9 (C, O=C-O), 162.6 (C, d, *J* = 245.6 Hz, *C*-F), 135.2 (C, d, *J* = 3.0 Hz, C-7), 127.7 (2 × CH, d, *J* = 8.2 Hz), 115.5 (2 × CH, d, *J* = 21.5 Hz), 82.1 (C, C-2), 74.9 (CH, C-6), 62.65 (CH$_2$, O*C*H$_2$CH$_3$), 62.60 (CH$_2$, O*C*H$_2$CH$_3$), 47.8 (CH$_2$), 44.1 (CH$_2$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS: *m/z* 339.20 (M + 1), calcd for $C_{17}H_{19}FO_6$ 338.1166.

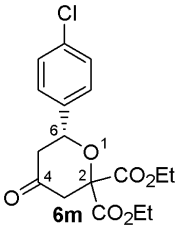
2-[4-(4-Fluorophenyl)-2-oxobut-3-enyl]-2-hydroxymalonic acid diethyl ester (7l).



Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3482 (O-H), 2926, 1747 (C=O, O-C=O), 1603 (C=C), 1508, 1364, 1190, 1082, 849, 779, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 16.4 Hz), 7.53 (2H, m), 7.09 (2H, t, *J* = 8.8 Hz), 6.66 (1H, d, *J* = 16.4 Hz), 4.29 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.52 (2H, s, C*H*$_2$), 1.30 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 195.9 (C, C=O), 167.5 (2 × C, O=C-O), 163.0 (C, d, *J* = 245.0 Hz, *C*-F), 142.6 (CH), 136.0 (C), 130.3 (2 × CH, d, *J* = 8.7

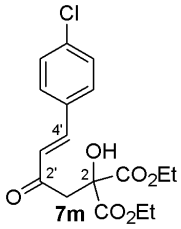
Hz, Ph-*C*H), 125.4 (CH), 116.1 (2 × CH, d, *J* = 21.8 Hz, Ph-*C*H), 76.8 (C, C-OH), 45.0 (CH_2), 13.8 (2 × CH_3, OCH_2CH_3); LRMS: *m/z* 339.20 (M + 1), calcd for $C_{17}H_{19}FO_6$ 338.1166.

6-(4-Chlorophenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6m).



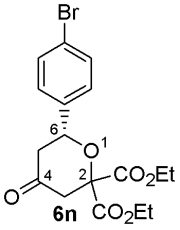
Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2986, 1742 (C=O, O-C=O), 1493, 1369, 1231, 1088, 1014, 812, 737, 652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, d, *J* = 8.0 Hz), 7.37 (2H, d, *J* = 8.0 Hz) [Ph–*H*]; 4.95 (1H, dd, *J* = 10.8, 3.2 Hz, C_6-H), 4.28 (4H, m, 2 × OCH_2CH_3), 3.18 (1H, d, *J* = 15.6 Hz), 2.85 (1H, d, *J* = 15.6 Hz), 2.69-2.56 (2H, m), 1.29 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 201.7 (C, C=O), 167.4 (C, O=C-O), 166.8 (C, O=C-O), 137.8 (C), 132.5 (C), 129.2 (2 × CH, Ph-*C*H), 127.2 (2 × CH, Ph-*C*H), 82.1 (C, C-2), 74.8 (CH, C-6), 62.65 (CH_2, OCH_2CH_3), 62.62 (CH_2, OCH_2CH_3), 45.1 (CH_2), 44.1 (CH_2), 13.9 (CH_3, OCH_2CH_3), 13.8 (CH_3, OCH_2CH_3); LRMS: *m/z* 355.15 (M + 1), calcd for $C_{17}H_{19}ClO_6$ 354.0870.

2-[4-(4-Chlorophenyl)-2-oxobut-3-enyl]-2-hydroxymalonic acid diethyl ester (7m).



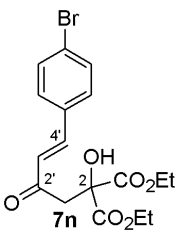
Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3497 (O-H), 2986, 1742 (C=O, O-C=O), 1665 (C=C-C=O), 1613 (C=C), 1493, 1369, 1231, 1088, 1014, 812, 737, 652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (1H, d, *J* = 15.6 Hz, olefinic-H), 7.36 (4H, br s, Ph-*H*), 6.70 (1H, d, *J* = 15.6 Hz, olefinic-*H*), 4.29 (4H, m, 2 × OCH_2CH_3), 3.52 (2H, s, CH_2), 1.30 (6H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 195.9 (C, C=O), 169.4 (2 × C, O=C-O), 142.4 (CH, olefinic-CH), 136.7 (C), 134.2 (C), 129.5 (2 × CH, Ph-*C*H), 128.8 (2 × CH, Ph-*C*H), 126.1 (CH, olefinic-CH), 76.7 (C, *C*-OH), 62.6 (2 × CH_2, OCH_2CH_3), 47.6 (CH_2), 13.8 (2 × CH_3, OCH_2CH_3); LRMS: *m/z* 355.15 (M + 1), calcd for $C_{17}H_{19}ClO_6$ 354.0870.

6-(4-Bromophenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6n).



Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2980, 1740 (C=O, O-C=O), 1653, 1582, 1489, 1286, 1232, 1072, 1009, 810, 640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (2H, d, *J* = 8.4 Hz), 7.30 (2H, d, *J* = 8.4 Hz) [Ph-*H*]; 4.94 (1H, dd, *J* = 10.8, 5.2 Hz, C_6-H), 4.32-4.27 (4H, m, 2 × OCH_2CH_3), 3.17 (1H, d, *J* = 16.0 Hz), 2.85 (1H, d, *J* = 15.6 Hz), 2.69-2.57 (2H, m), 1.32-1.26 (6H, m, 2 × OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT) δ 201.7 (C, C=O), 167.4 (C, O=C-O), 166.8 (C, O=C-O), 138.4 (C, C-Br), 131.8 (2 × CH, Ph-*C*H), 127.6 (2 × CH, Ph-*C*H), 122.3 (C), 82.1 (C, C-2), 74.8 (CH, C-6), 62.7 (2 × CH_2, OCH_2CH_3), 47.6 (CH_2), 44.1 (CH_2), 13.94 (CH_3, OCH_2CH_3), 13.90 (CH_3, OCH_2CH_3); LRMS: *m/z* 421.05 (M + Na^+), calcd for $C_{17}H_{19}BrO_6Na^+$ 421.0262.

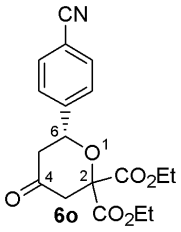
2-[4-(4-Bromophenyl)-2-oxobut-3-enyl]-2-hydroxymalonic acid diethyl ester (7n).



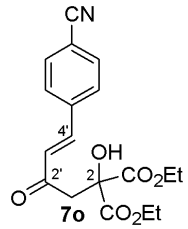
Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3420 (O-H), 2980, 1740 (C=O, O-C=O), 1653, 1582, 1489, 1286, 1232, 1072, 1009, 810, 640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (1H, d, *J* = 16.0 Hz, olefinic-β-H), 7.53 (2H, d, *J* = 8.4 Hz), 7.41 (2H, t, *J* = 8.0 Hz), 6.71 (1H, d, *J* = 16.0 Hz, olefinic-α-H), 4.32- 4.27 (4H, m, 2 × OCH_2CH_3), 3.52 (2H, s, CH_2), 1.32-1.26 (6H, m, 2 × OCH_2CH_3); ^{13}C NMR

($CDCl_3$, DEPT) δ 195.9 (C, C=O), 169.4 (2 × C, O=C-O), 142.6 (CH, olefinic-CH), 132.9 (C, C-Br), 132.2 (2 × CH, Ph-*C*H), 129.7 (2 × CH, Ph-*C*H), 126.2 (CH, olefinic-CH), 125.1 (C), 76.7 (C, C-OH), 62.6 (2 × CH_2, O*C*H_2CH$_3$), 45.1 (CH_2), 13.89 (2 × CH_3, OCH$_2$*C*H_3); LRMS: *m/z* 421.05 ($M + Na^+$), calcd for $C_{17}H_{19}BrO_6Na^+$ 421.0262.

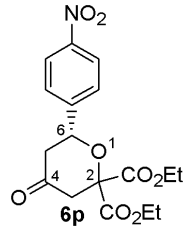
6-(4-Cyanophenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6o). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2984, 2229 (C≡N), 1740 (C=O, O-C=O), 1612, 1506, 1468, 1369, 1283, 1227, 1072, 1018, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (2H, d, *J* = 7.6 Hz), 7.54 (2H, d, *J* = 7.6 Hz) [Ph-*H*]; 5.04 (1H, br d, *J* = 11.6 Hz, C_6-H), 4.30 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.17 (1H, d, *J* = 15.6 Hz), 2.86 (1H, d, *J* = 15.6 Hz), 2.70 (1H, d, *J* = 14.4 Hz), 2.56 (1H, dd, *J* = 14.4, 11.6 Hz), 1.28 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 201.1 (C, C=O), 167.2 (C, O=C-O), 166.7 (C, O=C-O), 144.5 (C, *C*-CN), 132.5 (2 × CH, Ph-*C*H), 126.4 (2 × CH, Ph-*C*H), 118.4 (C), 112.2 (C, *C*≡N), 82.1 (C, C-2), 74.5 (CH, C-6), 62.8 (2 × CH_2, O*C*H_2CH$_3$), 47.4 (CH_2), 44.1 (CH_2), 13.95 (CH_3, OCH$_2$*C*H_3), 13.92 (CH_3, OCH$_2$*C*H_3); HRMS (ESI-TOF): *m/z* 368.1118 ($M + Na^+$), calcd for $C_{18}H_{19}NO_6Na^+$ 368.1110.



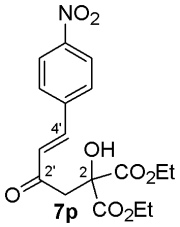
2-[4-(4-Cyanophenyl)-2-oxobut-3-enyl]-2-hydroxymalonic acid diethyl ester (7o). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3458 (O-H), 2984, 2229 (C≡N), 1740 (C=O, O-C=O), 1612, 1506, 1468, 1369, 1283, 1227, 1072, 1018, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69-7.53 (5H, m, Ph-*H*, olefinic-β-H), 6.78 (1H, d, *J* = 16.0 Hz, olefinic-α-H), 4.39-4.22 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.52 (2H, s, CH_2), 1.28 (6H, t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 195.5 (C, C=O), 169.4 (2 × C, O=C-O), 141.2 (CH, olefinic-β-CH), 138.4 (C), 132.6 (2 × CH, Ph-*C*H), 128.7 (2 × CH, Ph-*C*H), 128.5 (CH, olefinic-α-CH), 118.2 (C), 113.8 (C, *C*N), 76.7 (C, *C*-OH), 62.8 (2 × CH_2, O*C*H_2CH$_3$), 45.4 (CH_2), 13.9 (2 × CH_3, OCH$_2$*C*H$_3$); HRMS (ESI-TOF): *m/z* 368.1118 ($M + Na^+$), calcd for $C_{18}H_{19}NO_6Na^+$ 368.1110.



6-(4-Nitrophenyl)-4-oxotetrahydropyran-2,2-dicarboxylic acid diethyl ester (6p). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2938, 1742 (C=O, O-C=O), 1603, 1524, 1468, 1348, 1290, 1227, 1165, 1072, 1014, 856, 748, 698, 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (2H, d, *J* = 8.4 Hz), 7.62 (2H, d, *J* = 8.4 Hz) [Ph-*H*]; 5.13 (1H, br d, *J* = 11.6 Hz, C_6-H), 4.34-4.26 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.20 (1H, d, *J* = 15.6 Hz), 2.90 (1H, d, *J* = 15.6 Hz), 2.75 (1H, br d, *J* = 15.6 Hz), 2.59 (1H, br t, *J* = 15.6 Hz), 1.31 (6H, br t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT) δ 200.9 (C, C=O), 169.4 (C, O=C-O), 167.2 (C, O=C-O), 147.7 (C), 146.3 (C), 126.6 (2 × CH, Ph-*C*H), 123.9 (2 × CH, Ph-*C*H), 82.1 (C, C-2), 74.3 (CH, C-6), 62.8 (2 × CH_2, O*C*H_2CH$_3$), 47.5 (CH_2), 44.1 (CH_2), 13.93 (CH_3, OCH$_2$*C*H_3), 13.91 (CH_3, OCH$_2$*C*H_3); LRMS: *m/z* 388.25 ($M + Na^+$), calcd for $C_{17}H_{19}NO_8Na^+$ 388.1008.



2-Hydroxy-2-[4-(4-nitrophenyl)-2-oxobut-3-enyl]malonic acid diethyl ester (7p). Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3651 (O-H), 3078, 2984, 2938, 1742 (C=O, O-C=O), 1603, 1524, 1468, 1348, 1290, 1227, 1165, 1072, 1014, 856, 748, 698, 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (2H, d, *J* = 8.4 Hz), 7.72 (2H,



d, *J* = 8.8 Hz) [Ph-*H*]; 7.61 (1H, d, *J* = 16.4 Hz, olefinic-β-H), 6.84 (1H, d, *J* = 16.4 Hz, olefinic-α-H), 4.34-4.26 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.56 (2H, s, CH$_2$), 1.30 (6H, br t, *J* = 7.2 Hz, 2 × OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT) δ 195.5 (C, C=O), 166.6 (2 × C, O=C-O), 148.7 (C), 140.7 (CH, olefinic-β-CH), 140.2 (C), 129.1 (CH, olefinic-α-CH), 128.9 (2 × CH, Ph-CH), 124.1 (2 × CH, Ph-CH), 76.6 (C, C-OH), 62.8 (2 × CH$_2$, OC*H*$_2$CH$_3$), 45.4 (CH$_2$), 13.91 (2 × CH$_3$, OCH$_2$C*H*$_3$); LRMS: ***m/z*** 388.25 (M + Na$^+$), calcd for C$_{17}$H$_{19}$NO$_8$Na$^+$ 388.1008.

Acknowledgments

We thank DST, New Delhi (DBR and RM) and UGC Networking Resource Centre (DBR and SJ) for support of this project. RM thanks CSIR (New Delhi) for her research fellowship.

Supporting information available

Experimental procedures, compound characterization, and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. This material is available on the WWW at http://www.arkat-usa.org/get-file/54850/ or from the author.

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