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Microwave-assisted tandem Wittig–intramolecular Diels–Alder cycloaddition. Product distribution and stereochemical assignment

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Abstract—The IMDA cycloadditions of 10 different ester-tethered 1,3,8-nonatrienes have been examined under controlled microwave heating (MeCN, 180 °C, 30 min), giving 90–99% yields, and the stereochemical outcome of the *exo* and *endo* adducts established together with X-ray crystal structural analysis. A microwave-assisted tandem Wittig–IMDA cycloaddition protocol has been established for a modular synthesis of the bicyclic lactones starting from α-bromoacetates of 2,4-pentadien-1-ols and α-oxo carbonyl compounds in the presence of PPh_3 and 2,6-lutidine (MeCN, 180 °C, 30 min). The overall yields of the tandem reactions are 68–80% and the stereoselectivity of the major adducts formed from *E*-substituted 1,3,8-nonatriene is the same as that observed for the purified 1,3,8-nonatrienes.

1. Introduction

The Diels–Alder cycloaddition remains the most powerful and efficient synthetic tool for accessing highly functionalized carbocycles, possibly generating up to four continuous stereogenic centers in one operation.[1] In particular, the intramolecular Diels–Alder (IMDA) cycloaddition has been extensively used for assembly of complex molecular architectures of designed or natural products origin.[2] Biosynthetic pathways incorporating IMDA reactions have been recognized and examples of biomimetic total synthesis of natural products by using a key IMDA cycloaddition are known.[2i] A good understanding on stereocontrol is fundamental to application of IMDA reactions in organic synthesis. A number of theoretical[3,4b–e,5e–h,j,7d] and experimental[4–8] studies have addressed the stereoselectivity of IMDA cycloadditions of the ester-tethered 1,3,8-nonatrienes[9] (Chart 1). The type **I** substrates have been extensively studied for formation of bicyclic lactones **A**. The acrylates **Ia**[4] undergo IMDA reactions at 132–250 °C while the doubly activated *E*- and *Z*-substituted 1,3,8-nonatrienes **Ib**,**c** cyclize, respectively, in PhMe (100–130 °C for **Ib**)[5,6] and in refluxing PhMe or xylene (110–140 °C for **Ic**).[7] As similar to the reactivity of **Ia**, the substrates **II**[8] afford the IMDA adducts **B** at temperatures of 135–250 °C depending on the nature of substituents R^1 and R^2. Synthetically useful stereoselectivity has been achieved for the lactones **A** by using a stereogenic substituent R^1 or R^4 at the position C1 or C5,[4a,b,5a–d,f,g,j,k,6p] a cooperative effect[4d–h] of two substituents R^3 and R^4 at the positions C3 and C5, and an internal hydrogen bonding interaction[5h] with CH_2OH (=R^2) at the position C2. We report here our original results on the IMDA cycloadditions of the type **Ib** substrates under controlled microwave heating.[10]

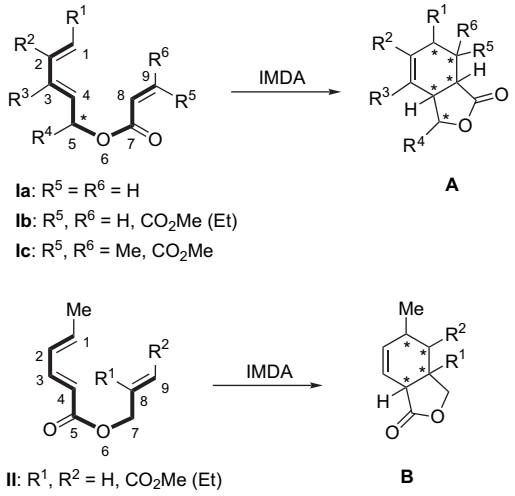

Chart 1. Ester-tethered 1,3,8-nonatrienes **I** and **II** and the IMDA adducts **A** and **B**.

Keywords: Wittig; IMDA; Microwave; Lactones; Tandem reactions.
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We also disclose results on the tandem Wittig–IMDA reactions for a modular synthesis of the bicyclic lactones **C** by using α-bromoacetates **III** and α-oxo carbonyl compounds **IV** as the building blocks (Chart 2).

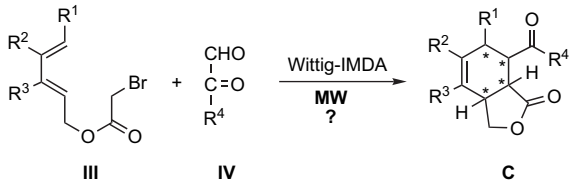
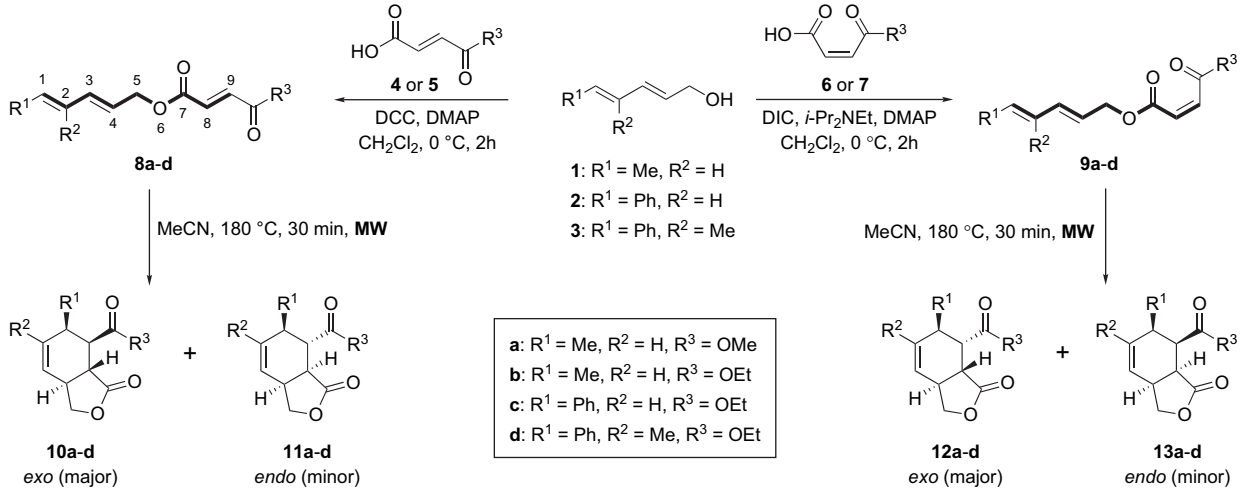


Chart 2. Proposed tandem Wittig–IMDA reactions of **III** under controlled microwave heating.

2. Results and discussion

2.1. Microwave-assisted IMDA cycloadditions of ester-tethered 1,3,8-nonatrienes

As reported by Arseniyadis et al.[5b] and Paddon-Row et al.,[5e,j] the terminally activated *E*-isomers of 1,3,8-nonatrienes **8a**,**b** underwent the IMDA reactions in PhMe at 100–110 °C for 23–24 h to provide the bicyclic lactones *exo*-**10a**,**b** and *endo*-**11a**,**b** in 78–85% combined yields and with *exo*:*endo* ratios of 60:40–65:35 (Scheme 1; Table 1, entries 2 and 5). The *Z*-substituted 1,3,8-nonatrienes **9a** showed a higher reactivity toward cycloaddition (110 °C, 2 h) and gave the bicyclic lactones *exo*-**12a** and *endo*-**13a** in 79% combined yield and with an *exo*:*endo* ratio of 79:21 (Table 1, entry 12).[5e,j] In connection with our interest in applying controlled microwave heating in closed reaction vials to solution[11] and solid-phase[12] organic synthesis, we assumed that the IMDA cycloadditions of the ester-linked 1,3,8-nonatrienes could be facilitated at higher temperatures, which are applicable on a technical microwave reactor with temperature and pressure regulation capability. The specific question we need to address centers on whether stereocontrol in the microwave-assisted IMDA reactions decreases due to a temperature effect.[13] As illustrated in Schemes 1 and 2, we prepared 10 different *E*- and *Z*-substituted 1,3,8-nonatrienes **8a–e** and **9a–e** and the yields are listed in Table 1. Condensation of **1–3** with fumaric acid monomethyl ester **4** or monoethyl ester **5**[14] in the presence of DCC–DMAP at 0 °C for 2 h afforded the *E*-substituted **8a–d** in 85–90% yields. It was found that the combination of DIC–*i*-Pr_2NEt–DMAP[15] was more suitable for the formation of the *Z*-substituted trienes **9a–d**, which were obtained in 65–71% yields from **1–3** and maleic acid monomethyl ester **6** or monoethyl ester **7**.[16] The ketoesters **8e** and **9e** were prepared by a modified Wittig olefination procedure by using MeOH as the solvent[17] in order to get much more amount of the *Z*-isomer **9e**. The α-bromoacetate **14** was treated with PPh_3 in MeCN at room temperature for overnight to give quantitatively the phosphonium salt **20**, which reacts with phenylglyoxal monohydrate in the presence of Et_3N in MeOH (0 °C, 30 min), giving **8e** and **9e** in 37 and 18% yields. We used MeCN as the solvent for the microwave-assisted IMDA reactions[18] due to its better microwave energy absorption property than PhMe[10b] and easy workup with its low boiling point. Moreover, it is advantageous to use MeCN in IMDA cycloadditions of the ester-linked substrates because a polar solvent effect was known, resulting in a significant rate acceleration.[13c–e] After heating a MeCN solution of **8a** in a closed pressurized reaction vial at 180 °C for 30 min, the adducts *exo*-**10a** and *endo*-**11a** were isolated in 91% combined yield and in a 67:33 isomer ratio (Table 1, entry 1). Similarly, *exo*-**10b** and *endo*-**11b** were isolated from the triene **8b** in 90% combined yield and in a 66:34 isomer ratio (Table 1, entry 3). For the purpose of the tandem Wittig–IMDA cycloadditions discussed below, we applied the same microwave heating conditions for the IMDA reactions of *Z*-isomers **9a**,**b** although they could cyclize at a lower temperature. The expected *exo*-**12a**,**b** and *endo*-**13a**,**b** were produced in 98% combined yield for each and in 68:32–76:24 isomer ratios (Table 1, entries 11 and 13). These results confirm two findings: (a) higher product yields with significantly shortened reaction time can be achieved by applying controlled microwave heating; and (b) the same level of stereoselectivity can be maintained for the IMDA cycloadditions in different solvents (MeCN vs PhMe) and at a higher reaction temperature (180 °C vs 100–110 °C) although an exceptional case was



Scheme 1. Synthesis and microwave-assisted IMDA of 1,3,8-nonatrienes **8a–d** and **9a–d**.

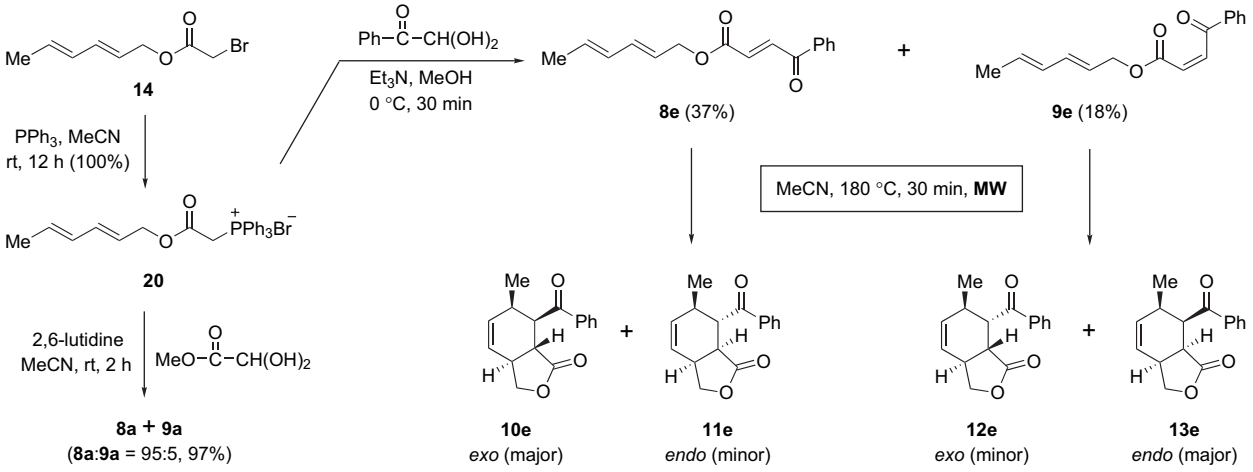
Table 1. Synthesis and IMDA of *E*- and *Z*-substituted 1,3,8-nonatrienes **8a–e** and **9a–e**[a]

Entry	Esters	Yield (%)	Solvent	Lactones	Yield (%)[b]	*exo*:*endo* Ratio[c]
1	(*E*)-**8a**	88	MeCN	**10a+11a**	91	67:33[d] (73:27)
2	(*E*)-**8a**		PhMe	**10a+11a**	85[f]	65:35[f]
3	(*E*)-**8b**	90	MeCN	**10b+11b**	90	66:34[d] (66:34)
4	(*E*)-**8b**		MeCN[h]	**10b+11b**	88	64:36[d]
5	(*E*)-**8b**		PhMe	**10b+11b**	78[g]	60:40[g]
6	(*E*)-**8c**	83	MeCN	**10c+11c**	95	76:24[d] (74:26)
7	(*E*)-**8c**		PhMe[i]	**10c+11c**	55	71:29[d]
8	(*E*)-**8d**	85	MeCN	**10d+11d**	91	68:32[d] (67:33)
9	(*E*)-**8e**	37	MeCN	**10e+11e**	99	73:27[e] (71:29)
10	(*E*)-**8e**		PhMe[i]	**10e+11e**	99	74:26[d]
11	(*Z*)-**9a**	65	MeCN	**12a+13a**	98	76:24[e] (67:33)
12	(*Z*)-**9a**		PhMe	**12a+13a**	79[f]	79:21[f]
13	(*Z*)-**9b**	69	MeCN	**12b+13b**	98	68:32[d] (NA)[j]
14	(*Z*)-**9c**	70	MeCN	**12c+13c**	97	71:29[e] (77:23)
15	(*Z*)-**9d**	71	MeCN	**12d+13d**	97	71:29[e] (NA)[j]
16	(*Z*)-**9e**	18	MeCN	**12e+13e**	99	45:55[d] (47:53)
17	(*Z*)-**9e**		MeCN[h]	**12e+13e**	ND[k]	44:56[d]
18	(*Z*)-**9e**		PhMe[i]	**12e+13e**	(100)[l]	65:35[d]

[a] Except for otherwise stated, all IMDA cycloadditions were carried out in MeCN at 180 °C for 30 min in closed pressurized vials with the reaction temperature measured by an IR sensor.
[b] Combined isolated yields.
[c] The numbers in the parentheses are taken from Table 3 for the tandem reactions.
[d] The ratio was determined by ^{1}H NMR of the product mixtures.
[e] The ratio was calculated based on the weights of the isolated products.
[f] Data taken from Ref. 5e. Compounds **8a** and **9a** were heated in PhMe at 110 °C for 23 and 2 h, respectively.
[g] Data taken from Ref. 5b. Compound **8b** was heated in PhMe at 100 °C for 24 h.
[h] 2,6-Lutidine (1.3 equiv) was added.
[i] Heated in PhMe in an oil bath at 110 °C for 80 and 1 h for **8c** and **9e**, respectively, or in a microwave reactor at 150 °C for 1 h for **8e**.
[j] Not available.
[k] Not determined.
[l] Conversion of **9e** as determined by ^{1}H NMR of the product mixture.

found for the reaction of *Z*-substituted 1,3,8-nonatriene **9e** (vide infra).

With the above encouraging results, we turned our attention to the IMDA reactions of the 1,3,8-nonatrienes **8c–e** and **9c–e**, which were not covered in a recent study by Paddon-Row and Sherburn.[5j] For comparison, the triene **8c** possessing a C1-phenyl group was subjected to cycloaddition in PhMe at 110 °C for 80 h, giving the adducts **10c** and **11c** in 55% combined yield and in a 71:29 *exo*:*endo* ratio (Table 1, entry 7). The stereoselectivity of **8c** is slightly better than the C1-methyl analog **8b** (Table 1, entry 5)[5g] although **8c** showed a diminished reactivity toward cycloaddition. For the microwave-heated cycloadditions, the paired adducts **10c–e/11c–e** and **12c,d/13c,d** were obtained in 91–99% combined yields and in 68:32–76:24 isomer ratios in favor of the *exo* isomers (Table 1, entries 6, 8, 9, 14, and 15), except for the adducts **12e** and **13e**, whose ratio is 45:55 (Table 1, entry 16). We repeated the cycloaddition of **9e** in MeCN at 180 °C for several times and obtained the same isomer ratio in all cases. It was reported that treatment of the *trans*-fused lactone **A** with a catalytic NaOMe gave the corresponding cis-fused isomer.[7b] We carried out the microwave-assisted IMDA reactions of **8b** and **9e** in the presence of 2,6-lutidine and obtained almost the same results in both cases (Table 1, entries 4 and 17). Moreover, we did not find any structural



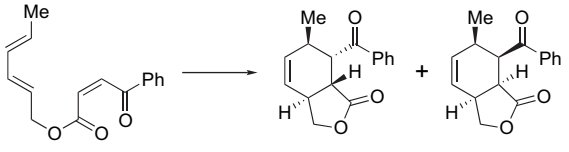
Scheme 2. Synthesis and microwave-assisted IMDA of 1,3,8-nonatrienes **8e** and **9e**.

change after heating each pure adducts **10e**, **11e**, **12e**, and **13e** at 180 °C for 30 min in MeCN in the presence of 2,6-lutidine. The results confirmed that isomerization of the adducts did not happen even in the presence of a base. When **9e** was heated in PhMe at 110 °C for 1 h, the adducts **12e** and **13e** were formed in a 65:35 ratio in favor of the *exo* isomer **12e** (Table 1, entry 18). Similarly, the IMDA reaction of the *E*-substituted **8e**, after heated in PhMe at 150 °C for 1 h under microwave irradiation, afforded a 74:26 ratio of **10e**:**11e** in 99% combined yield (Table 1, entry 10). The results indicated that the solvent-dependent stereoselectivity is unique to the (*Z*)-9-acyl-substituted 1,3,8-nonatrienes.

We decided to examine the solvent and temperature effects on the IMDA cycloaddition of the 9-benzoyl-substituted triene **9e**. The results are summarized in Table 2. The triene **9e** was the most reactive among the 10 substrates we studied and it underwent the IMDA reaction at ambient temperature (Table 2, entries 1–3). After stirring at 20 °C for 70 h, the conversion of **9e** was measured by ^{1}H NMR spectroscopy of the reaction mixtures. The reactivity of **9e** parallels with the polarity of the solvent in the order of PhMe< $CDCl_3$<MeCN and the conversions are 60, 85, and 95%, respectively. The results consist with the rate enhancement observed in polar solvents.[13c–e] Moreover, it is interesting to find that the nonpolar solvent, PhMe favored for the *exo* isomer **12e** while the polar solvent, MeCN promoted the formation of the *endo* isomer **13e**. We observed that the ratios of **12e**:**13e** increased from 56:44 to 65:35 in PhMe at 110 °C (Table 2, entry 1 vs entry 4) and from 36:64 to 45:55 in MeCN at 82 °C (Table 2, entry 3 vs entry 5). We attempted to modify the preformed adduct ratios by switching solvent or temperature without success (Table 2, entries 6 and 7). It suggests that an equilibrium through IMDA–retro-IMDA pathways does not exist.

We carefully secured the stereochemistry of **12e** with the help of X-ray crystal structural analysis. As shown in Figure 1, the compound **12e** features a trans-fused bicyclic

Table 2. Solvent effect on IMDA of **9e**



9e *exo* **-12e** *endo* **-13e**

Entry	Solvent	*T* (°C); *t* (h)	Conversion (%)[a]	**12e**:**13e**[a]
1	PhMe	20; 70	60	56:44
2	$CDCl_3$	20; 70	85	54:46
3	MeCN	20; 70	95	36:64
4	PhMe	110; 1	100[b]	65:35[b]
5	MeCN	82; 1	100	45:55
6	PhMe[c]	150; 0.5	—	45:55
7	MeCN[d]	180; 0.5	—	35:65

[a] The conversion of **9e** and the ratio of the adducts **12e**:**13e** were determined by ^{1}H NMR of the crude reaction mixture.
[b] Data taken from entry 18 of Table 1.
[c] The 45:55 adduct mixture of entry 5, instead of **9e**, was heated on the microwave reactor.
[d] The 36:64 adduct mixture of entry 3, instead of **9e**, was heated on the microwave reactor.

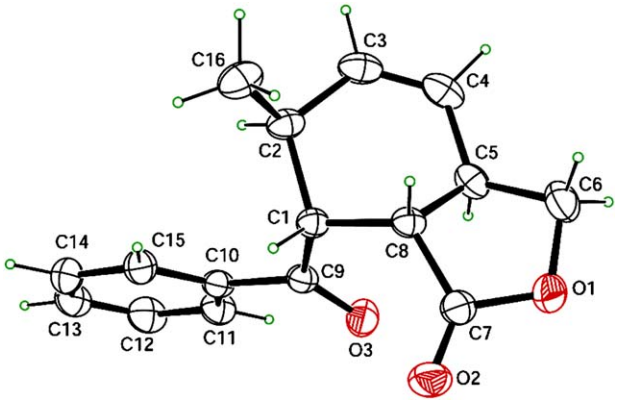


Figure 1. X-ray crystal structure of **12e** (shown as the enantiomer).

skeleton with both trans-oriented substituents sitting at the axial positions of the half-chair-like cyclohexene ring. Indeed, **12e** is the expected *exo* adduct of the *Z*-substituted 1,3,8-nonatriene system. The IMDA cycloadditions of the related *E*-substituted 1,3,8-nonatrienes, similar to **8e**, possessing a C9-keto unit were reported to yield the adducts in the *exo*:*endo* ratios of 61:39–80:20 (PhMe, 120–140 °C, 12–20 h).[6o] Our observation for the reaction of **8e** is consistent with the reported stereoselectivity (Table 1, entry 9). We also carried out X-ray crystal structural analysis for the adducts **10c** and **13d** derived from the 1-phenyl-substituted[6g,19] 1,3,8-nonatrienes. Figure 2 is the drawing of the *exo* adduct **10c**, depicting a trans-fused bicycle with the phenyl group placing in the pseudo axial and the ester moiety in the pseudo equatorial positions. The structural drawing of the *cis*-fused bicyclic lactone **13d** is shown in Figure 3. The phenyl group is placed in the pseudo axial position while the ester moiety occupies the pseudo equatorial orientation. On the basis of our results on IMDA cycloadditions of the 10 different *E*- and *Z*-substituted 1,3,8-nonatrienes **8a–e** and **9a–e** possessing an ester linkage, *exo* selectivity is generally observed irrespective of the nature of C1-substituent (Me vs Ph) and C9-activator (ester vs keto).[5i] The 'abnormal' *exo*:*endo* ratio for the adducts **12e**/**13e** obtained from the (*Z*)-9-acyl-substitued **9e** in MeCN originates from a polar solvent effect, which favors formation of the *endo* isomer. Its nature is not fully understood.[13c,e]

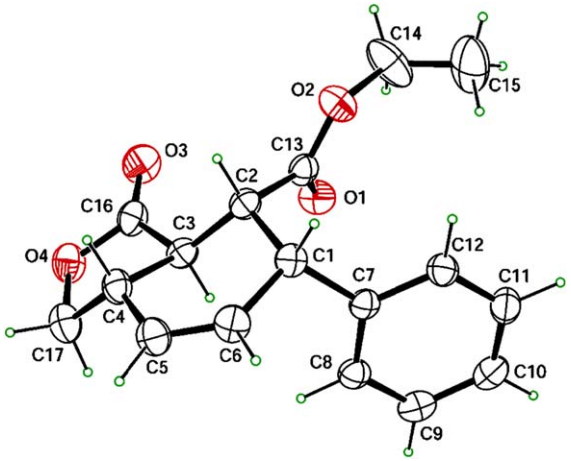


Figure 2. X-ray crystal structure of **10c**.

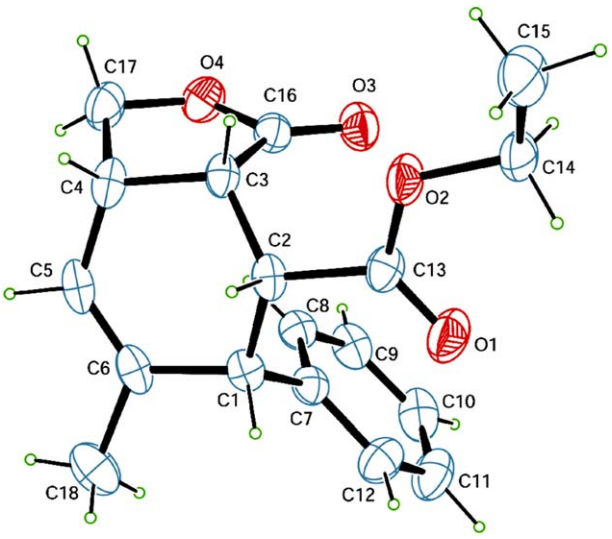
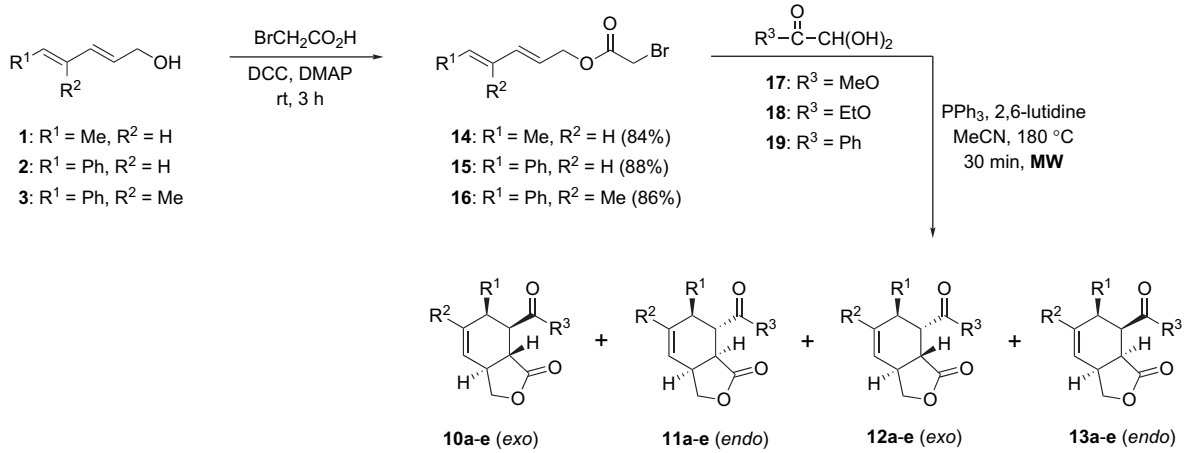


Figure 3. X-ray crystal structure of **13d**.

2.2. Microwave-assisted tandem Wittig–IMDA cycloadditions

The Wittig olefination[20] is another powerful methodology for synthesis of functionalized olefins from halides and carbonyl compounds. The stabilized phosphorus ylides are easily prepared and purified in pure forms. However, the reactivity of stabilized ylides is relatively lower and heating conditions are frequently required with prolonged reaction times. The microwave-assisted Wittig reactions of stabilized phosphorus ylides with aldehydes,[21] ketones,[11a,d,22] and lactones[23] have been explored although the majority was done in domestic microwave ovens. Mechanistically speaking, the Wittig reaction consists of three steps: (a) phosphonium salt formation; (b) ylide formation via deprotonation; and (c) olefination of carbonyl substrates. The step (a) is often carried out under forced conditions such as microwave heating.[24] The most efficient way to conduct a Wittig reaction should begin with the ylide precursor but not the preformed ylide. Development of the so-called 'one-pot' Wittig reaction has been the focus of considerable research efforts,[25] including the work of Westman[25g] for demonstrating the one-pot Wittig reaction of a resin-bound phosphine under controlled microwave heating. As a continuation of our previous studies on the Wittig reactions with microwave irradiation,[11a,d] in aqueous media,[26c,d] and in the asymmetric versions,[24b,26a,b] we proposed to establish a microwave-assisted tandem Wittig–IMDA cycloaddition protocol[27] for a modular synthesis of the bicyclic lactones **C**, starting from the α-bromoacetates **III** and the α-oxo carbonyl compounds **IV** (Chart 2). To the best of our knowledge, no prior example of this sort is known in the literature. As a proof-of-concept study, we selected three each of the α-bromoacetates **14**–**16** and the hydrate forms of α-oxo carbonyl compounds **17**–**19** in our current work. The results are summarized in Scheme 3 and Table 3.

According to the synthesis of **8a** and **9a** shown in Scheme 2, formation of the phosphonium salt **20** from **14** and subsequent olefination could proceed at room temperature. Therefore, the rate-limiting step for our proposed tandem process should be the IMDA cycloaddition. To our delight, the cascade reaction sequence took place at 180 °C consisting of alkylation of PPh_3 with the bromides **14**–**16**, deprotonation of the phosphonium salts with 2,6-lutidine, olefination of the ylides with the α-oxo carbonyls **17**–**19**, and finally the IMDA cycloadditions. Thus, after heating on a technique microwave reactor in a closed vial at 180 °C for 30 min in MeCN, the bicyclic lactones were produced in 68–80% isolated yields by a single operation. Other bases such as Et_3N could be used for the Wittig reaction as shown in Scheme 2. In order to avoid formation of a quaternary ammonium salt from Et_3N at the high temperature, 2,6-lutidine was selected. Four isomeric adducts were formed in all reactions and the *exo*:*endo* ratios are almost identical to those obtained for the IMDA reactions of the purified 1,3,8-nonatrienes **8a**–**e** and **9a**–**e** (Table 1, entries 1, 3, 6, 8, 9, 11, 14, and 16). On the basis of the ratios of (**10**+**11**):(**12**+**13**) in the entries 1, 3, and 5 of Table 3, it is estimated that the olefins **8**:**9** are formed in 78:22–88:12 mixtures of *E*- and *Z*-isomers at 180 °C. It is clear that the stereoselectivity of the Wittig olefination at high temperature somewhat deteriorated as compared to the room temperature version, which gave a 95:5 ratio for the *E*- and *Z*-isomers **8a** and **9a** (Scheme 2). Aside from the olefination stereoselectivity, our tandem Wittig–IMDA cycloaddition protocol, in combination with controlled microwave heating,



Scheme 3. Synthesis of α-bromoacetates **14**–**16** and tandem Wittig–IMDA under microwave heating.

Table 3. Microwave-assisted tandem Wittig–IMDA of **14–16** with **17–19**[a]

Entry	Substrates	Lactones	Yield (%)[b]	Isomer ratio (**10a**:**11a**:**12a**:**13a**)	*exo*:*endo* Ratios (**10**:**11**; **12**:**13**)
1	**14+17**	**10a+11a+12a+13a**	68	64:24:8:4[c]	73:27; 67:33
2	**14+18**	**10b+11b+12b+13b**	71	57:29:14:0[d,e]	66:34; NA[g]
3	**15+18**	**10c+11c+12c+13c**	80	58:20:17:5[c]	74:26; 77:23
4	**16+18**	**10d+11d+12d+13d**	76	56:28:16:0[d,e]	67:33; NA[g]
5	**14+19**	**10e+11e+12e+13e**	77	59:24:8:9[c,f]	71:29; 47:53

[a] All IMDA were carried out in closed pressurized vials with the reaction temperature measured by an IR sensor.
[b] Combined isolated yields.
[c] The ratio was determined by ^{1}H NMR of the crude product mixtures. Copies of the ^{1}H NMR charts are found in Supplementary data.
[d] Due to overlapping of ^{1}H NMR signals of the stereoisomers, the ratio was calculated based on the weights of the isolated products.
[e] The minor isomer **13** was not isolated, probably lost during purification.
[f] Average values of two runs.
[g] Not available.

provides a high-throughput synthesis of the bicyclic lactones by using the appropriate bromide and aldehyde building blocks in a combinatorial approach. Structural complexity and functional groups of the lactones **A** (Chart 1) can be easily introduced according to the known chemistry developed for their syntheses over the years.[4–7]

3. Conclusion

We have studied the IMDA cycloaddition of the ester-tethered 1,3,8-nonatrienes possessing substituents at both C1 and C9 under controlled microwave heating at 180 °C for 30 min in a polar solvent, MeCN. In general, the predicted *exo* stereoselectivity[5j] for both pentadienyl maleates (**8b–d**) and fumarates (**9a–d**) has been confirmed. A similar *exo* stereoselectivity is obtained for IMDA cycloaddition of the C1-substituted pentadienyl (*E*)-4-oxobut-2-enoate **8e**[6o] although (*Z*)-4-oxobut-2-enoate **9e** demonstrates an unusual solvent-dependent stereoselectivity. Our findings suggest that the IMDA cycloadditions can be significantly accelerated with microwave irradiation without deteriorating stereoselectivity. We have also realized a tandem Wittig–IMDA cycloaddition protocol illustrated in Chart 2 for an expedite synthesis of the bicyclic lactones **C** starting from the bromide and aldehyde building blocks. Our synthetic strategy in combination with controlled microwave heating offers an efficient synthesis of the bicyclic lactones, whose applications can be amplified subject to improvement of the stereoselectivity.

4. Experimental

4.1. General information and the microwave reactor

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (300, 400, or 500 MHz for ^{1}H, 75, 100, or 125 MHz for ^{13}C, and 121 MHz for ^{31}P). IR spectra were taken on an FTIR spectrophotometer. Mass spectra (MS) were measured by the +ESI or +EI method. Melting points are uncorrected. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Petroleum ether of 60–90 °C fraction was used in this work. *trans*,*trans*-2,4-Hexadien-1-ol **1**, fumaric acid monoethyl ester **5**, and phenylglyoxal hydrate **19**, and other reagents were obtained commercially and used as received. Fumaric acid monomethyl ester **4**,[14] maleic acid monomethyl ester **6**,[16] and monoethyl ester **7**,[16] methyl glyoxalate hydrate **17**,[28] and ethyl glyoxalate hydrate **18**[28] were prepared according to the reported procedures. All microwave-assisted reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala, Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature.

4.2. General procedure for synthesis of alcohols 2 and 3

To a solution of the dienonate (5 mmol) in dry CH_2Cl_2 (15 mL) cooled in an ice-water bath under a nitrogen atmosphere was added DIBAL-H (11 mL, 1.0 M in hexane) dropwise. The resultant mixture was stirred for 45 min at the same temperature and the reaction was quenched with saturated aqueous sodium potassium tartrate (Rochelle's salt). The mixture was stirred at ambient temperature for 2 h, and then diluted with Et_2O (10 mL). The aqueous layer was extracted with Et_2O (10 mL×2) and the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in petroleum ether) to give the 2,4-pentadien-1-ols.

4.2.1. (2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-ol (2). Prepared from ethyl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate[29,30] in 95% yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H), 6.79 (dd, J=15.6, 10.6 Hz, 1H), 6.57 (d, J=15.6 Hz, 2H), 6.43 (dd, J=15.2, 10.6 Hz, 1H), 5.97 (dt, J=15.2, 6.0 Hz, 1H), 4.26 (d, J=5.6 Hz, 2H), 1.75–1.50 (br s, 1H).

4.2.2. (2*E*,4*E*)-4-Methyl-5-phenylpenta-2,4-dien-1-ol (3). Prepared from ethyl (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dienoate[30] in 95% yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 6.60 (s, 1H), 6.52 (d, J=15.2 Hz, 1H), 6.00 (dt, J=15.6, 6.0 Hz, 1H), 4.34 (d, J=5.6 Hz, 2H), 2.89 (s, 1H), 2.08 (s, 3H).

4.3. General procedure for synthesis of *E*-substituted 1,3,8-nonatrienes 8a–d

To a solution of the alcohol (1.5 mmol), 4-dimethylaminopyridine (DMAP, 0.15 mmol), and fumaric acid monomethyl

ester **4**[14] or monoethyl ester **5**[16] (2 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under a nitrogen atmosphere was added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 2.0 mmol) in one portion. After stirring for 30 min at the same temperature, the reaction mixture was allowed to warm up to room temperature followed by stirring for another 3 h. Celite was added to the reaction vessel and the mixture, after stirring for 30 min, was then filtered with washing by CH_2Cl_2. The combined filtrate was evaporated under reduced pressure to give the crude product, which was purified by silica gel chromatography (3% EtOAc in petroleum ether) to provide the pure product. The yields are given in Table 1.

4.3.1. Methyl (2*E*,4*E*)-hexa-2,4-dien-1-yl fumarate (8a).[5b] Prepared from (2*E*,4*E*)-hexa-2,4-dien-1-ol **1** and fumaric acid monomethyl ester **4** in 88% yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J=0.4 Hz, 2H), 6.27 (dd, J=15.2, 10.4 Hz, 1H), 6.03 (ddd, J=14.8, 10.0, 1.6 Hz, 1H), 5.75 (dq, J=14.8, 6.8 Hz, 1H), 5.62 (dt, J=15.2, 6.8 Hz, 1H), 4.68 (d, J=7.2 Hz, 2H), 3.78 (s, 3H), 1.75 (d, J=6.8 Hz, 3H).

4.3.2. Ethyl (2*E*,4*E*)-hexa-2,4-dien-1-yl fumarate (8b).[5e] Prepared from (2*E*,4*E*)-hexa-2,4-dien-1-ol **1** and fumaric acid monoethyl ester **5** in 90% yield as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.29 (dd, J=15.6, 10.4 Hz, 1H), 6.06 (dd, J=15.6, 10.0 Hz, 1H), 5.78 (dq, J=15.2, 6.4 Hz, 1H), 5.65 (dt, J=15.6, 6.4 Hz, 1H), 4.70 (d, J=6.8 Hz, 2H), 4.26 (q, J=7.2 Hz, 2H), 1.76 (d, J=6.4 Hz, 3H), 1.32 (t, J=7.2 Hz, 3H).

4.3.3. Ethyl (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl fumarate (8c). Prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol **2** and fumaric acid monoethyl ester **5** in 83% yield as a colorless oil; R_f=0.35 (4.8% EtOAc in hexane); IR (film) 3026, 2984, 1721, 1645, 1294, 1258, 1153, 988 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (m, 5H), 6.85 (s, 2H), 6.74 (dd, J=15.6, 10.4 Hz, 1H), 6.57 (d, J=15.6 Hz, 1H), 6.45 (dd, J=15.2, 10.4 Hz, 1H), 5.84 (dt, J=14.8, 6.8 Hz, 1H), 4.75 (d, J=6.8 Hz, 2H), 4.23 (q, J=7.2 Hz, 2H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 164.7, 136.7, 135.1, 134.2, 134.0, 133.3, 128.6 (×2), 127.9, 127.4, 126.5 (×2), 125.9, 65.5, 61.3, 14.1; MS (+ESI) m/z 595 (2M+Na$^+$, 100), 309 (M+Na$^+$, 82); HRMS (+ESI) calcd for $C_{17}H_{18}O_4Na$ (M+Na$^+$), 309.1097; found, 309.1085.

4.3.4. Ethyl (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dien-1-yl fumarate (8d). Prepared from (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dien-1-ol **3** and fumaric acid monoethyl ester **5** in 85% yield as a colorless oil; R_f=0.38 (4.8% EtOAc in hexane); IR (film) 2984, 1721, 1645, 1294, 1258, 1153, 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 6.88 (d, J=0.8 Hz, 2H), 6.55 (s, 1H), 6.50 (d, J=15.6 Hz, 1H), 5.84 (dt, J=15.6, 6.4 Hz, 1H), 4.80 (d, J=6.8 Hz, 2H), 4.24 (q, J=6.8 Hz, 2H), 1.99 (s, 3H), 1.30 (td, J=7.2, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 164.8, 140.3, 137.3, 134.5, 134.0, 133.4, 133.0, 129.2 (×2), 128.1 (×2), 126.8, 121.5, 66.0, 61.3, 14.1, 13.8; MS (+ESI) m/z 623 (2M+Na$^+$, 87), 323 (M+Na$^+$, 100); HRMS (+ESI) calcd for $C_{18}H_{20}O_4Na$ (M+Na$^+$), 323.1254; found, 323.1244.

4.4. General procedure for synthesis of *Z*-substituted 1,3,8-nonatrienes 9a–d

To a solution of maleic acid monomethyl ester **6** or monoethyl ester **7**[16] (3.7 mmol) in dry CH_2Cl_2 was added *N*,*N*′-diisopropylcarbodiimide (DIC, 1.85 mmol) and the mixture was stirred at 0 °C for 1 h. The insoluble urea was filtered off and the filtrate was added to a solution of the alcohol (1.23 mmol) followed by addition of *i*-Pr_2NEt (DIEA, 3.70 mmol) and 4-dimethylaminopyridine (DMAP, cat.). The resultant mixture was stirred at 0 °C for 1 h and at ambient temperature for another 1 h. The reaction mixture was diluted with CH_2Cl_2 and successively washed with saturated aqueous NH_4Cl and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product, which was purified by silica gel chromatography (9% EtOAc in petroleum ether) to provide the pure product. The yields are given in Table 1.

4.4.1. Methyl (2*E*,4*E*)-hexa-2,4-dien-1-yl maleate (9a).[5b] Prepared from (2*E*,4*E*)-hexa-2,4-dien-1-ol **1** and maleic acid monomethyl ester **6** in 65% yield as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2H), 6.27 (dd, J=15.2, 10.4 Hz, 1H), 6.05 (ddd, J=15.2, 10.0, 1.2 Hz, 1H), 5.76 (dq, J=15.2, 6.8 Hz, 2H), 4.68 (d, J=6.8 Hz, 2H), 3.77 (s, 3H), 1.75 (d, J=6.8 Hz, 3H).

4.4.2. Ethyl (2*E*,4*E*)-hexa-2,4-dien-1-yl maleate (9b). Prepared from (2*E*,4*E*)-hexa-2,4-dien-1-ol **1** and maleic acid monoethyl ester **7** in 69% yield as a colorless oil; R_f=0.43 (9.1% EtOAc in hexane); IR (film) 2984, 1735, 1725, 1642, 1403, 1209, 1160, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (dd, J=15.6, 10.8 Hz, 1H), 6.21 (s, 2H), 6.07–5.98 (m, 1H), 5.73 (dq, J=15.2, 6.4 Hz, 1H), 5.61 (dt, J=14.8, 6.8 Hz, 1H), 4.65 (d, J=6.8 Hz, 2H), 4.21 (q, J=7.2 Hz, 2H), 1.73 (d, J=6.4 Hz, 3H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.8, 135.4, 131.4, 130.2, 130.0, 129.3, 122.8, 65.6, 61.1, 18.0, 13.8; MS (+ESI) m/z 471 (2M+Na$^+$, 100), 247 (M+Na$^+$, 49); HRMS (+ESI) calcd for $C_{12}H_{16}O_4Na$ (M+Na$^+$), 247.0941; found, 247.0934.

4.4.3. Ethyl (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl maleate (9c). Prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol **2** and maleic acid monoethyl ester **7** in 70% yield as a colorless oil; R_f=0.34 (9.1% EtOAc in hexane); IR (film) 2983, 1728, 1643, 1403, 1210, 1162, 989 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 6.70 (dd, J=15.6, 10.4 Hz, 1H), 6.52 (d, J=15.6 Hz, 1H), 6.41 (dd, J=14.8, 10.0 Hz, 1H), 6.19 (s, 2H), 5.83 (dt, J=15.2, 6.8 Hz, 1H), 4.78 (d, J=6.4 Hz, 2H), 4.25 (q, J=7.6 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.9, 136.8, 135.1, 134.0, 130.2, 129.4, 128.6 (×2), 127.9, 127.5, 126.5 (×2), 126.1, 65.5, 61.2, 14.0; MS (+ESI) m/z 595 (2M+Na$^+$, 100), 309 (M+Na$^+$, 57); HRMS (+ESI) calcd for $C_{17}H_{18}O_4Na$ (M+Na$^+$), 309.1097; found, 309.1086.

4.4.4. Ethyl (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dien-1-yl maleate (9d). Prepared from (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dien-1-ol **3** and maleic acid monoethyl ester **7** in 71% yield as a colorless oil; R_f=0.4 (9.1% EtOAc in hexane); IR (film) 2983, 1728, 1643, 1403, 1210, 1161 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5H), 6.66

(s, 1H), 6.61 (d, J=15.5 Hz, 1H), 6.36 (s, 2H), 5.96 (dt, J=15.5, 6.5 Hz, 1H), 4.90 (d, J=6.5 Hz, 2H), 4.35 (q, J=7.0 Hz, 2H), 2.10 (d, J=0.5 Hz, 3H), 1.40 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 164.9, 140.1, 137.3, 134.5, 132.8, 130.1, 129.4, 129.1 (×2), 128.1 (×2), 126.7, 121.5, 65.9, 61.2, 13.9, 13.7; MS (+ESI) m/z 623 (2M+Na$^+$, 79), 323 (M+Na$^+$, 100); HRMS (+ESI) calcd for $C_{18}H_{20}O_4Na$ (M+Na$^+$), 323.1254; found, 323.1239.

4.5. General procedure for synthesis of the α-bromoacetates 14–16

To a suspension of the alcohols **1–3** (1.5 mmol), 4-dimethylaminopyridine (DMAP, 0.15 mmol), and bromoacetic acid (2.0 mmol) in dry CH_2Cl_2 (15 mL) cooled in an ice-water bath (0 °C) under a nitrogen atmosphere was added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 2.0 mmol) in one portion. After stirring for 30 min at 0 °C, the reaction was allowed to warm up to ambient temperature followed by stirring for 3 h. Celite was added to the reaction mixture and, after stirring for 30 min, the mixture was filtered with washing by CH_2Cl_2. The combined filtrate was evaporated under reduced pressure and the residue was purified by silica gel chromatography (3% EtOAc in petroleum ether) to provide the products **14–16**.

4.5.1. (2*E*,4*E*)-Hexa-2,4-dien-1-yl α-bromoacetate (14). Prepared from (2*E*,4*E*)-hexa-2,4-dien-1-ol **1** and α-bromoacetic acid in 84% yield as a colorless oil; R_f=0.44 (4.8% EtOAc in hexane); IR (film) 3026, 2959, 1739, 1678, 1449, 1276, 1159, 1123, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, J=15.2, 10.4 Hz, 1H), 6.06 (dd, J=15.2, 10.4 Hz, 1H), 5.79 (dq, J=15.2, 6.8 Hz, 1H), 5.63 (dt, J=15.2, 6.8 Hz, 1H), 4.67 (d, J=6.8 Hz, 1H), 3.85 (s, 3H), 1.77 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 135.7, 131.8, 130.1, 122.4, 66.6, 25.8, 18.0; MS (+ESI) m/z 243 (M+2+Na$^+$, 100), 241 (M+Na$^+$, 97); HRMS (+EI) calcd for $C_8H_{11}BrO_2$ (M$^+$), 217.9937; found, 219.9921 (M$^+$+2), 217.9939 (M$^+$).

4.5.2. (2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-yl α-bromoacetate (15). Prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol **2** and α-bromoacetic acid in 88% yield as a colorless oil; R_f=0.53 (4.8% EtOAc in hexane); IR (film) 3026, 2947, 1736, 1276, 1159, 989, 741, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.24 (m, 5H), 6.78 (dd, J=15.6, 10.8 Hz, 1H), 6.62 (d, J=15.2 Hz, 1H), 6.51 (dd, J=15.6, 10.4 Hz, 1H), 5.89 (dt, J=14.8, 6.8 Hz, 1H), 4.77 (d, J=6.8 Hz, 2H), 3.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 136.6, 135.4, 134.2, 128.5 (×2), 127.8, 127.3, 126.4 (×2), 125.5, 66.3, 25.8; MS (+ESI) m/z 305 (M+2+Na$^+$, 100), 303 (M+Na$^+$, 98); HRMS (+EI) calcd for $C_{13}H_{13}BrO_2$ (M$^+$), 280.0093; found, 282.0078 (M$^+$+2), 280.0100 (M$^+$).

4.5.3. (2*E*,4*E*)-4-Methyl-5-phenylpenta-2,4-dien-1-yl α-bromoacetate (16). Prepared from (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dien-1-ol **3** and α-bromoacetic acid in 86% yield as a colorless oil; R_f=0.43 (4.8% EtOAc in hexane); IR (film) 3022, 2950, 1736, 1274, 1157, 1111, 962 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.23 (m, 5H), 6.59 (s, 1H), 6.54 (d, J=16.0 Hz, 1H), 5.85 (dt, J=16.0, 6.4 Hz, 1H), 4.80 (d, J=7.2 Hz, 2H), 3.88 (d, J=1.2 Hz, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 140.5, 137.2, 134.4, 133.1, 129.1 (×2), 128.1 (×2), 126.8, 121.0, 66.9, 25.9, 13.7; MS (+ESI) m/z 319 (M+2+Na$^+$, 100), 317 (M+Na$^+$, 97); HRMS (+EI) calcd for $C_{14}H_{15}BrO_2$ (M$^+$), 294.0250; found, 296.0235 (M$^+$+2), 294.0255 (M$^+$).

4.5.4. Preparation of phosphonium salt (20). A solution of (2*E*,4*E*)-penta-2,4-dien-1-yl α-bromoacetate **14** (0.3 mmol) and PPh_3 (0.33 mmol) in MeCN (10 mL) was stirred at ambient temperature overnight (12 h). The reaction mixture was evaporated under reduced pressure to give a white solid, which was washed with dry benzene (9 mL×3) and dried in vacuum to provide quantitatively the salt **20**. The phosphonium salt was used without further purification. Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.59 (m, 15H), 6.04 (dd, J=15.0, 10.2 Hz, 1H), 5.85 (dd, J=15.0, 10.2 Hz, 1H), 5.67 (dq, J=14.4, 6.9 Hz, 1H), 5.44 (d, J=13.8 Hz, 2H), 5.23 (dt, J=15.0, 7.2 Hz, 1H), 4.41 (d, J=7.2 Hz, 2H), 1.71 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J_{P-C}=4.6 Hz), 136.2, 135.0 (d, J_{P-C}=3.1 Hz), 133.8 (d, J_{P-C}=10.9 Hz, ×2), 132.1, 130.1 (d, J_{P-C}=13.6 Hz, ×2), 129.8, 121.4, 117.6 (d, J_{P-C}=88.9 Hz), 67.0, 33.0 (d, J_{P-C}=55.0 Hz), 18.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.2.

4.5.5. Synthesis of (2′*E*,4′*E*)-hexa-2′,4′-dien-1-yl (2*E*)-4-phenyl-4-oxo-2-butenoate (8e) and (2′*E*,4′*E*)-hexa-2′,4′-dien-1-yl (2*Z*)-4-phenyl-4-oxo-2-butenoate (9e). To a solution of the phosphonium salt **20** (2 mmol) and phenylglyoxal hydrate **19** (2.2 mmol) in MeOH (15 mL) cooled in an ice-water bath (0 °C) was added Et_3N (2.1 mmol). The resultant mixture was stirred for 30 min at 0 °C and the reaction mixture was extracted with EtOAc (30 mL×2). The combined organic layer was washed with 6% aqueous HCl and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 9% EtOAc in petroleum ether) to give **8e** (37%) and **9e** (18%).

Compound **8e**. A yellow oil; R_f=0.56 (9.1% EtOAc in hexane); IR (film) 3026, 2936, 1723, 1673, 1292, 1262, 1164, 989 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.91 (d, J=16.0 Hz, 1H), 7.64–7.60 (m, 1H), 7.51 (t, J=7.6 Hz, 2H), 6.89 (d, J=15.2 Hz, 1H), 6.31 (dd, J=15.6, 11.2 Hz, 1H), 6.08 (ddd, J=15.2, 10.8, 1.6 Hz, 1H), 5.79 (dq, J=15.2, 6.8 Hz, 1H), 5.68 (dt, J=15.2, 6.8 Hz, 1H), 4.74 (d, J=6.8 Hz, 2H), 1.77 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 165.1, 136.4, 136.4, 135.4, 133.7, 132.2, 131.6, 130.2, 128.7 (×2), 128.7 (×2), 122.8, 65.7, 18.0; MS (+ESI) m/z 535 (2M+Na$^+$, 17), 279 (M+Na$^+$, 100), 257 (M+H$^+$, 92); HRMS (+ESI) calcd for $C_{16}H_{16}O_3Na$ (M+Na$^+$), 279.0992; found, 279.0982.

Compound **9e**. A yellow oil; R_f=0.24 (9.1% EtOAc in hexane); IR (film) 3026, 2933, 1722, 1673, 1203, 1165, 990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–792 (m, 2H), 7.61–7.44 (m, 3H), 6.89 (dd, J=11.7, 0.6 Hz, 1H), 6.29 (dd, J=12.6, 1.2 Hz, 1H), 6.11 (dd, J=15.0, 10.2 Hz, 1H), 5.96 (ddd, J=15.0, 10.5, 1.2 Hz, 1H), 5.70 (dq, J=15.0, 6.9 Hz, 1H), 5.40 (dt, J=15.0, 6.6 Hz, 1H), 4.49 (d, J=6.6 Hz, 2H), 1.75 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 194.0, 164.5, 141.3, 135.8, 135.4, 133.7, 131.5, 130.3, 128.8 (×2), 128.7 (×2), 125.9, 122.7, 65.7, 18.3.

*Note: The triene **9e** undergoes IMDA cycloaddition at ambient temperature and the adducts **12e** and **13e** were formed during the course of measurement of ^1H NMR. Therefore, mass data were not attempted for **9e**.*

4.6. General procedure for microwave-assisted intramolecular Diels–Alder reactions of *E*- and *Z*-substituted 1,3,8-nonatrienes 8a–e and 9a–e

To a 10-mL pressurized process vial was added the 1,3,8-nonatrienes (0.50 mmol) in CH_3CN (4 mL). The loaded vial was then sealed with a cap containing a silicon septum, and put into the microwave cavity and heated at 180 °C for 30 min. The reaction mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 20% EtOAc in petroleum ether) to give the desired products. The structures, isomer ratios, and yields are found in Schemes 1 and 2 and Table 1.

4.6.1. Methyl (3a*R,6*S**,7*R**,7a*S**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (10a).**[5e] The major isomer from IMDA reaction of **8a** was obtained as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddd, *J*=9.6, 1.5, 1.5 Hz, 1H), 5.70 (ddd, *J*=9.9, 3.0, 3.0 Hz, 1H), 4.46 (dd, *J*=8.1, 6.3 Hz, 1H), 3.93 (dd, *J*=11.4, 8.4 Hz, 1H), 3.77 (s, 3H), 2.97 (dd, *J*=11.1, 6.9 Hz, 1H), 2.91–2.61 (m, 2H), 2.59 (dd, *J*=13.2, 11.4 Hz, 1H), 0.98 (d, *J*=6.6 Hz, 3H).

4.6.2. Methyl (3a*R,6*S**,7*S**,7a*R**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (11a).**[5e] The minor isomer from IMDA reaction of **8a** was obtained as a colorless oil (this sample contains 8% **10a**); ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddd, *J*=9.9, 2.4, 2.4 Hz, 1H), 5.60 (ddd, *J*=10.5, 3.3, 2.1 Hz, 1H), 4.48 (dd, *J*=8.7, 7.5 Hz, 1H), 4.00 (dd, *J*=8.7, 6.3 Hz, 1H), 3.77 (s, 3H), 3.27–3.16 (m, 1H), 3.11 (dd, *J*=8.1, 8.1 Hz, 1H), 2.66 (dd, *J*=6.6, 6.6 Hz, 1H), 2.65–2.56 (m, 1H), 1.11 (d, *J*=7.2 Hz, 3H).

4.6.3. Methyl (3a*R,6*S**,7*R**,7a*R**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (12a).**[5e] The major isomer from IMDA reaction of **9a** was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, *J*=13.2, 1.8, 1.8 Hz, 1H), 5.65 (ddd, *J*=9.6, 3.2, 3.2 Hz, 1H), 4.52 (dd, *J*=7.4, 7.4 Hz, 1H), 3.86 (dd, *J*=11.6, 8.0 Hz, 1H), 3.69 (s, 3H), 3.25–3.15 (m, 1H), 2.96 (d, *J*=4.0 Hz, 1H), 2.97–2.89 (m, 1H), 2.35 (dd, *J*=13.2, 3.6 Hz, 1H), 1.19 (d, *J*=7.2 Hz, 3H).

4.6.4. Methyl (3a*R,6*S**,7*S**,7a*S**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (13a).**[5e] The minor isomer from IMDA reaction of **9a** was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, *J*=10.0, 4.0, 2.4 Hz, 1H), 5.60 (ddd, *J*=10.0, 2.4, 2.4 Hz, 1H), 4.44 (dd, *J*=8.4, 7.6 Hz, 1H), 4.17 (dd, *J*=8.4, 4.4 Hz, 1H), 3.75 (s, 3H), 3.34 (dd, *J*=9.6, 5.2 Hz, 1H), 3.24–3.17 (m, 1H), 3.09 (dd, *J*=5.2, 5.2 Hz, 1H), 2.75–2.65 (m, 1H), 1.15 (d, *J*=7.2 Hz, 3H).

4.6.5. Ethyl (3a*R,6*S**,7*R**,7a*S**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (10b).**[5b] The major isomer from IMDA reaction of **8b** was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J*=9.6, 1.6, 1.6 Hz, 1H), 5.72 (ddd, *J*=9.6, 3.0, 3.0 Hz, 1H), 4.47 (dd, *J*=8.0, 6.4 Hz, 1H), 4.28 (q, *J*=7.0 Hz, 2H), 3.95 (dd, *J*=10.8, 7.6 Hz, 1H), 2.97 (dd, *J*=11.6, 7.2 Hz, 1H), 2.92–2.79 (m, 2H), 2.61 (dd, *J*=13.2, 11.6 Hz, 1H), 1.33 (t, *J*=7.2 Hz, 3H), 1.02 (d, *J*=7.6 Hz, 3H).

4.6.6. Ethyl (3a*R,6*S**,7*S**,7a*R**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (11b).**[5b] The minor isomer from IMDA reaction of **8b** was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, *J*=10.4, 2.6, 2.6 Hz, 1H), 5.60 (ddd, *J*=10.4, 3.2, 2.4 Hz, 1H), 4.47 (dd, *J*=8.8, 8.0 Hz, 1H), 4.22 (qd, *J*=6.8, 1.2 Hz, 2H), 3.98 (dd, *J*=8.8, 6.4 Hz, 1H), 3.25–3.16 (m, 1H), 3.11 (dd, *J*=8.4, 8.4 Hz, 1H), 2.66–2.56 (m, 2H), 1.29 (t, *J*=7.2 Hz, 3H), 1.11 (d, *J*=7.2 Hz, 3H).

4.6.7. Ethyl (3a*R,6*S**,7*R**,7a*R**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (12b).** The major isomer from IMDA reaction of **9b** was obtained as a colorless oil; R_f=0.55 (25% EtOAc in hexane); IR (film) 2966, 1789, 1731, 1181, 1093, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, *J*=10.0 Hz, 1H), 5.63 (ddd, *J*=9.6, 3.0, 3.0 Hz, H), 4.49 (dd, *J*=7.6, 7.6 Hz, 1H), 4.20–4.08 (m, 2H), 3.83 (dd, *J*=11.6, 8.0 Hz, 1H), 3.19 (br dd, *J*=19.6, 12.4 Hz, 1H), 2.91 (br d, *J*=3.2 Hz, 2H), 2.33 (dd, *J*=13.6, 3.6 Hz, 1H), 1.22 (t, *J*=7.2 Hz, 3H), 1.17 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 171.7, 134.6, 123.0, 70.5, 60.9, 42.6, 41.4, 36.2, 33.9, 21.9, 13.9; MS (+ESI) *m/z* 471 ($2M+Na^+$, 100), 247 ($M+Na^+$, 16); HRMS (+ESI) calcd for $C_{12}H_{16}O_4Na$ ($M+Na^+$), 247.0941; found, 247.0940.

4.6.8. Ethyl (3a*R,6*S**,7*S**,7a*S**)-6-methyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (13b).** The minor isomer from IMDA reaction of **9b** was obtained as a colorless oil; R_f=0.43 (25% EtOAc in hexane); IR (film) 2976, 2932, 1770, 1728, 1176, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddd, *J*=9.6, 4.0, 1.6 Hz, 1H), 5.59 (ddd, *J*=10.0, 2.4, 2.4 Hz, 1H), 4.43 (dd, *J*=8.4, 8.4 Hz, 1H), 4.20 (q, *J*=6.8 Hz, 2H), 4.16 (dd, *J*=8.0, 4.0 Hz, 1H), 3.32 (dd, *J*=9.2, 5.2 Hz, 1H), 3.22–3.16 (m, 1H), 3.05 (dd, *J*=5.2, 5.2 Hz, 1H), 2.70–2.65 (m, 1H), 1.27 (t, *J*=7.2 Hz, 3H), 1.15 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 171.3, 134.0, 124.4, 71.3, 60.7, 42.0, 38.5, 35.1, 30.2, 17.6, 14.1; MS (+ESI) *m/z* 471 ($2M+Na^+$, 46), 247 ($M+Na^+$, 100); HRMS (+ESI) calcd for $C_{12}H_{16}O_4Na$ ($M+Na^+$), 247.0941; found, 247.0936.

4.6.9. Ethyl (3a*R,6*S**,7*R**,7a*S**)-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (10c).** The major isomer from IMDA reaction of **8c** was obtained as colorless needles; mp 156–157 °C (EtOAc–hexane); R_f=0.33 (25% EtOAc in hexane); IR (KBr) 3034, 2984, 1784, 1735, 1321, 1180, 1085, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 3H), 7.17–7.13 (m, 2H), 6.07 (ddd, *J*=10.0, 2.0, 2.0 Hz, 1H), 5.82 (ddd, *J*=10.0, 3.4, 3.4 Hz, 1H), 4.54 (dd, *J*=8.0, 6.0 Hz, 1H), 4.05 (dd, *J*=11.2, 8.4 Hz, 1H), 4.07–4.02 (m, 1H),

3.80–3.60 (m, 2H), 3.16 (dd, J=11.6, 8.0 Hz, 1H), 2.96–2.86 (m, 1H), 2.77 (dd, J=13.6, 11.6 Hz, 1H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.9, 139.2, 132.3, 129.4 (×2), 128.2 (×2), 127.6, 123.9, 70.3, 60.5, 45.5, 44.4, 40.6, 40.2, 30.9, 13.6; MS (+ESI) m/z 309 ($M+Na^+$, 98), 287 ($M+H^+$, 100). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.22; H, 6.33.

4.6.10. Ethyl (3a*R,6*S**,7*S**,7a*R**)-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (11c).** The minor isomer from IMDA reaction of **8c** was obtained as colorless needles; mp 117–118 °C (EtOAc–hexane); R_f=0.33 (25% EtOAc in hexane); IR (KBr) 2981, 1773, 1722, 1180, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 3H), 7.20–7.16 (m, 2H), 5.97 (ddd, J=10.0, 2.0, 2.0 Hz, 1H), 5.87 (ddd, J=10.4, 3.0, 3.0 Hz, 1H), 4.56 (dd, J=8.0, 8.0 Hz, 1H), 4.09 (d, J=8.4 Hz, 1H), 4.06 (q, J=6.4 Hz, 2H), 3.76 (ddd, J=8.0, 5.2, 2.0 Hz, 1H), 3.37–3.27 (m, 1H), 3.20 (dd, J=9.2, 9.2 Hz, 1H), 2.83 (dd, J=9.2, 8.4 Hz, 1H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.7, 141.4, 132.2, 128.6 (×2), 127.9 (×2), 127.3, 124.4, 71.5, 61.1, 46.1, 43.4, 40.1, 34.6, 13.9; MS (+ESI) m/z 309 ($M+Na^+$, 98), 287 ($M+H^+$, 100). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.36; H, 6.30.

4.6.11. Ethyl (3a*R,6*S**,7*R**,7a*R**)-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (12c).** The major isomer from IMDA reaction of **9c** was obtained as colorless needles; mp 69–71 °C (EtOAc–hexane); R_f=0.42 (25% EtOAc in hexane); IR (KBr) 2977, 1791, 1724, 1184, 987 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H), 6.08 (d, J=10.0 Hz, 1H), 5.81 (ddd, J=9.6, 3.4, 3.4 Hz, 1H), 4.53 (dd, J=7.4, 7.4 Hz, 1H), 4.27–4.14 (m, 3H), 3.90 (dd, J=11.2, 8.0 Hz, 1H), 3.32–3.20 (m, 1H), 3.17 (d, J=3.2 Hz, 1H), 2.39 (dd, J=13.6, 3.6 Hz, 1H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.2, 142.8, 130.5, 128.6 (×2), 127.7 (×2), 127.0, 125.3, 70.4, 61.1, 44.8, 44.1, 40.2, 36.1, 13.9; MS (+ESI) m/z 595 ($2M+Na^+$, 100), 309 ($M+Na^+$, 97). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.36; H, 6.30.

4.6.12. Ethyl (3a*R,6*S**,7*S**,7a*S**)-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (13c).** The minor isomer from IMDA reaction of **9c** was obtained as a colorless oil; R_f=0.32 (25% EtOAc in hexane); IR (film) 2918, 1773, 1722, 1179, 1163, 1033, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H), 6.05 (ddd, J=10.4, 2.0, 2.0 Hz, 1H), 5.93 (ddd, J=10.0, 3.0, 3.0 Hz, 1H), 4.55 (dd, J=8.6, 8.6 Hz, 1H), 4.37 (dd, J=8.4, 8.4 Hz, 1H), 3.88–3.77 (m, 2H), 3.68–3.60 (m, 1H), 3.45 (dd, J=6.0, 6.0 Hz, 1H), 3.35–3.24 (m, 1H), 3.18 (dd, J=10.8, 6.4 Hz, 1H), 0.81 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 171.2, 140.8, 128.2 (×2), 128.2 (×2), 128.1, 127.0, 126.0, 71.6, 60.4, 45.1, 42.1, 39.4, 33.4, 13.4; MS (+ESI) m/z 595 ($2M+Na^+$, 16), 309 ($M+Na^+$, 100); HRMS (+ESI) calcd for $C_{17}H_{18}O_4Na$ ($M+Na^+$), 309.1097; found, 309.1085.

4.6.13. Ethyl (3a*R,6*S**,7*R**,7a*S**)-5-methyl-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (10d).** The major isomer from IMDA reaction of **8d** was obtained as colorless needles; mp 127–129 °C (EtOAc–hexane); R_f=0.36 (25% EtOAc in hexane); IR (KBr) 2983, 1786, 1736, 1315, 1195, 1178, 1139, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 3H), 7.11 (d, J=6.4 Hz, 2H), 5.79 (s, 1H), 4.49 (dd, J=7.4, 7.4 Hz, 1H), 4.01 (dd, J=11.2, 8.4 Hz, 1H), 3.82 (d, J=8.8 Hz, 1H), 3.84–3.74 (m, 1H), 3.67–3.58 (m, 1H), 3.09 (dd, J=11.6, 7.2 Hz, 1H), 2.96–2.82 (m, 1H), 2.76 (dd, J=13.6, 12.4 Hz, 1H), 1.54 (s, 3H), 0.88 (q, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, taken at 25 °C) δ 174.1, 169.9, 138.7, 138.7, 128.4 (×2), 127.5, 119.9, 70.7, 60.4, 49.4, 45.9, 41.6, 39.6, 22.4, 13.6 (two aromatic carbon atoms are missing due to slow conformational rotation); ^{13}C NMR (125 MHz, DMSO-d_6, taken at 80 °C) δ 174.1, 169.5, 139.4, 137.1, 129.4 (×2), 128.0 (×2), 127.1, 120.7, 70.4, 59.4, 49.0, 45.1, 40.7, 39.3, 21.9, 13.5; MS (+ESI) m/z 623 ($2M+Na^+$, 100), 323 ($M+Na^+$, 59). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.18; H, 6.71.

4.6.14. Ethyl (3a*R,6*S**,7*S**,7a*R**)-5-methyl-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (11d).** The minor isomer from IMDA reaction of **8d** was obtained as an inseparable mixture with **10d**; R_f=0.36 (25% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, *only partial signals shown*) δ 5.64 (s, 1H), 4.12–4.09 (m, 1H), 3.30–3.25 (m, 1H), 3.17–3.13 (m, 1H), 1.59 (s, 3H), 1.14 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 172.9, 140.1, 136.5, 128.5 (×2), 128.3 (×2), 127.1, 121.8, 72.1, 61.2, 46.3, 46.3, 38.4, 34.4, 22.8, 14.0.

4.6.15. Ethyl (3a*R,6*S**,7*R**,7a*R**)-5-methyl-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (12d).** The major isomer from IMDA reaction of **9d** was obtained as a colorless oil; R_f=0.49 (25% EtOAc in hexane); IR (film) 2980, 1785, 1731, 1229, 1184, 1093, 1002 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J=7.4 Hz, 2H), 7.25 (d, J=6.4 Hz, 1H), 7.21 (d, J=7.6 Hz, 2H), 5.82 (s, 1H), 4.53 (dd, J=7.4, 7.4 Hz, 1H), 4.29–4.13 (m, 2H), 4.03 (s, 1H), 3.91 (dd, J=11.2, 8.0 Hz, 1H), 3.29–3.16 (m, 1H), 3.10 (d, J=2.8 Hz, 1H), 2.46 (dd, J=14.0, 3.2 Hz, 1H), 1.63 (s, 3H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 171.1, 142.2, 137.4, 128.8 (×2), 128.0 (×2), 127.0, 121.1, 70.9, 61.2, 48.9, 45.2, 39.7, 37.2, 22.5, 14.0; MS (+ESI) m/z 623 ($2M+Na^+$, 100), 323 ($M+Na^+$, 8), 301 ($M+H^+$, 10); HRMS (+ESI) calcd for $C_{18}H_{20}O_4Na$ ($M+Na^+$), 323.1254; found, 323.1244.

4.6.16. Ethyl (3a*R,6*S**,7*S**,7a*S**)-5-methyl-6-phenyl-1-oxo-3,3a,6,7,7a-hexahydroisobenzofuran-7-carboxylate (13d).** The minor isomer from IMDA reaction of **9d** was obtained as colorless needles; mp 111–112 °C (EtOAc–hexane); R_f=0.23 (25% EtOAc in hexane); IR (KBr) 2924, 1772, 1731, 1193, 1179, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5H), 5.67 (s, 1H), 4.44 (dd, J=8.2, 8.2 Hz, 1H), 4.31 (d, J=8.8 Hz, 1H), 4.25–4.10 (m, 2H), 3.91 (d, J=4.8 Hz, 1H), 3.43 (dd, J=9.6, 5.2 Hz, 1H), 3.36–3.27 (m, 1H), 3.29 (dd, J=9.6, 4.8 Hz, 1H), 1.65 (s, 3H), 1.23 (td, J=7.0, 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 170.4, 138.1, 137.2, 130.5 (×2), 127.4 (×2), 127.1, 122.9, 71.2, 60.7, 44.8, 43.9, 36.4, 36.1, 22.8, 13.9; MS (+ESI) m/z 623 ($2M+Na^+$, 98), 323 ($M+Na^+$, 60), 301 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.78; H, 6.67.

4.6.17. (3a*R,6*S**,7*R**,7a*S**)-7-Benzoyl-6-methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (10e).** The major isomer from IMDA reaction of **8e** was obtained as a white crystalline solid; mp 197–198 °C (EtOAc–hexane); R_f=0.30 (25% EtOAc in hexane); IR (KBr) 2955, 2925, 1765, 1683, 1176, 1095, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J=7.6 Hz, 1H), 7.59 (t, J=7.2 Hz, 1H), 7.49 (t, J=7.6 Hz, 2H), 5.82 (d, J=9.6 Hz, 1H), 5.71 (br d, J=10.0 Hz, 1H), 4.48 (dd, J=7.2, 7.2 Hz, 1H), 3.98 (dd, J=10.4, 5.2 Hz, 1H), 3.97 (dd, J=10.4, 4.4 Hz, 1H), 3.03–2.69 (m, 3H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 174.5, 136.4, 135.8, 133.4, 128.8 (×2), 128.2 (×2), 122.2, 70.3, 44.5, 41.0, 40.4, 33.5, 17.6; MS (+ESI) m/z 535 ($2M+Na^+$, 18), 279 ($M+Na^+$, 100). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.73; H, 6.27.

4.6.18. (3a*R,6*S**,7*S**,7a*R**)-7-Benzoyl-6-methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (11e).** The minor isomer from IMDA reaction of **8e** was obtained as colorless needles; mp 99–100 (EtOAc–hexane); R_f=0.45 (25% EtOAc in hexane); IR (KBr) 2964, 2905, 1765, 1678, 1269, 1207, 1157, 1120, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J=7.6 Hz, 2H), 7.60 (t, J=7.4 Hz, 1H), 7.50 (t, J=7.6 Hz, 2H), 5.76 (ddd, J=10.4, 4.0, 2.0 Hz, 1H), 5.62 (ddd, J=10.0, 2.4, 2.4 Hz, 1H), 4.48 (dd, J=8.4, 7.2 Hz, 1H), 4.15 (dd, J=9.2, 3.6 Hz, 1H), 3.94 (dd, J=3.8, 3.8 Hz, 1H), 3.45–3.36 (m, 1H), 3.18 (dd, J=8.4, 4.4 Hz, 1H), 2.70–2.50 (m, 1H), 1.21 (d, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 178.1, 136.0, 133.4, 133.2, 128.9 (×2), 128.4 (×2), 124.1, 71.9, 44.9, 39.0, 34.0, 31.0, 21.3; MS (+ESI) m/z 535 ($2M+Na^+$, 78), 279 ($M+Na^+$, 46), 257 ($M+H^+$, 100). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.72; H, 6.27.

4.6.19. (3a*R,6*S**,7*R**,7a*R**)-7-Benzoyl-6-methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (12e).** The *minor isomer* from IMDA reaction of **9e** was obtained as colorless needles; mp 144–145 °C (EtOAc–hexane); R_f=0.39 (25% EtOAc in hexane); IR (KBr) 2993, 2962, 1770, 1669, 1184, 1093, 982 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J=7.5 Hz, 1H), 7.61–7.57 (m, 1H), 7.49 (t, J=7.5 Hz, 2H), 5.85 (ddd, J=9.5, 1.8, 1.8 Hz, 1H), 5.62 (ddd, J=10.0, 3.3, 3.3 Hz, 1H), 4.59 (dd, J=7.5, 7.5 Hz, 1H), 3.90 (dd, J=12.0, 8.0 Hz, 1H), 3.81 (d, J=4.0 Hz, 1H), 3.72–3.69 (m, 1H), 2.76–2.70 (m, 1H), 2.49 (dd, J=13.5, 4.0 Hz, 1H), 1.36 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 175.3, 136.3, 134.0, 133.3, 128.7 (×2), 128.4 (×2), 123.6, 71.1, 44.3, 42.0, 36.1, 34.4, 22.5; MS (+ESI) m/z 535 ($2M+Na^+$, 49), 279 ($M+Na^+$, 100), 257 ($M+H^+$, 98). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.80; H, 6.28.

4.6.20. (3a*R,6*S**,7*S**,7a*S**)-7-Benzoyl-6-methyl-3,3a,6,7,7a-hexahydroisobenzofuran-1-one (13e).** The *major isomer* from IMDA reaction of **9e** was obtained as a colorless oil; R_f=0.23 (25% EtOAc in hexane); IR (film) 2967, 1767, 1678, 1226, 1177, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2H), 7.56–7.52 (m, 1H), 7.47–7.42 (m, 2H), 5.74 (ddd, J=10.0, 2.6, 2.6 Hz, 1H), 5.64 (ddd, J=10.4, 2.4, 2.4 Hz, 1H), 4.50 (dd, J=8.4, 8.4 Hz, 1H), 4.39 (dd, J=9.6, 6.0 Hz, 1H), 4.19 (dd, J=5.4, 5.4 Hz, 1H), 3.30–3.20 (m, 2H), 2.87–2.78 (m, 1H), 0.95 (d, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 177.6, 138.9, 132.7, 131.9, 128.5 (×2), 128.0 (×2), 125.3, 71.5, 44.2, 39.6, 34.6, 31.9, 18.6; MS (+ESI) m/z 535 ($2M+Na^+$, 100), 257 ($M+H^+$, 40); HRMS (+ESI) calcd for $C_{16}H_{16}O_3Na$ ($M+Na^+$), 279.0992; found, 279.0985.

4.7. General procedure for microwave-assisted tandem Wittig–IMDA cycloadditions

To a 10-mL pressurized process vial was added one of the 2,4-pentadienyl α-bromoacetates **14**–**16** (0.30 mmol), PPh_3 (0.36 mmol), 2,6-lutidine (0.39 mmol), and one of the α-oxo carbonyl compounds **17**–**19** in MeCN (4 mL). The loaded vial was then sealed with a cap containing a silicon septum, and put into the microwave cavity and heated at 180 °C for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and washed with 6% aqueous HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with EtOAc and petroleum ether (60–90 °C) to afford the adducts. The structures and yields are given in Scheme 3 and Table 3.

4.8. X-ray crystallographic structural determination of 12e, 10c, and 13d

The X-ray crystal structures of **12e**, **10c**, and **13d** are given in Figures 1–3 and the crystal data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 604672, CCDC 604671, and CCDC 604673, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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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.2006.06.039.

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