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PAPER

Tandem allylic oxidation–condensation/esterification catalyzed by silica gel: an expeditious approach towards antimalarial diaryldienones and enones from natural methoxylated phenylpropenes†

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A new one-pot strategy has been developed, wherein abundantly available methoxylated phenylpropenes are directly transformed into corresponding dienones (1,5-diarylpenta-2,4-dien-1-ones) and enones (chalcones and cinnamic esters) *via* allylic oxidation–condensation or allylic oxidation–esterification sequences. Preliminary antimalarial activity studies of the above synthesized diaryldienones and enones against *Plasmodium falciparum* (*Pf* 3D7) have shown them to be promising lead candidates for developing newer and economical antimalarial agents. In particular, two enones (**12b** and **13b**) were found to possess comparatively better activity (IC_{50} = 4.0 and 3.4 μM, respectively) than licochalcone (IC_{50} = 4.1 μM), a well known natural antimalarial compound.

Introduction

The utilization of abundantly available plant-based feedstocks for synthesis of value added compounds is one of the most cherished goals of contemporary organic synthesis.[1] In this context, it would be doubly beneficial if newer one-pot[2] approaches could be developed for direct conversion of such *natural synthons* into functionalized molecules.

For instance, phenylalkenes (C_6–C_2 to C_6–C_4 skeleton) are produced by a majority of plants for diverse roles including chemical defense and biosynthesis of other plant derivatives like flavonols and lignans *etc.*[3a] In particular, the phenylpropenes[3b] (C_6–C_3 skeleton) are valuable plant derived raw materials for synthesis/semi-synthesis of bioactive organic compounds. The majority of the phenylpropenes are obtained in high concentration from essential oil fractions of plant tissues.[3b] For instance, β-asarone (*cis*-2,4,5-trimethoxyphenyl-propene) and isosafrole (*trans*-3,4-dioxymethylenephenyl-propene) *etc.* are widely found in the essential oils of *Acorus calamus* and *Illicium religiosum*, respectively.[3a] Recently, it has been found that the *trans*-isomers of phenylpropenes, *e.g.* α-asarone, are safe[4a] for human consumption while *cis*- and allyl-isomers (*e.g.* , β-asarone and safrole) are mostly toxic.[4b] These revelations have adversely affected the economic demand of phenylpropene-rich essential oils.

Therefore, the development of newer *tandem oxidation strategies*[5] have generated considerable interest as they allow facile conversion of unfunctionalized raw materials into valuable oxygenated compounds. In this context, some attractive benzylic oxidation based C–C bond forming approaches have been disclosed.[5] However, to the best of our knowledge, a one-pot *tandem allylic oxidation*[6]*–condensation strategy enabling the conversion of natural phenylpropenes into various important α,β-unsaturated conjugated compounds has not yet been described*. For instance, 1,5-diarylpenta-2,4-dien-1-ones are valuable scaffolds having diverse applications in medicinal chemistry[7a] besides their use in optoelectronics, polychromatic flow cytometry and light harvesting energy cascade schemes.[7b] Similarly, the enones, *i.e.*, chalcones and cinnamic esters, represent another important class of α,β-unsaturated conjugated compounds having wide ranging utility in pharmaceutical and industrial domains.[8]

The 1,5-diarylpenta-2,4-dien-1-ones are generally obtained *via* condensation of cinnamaldehydes with acetophenones.[9] However, a number of substituted cinnamaldehydes are not commercially available and thus have to be synthesized involving additional reaction steps and isolation manipulations. In the case of cinnamic esters, though various useful synthetic protocols have been disclosed,[10] *to date the direct synthesis of cinnamic esters from readily available phenylpropenes has not been described*.

Herein, we disclose *two novel one-pot approaches* involving sequential allylic oxidation–condensation and allylic oxidation–esterification so as to afford the first direct conversion of readily available phenylpropenes into diaryldienones and enones.

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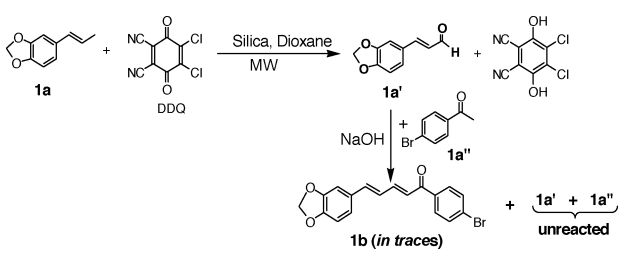
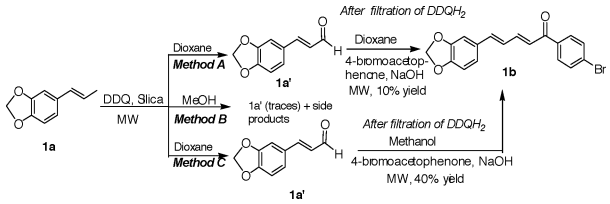
Results and discussion

In the course of our programme towards catalytic synthesis of biologically important phenolics,[11] we became interested in exploring a one-pot, two-step synthesis of α,β-unsaturated carbonyl compounds like 1,5 diarylpenta-2,4-dien-1-ones from readily available phenylpropenes *via* a sequential oxidation–condensation process. In this context, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) was chosen as the oxidizing agent (for the first step) due to its propensity for allylic oxidation[11e] of phenylpropenes (including their isomeric mixture, *i.e.*, {α, β, γ}) preferably under ultrasound/microwaves (MW). Thus, **1a** (3,4-dioxymethylene phenylpropene, 0.61 mmol) was initially treated with DDQ (2.3 eq.) under sonication or MW irradiation in the presence of silica gel (0.2 g) using dioxane as the solvent of choice over DCM or toluene *etc.* Interestingly, MW irradiation was found to provide the corresponding cinnamaldehyde (**1a′**) in shorter time (25 min) as compared to ultrasound (120 min). Subsequently, 4-bromoacetophenone (**1a″**, 1.7 eq.) and NaOH (2.5 eq.) were added to the same pot (for condensation) and the reaction mixture was further irradiated under MW irradiation for 20 min. Surprisingly, the above one-pot oxidation–condensation provided the expected 1-(4-bromophenyl)-5-(3,4-dioxymethylenephenyl)-penta-2,4-dien-1-one (**1b**) in only trace amounts while the initially formed cinnamaldehyde remained unreacted along with the 4-bromoacetophenone even after further MW irradiation for 40 min or more. Thereafter, it was hypothesized that presence of $DDQH_2$ in the reaction mixture (precipitated from the initial oxidation reaction, Scheme 1) might be hindering the subsequent base catalyzed condensation due to the competing reaction of $DDQH_2$ with NaOH. Consequently, the above reaction was conducted by adding 4-bromoacetophenone along with *an increased amount of NaOH* (4 eq.), after filtration of $DDQH_2$ from the reaction mixture and further irradiated under MW for 40 min. Interestingly, such an approach appeared promising as it afforded **1b** in 10% yield. In order to enhance the performance of the above condensation reaction, the use of a more polar solvent like methanol appeared advantageous as it has been known[9d–f] to shift the equilibrium towards condensation product, *i.e.*, α,β-unsaturated carbonyl compounds which are usually not completely soluble in such alcoholic solvents. However, when **1a** was oxidized with DDQ in methanol (in place of dioxane), the initial product, *i.e.*, cinnamaldehyde, was itself formed in trace amounts (Scheme 2). Consequently, this approach was not further taken up for the subsequent condensation step. As dioxane or methanol alone couldn't provide a compatible solvent system for one-pot oxidation, it appeared attractive to explore a mixture of these two solvents. Thus, it was found that addition of



Scheme 1

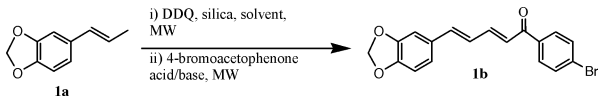


Scheme 2

some methanol (5 ml), 4-bromoacetophenone (1.7 eq.) and NaOH (4 eq.) to the same pot after the initial oxidation of **1a** in dioxane led to a comparatively improved reaction performance after 40 min of MW irradiation (**1b**, 40% yield, Scheme 2). It was evident from the above results that between the two individual steps of the one-pot oxidation–condensation sequence, the condensation reaction required careful selection of conditions as the initially formed $DDQH_2$ had to be filtered before addition of a base. In order to further explore suitable conditions for the above one-pot condensation, various other bases/acids were subsequently evaluated (Table 1). In particular, the acid catalyzed condensation step was conducted without filtration of $DDQH_2$. Surprisingly, the use of acetic acid as a solvent, even along with the catalytic amount of various strong acids like sulfuric acid, TFA (trifluoroacetic acid) and PTSA (*p*-toluenesulfonic acid), provided the expected **1b** in only trace amounts (Table 1, entries 4–6). Later on, it was decided to conduct the above one-pot condensation using thionyl chloride ($SOCl_2$) as an *in situ* source of HCl gas.[12] Thus, after the oxidation of **1a** into the respective cinnamaldehyde, methanol (5 mL), 4-bromoacetophenone (1.7 eq.) and $SOCl_2$ (0.5 mL) were added followed by shaking of the reaction mixture and irradiation under MW (40 min, 90 °C, 100 W) to provide the desired **1b** in 51% yield (Table 1, entry 7) even without the initial filtration of $DDQH_2$. Similarly, the above reaction was also conducted using various other sources of HCl like acetyl chloride and phosphoryl chloride; however, these were not found to be compatible as **1b** was obtained in reduced yields (Table 1, entries 8–9). Interestingly, the treatment of **1a** using the above optimized conditions under *conventional heating* provided lower reaction performance besides longer reaction time (12 h). In order to evaluate the substrate scope of the above methodology, various other methoxylated phenylpropenes (Table 2) were treated under the optimized conditions. It is apparent from Table 2 that the protocol was applicable for a facile one-pot synthesis of various methoxylated dienones from corresponding phenylpropenes (42–52% yield). In contrast, the phenylpropene possessing an electron withdrawing group (Table 2, entry 11) provided relatively lower reaction performance (17% yield). Further, the halo-substituted acetophenones (Table 2 entries 1–6, 8–9, 11) provided better reaction performance[13] towards formation of dienones as compared to unsubstituted or methoxy-substituted counterparts (Table 2, entry 7, 10).

The successful development of the above tandem synthesis of dienones (Table 2, **1–11b**) from phenylpropenes further inspired the possibility of converting these abundantly available raw materials into various other α,β-unsaturated carbonyl compounds like chalcones (enones). In particular, it appeared attractive to explore C═C oxidative cleavage of phenylpropenes (C_6–C_3 unit) followed by *in situ* condensation of the resulting benzaldehydes (C_6–C_1 unit) with acetophenones. Thus, β-asarone (**5a**) was treated with PDC (pyridinium dichromate, 3.5 eq.) in the presence of acetic acid

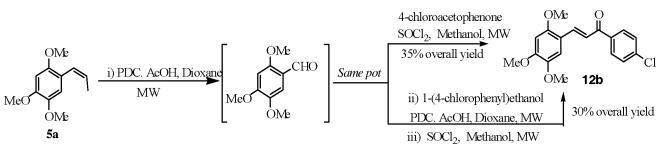
Table 1 Optimization data for tandem allylic oxidation–condensation of phenylpropene under MW irradiation[a]



Entry	Solvent	Base/acid	Amount of acid/base	Yield (%)[b]
1	Dioxane	NaOH	4 eq.	40
2	Dioxane	LiOH	1–4 eq.	27
3	Methanol	NaOH	4 eq.	traces
4	Acetic acid	H_2SO_4	2 eq.	traces
5	Acetic acid	TFA	2 eq.	traces
6	Acetic acid	PTSA	1 eq.	traces
7	Dioxane	$SOCl_2$	0.5 ml	51
8	Dioxane	CH_3COCl	0.5 ml	32
9	Dioxane	$POCl_3$	0.5 ml	20

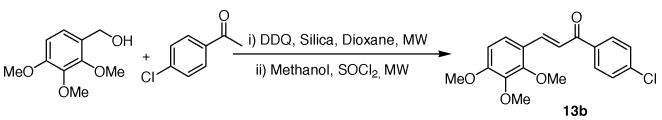
[a] CEM monomode microwave. [b] Isolated yield. General conditions: entries 3–9; **1a** (0.61 mmol), DDQ (1.41 mmol), silica gel (0.2 g), solvent (6 mL) were heated under MW irradiation (90 °C, 100 W) for 25 min; followed by addition of methanol (5 mL), 4-bromoacetophenone (0.95 mmol), acid/base and MW irradiation (90 °C, 100 W) for 40 min. In the case of entries 1–2; methanol (5 mL), 4-bromoacetophenone (0.95 mmol) and base were added after filtration of $DDQH_2$ from the first step while the rest of the conditions were the same.

(3 drops) in dioxane under MW irradiation to give the respective asaronaldehyde which was allowed to undergo one-pot condensation with 4-chloroacetophenone or 1-(4-chorophenyl)ethanol using methanol (5 mL) and $SOCl_2$ (0.5 mL) to afford facile access to the corresponding chalcone **12b** (*i.e.*, enone with C_6–C_3 skeleton) in 35 or 30% yield (Scheme 3).



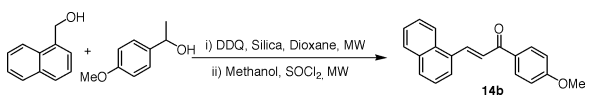
Scheme 3

Similarly, an analogous one-pot oxidation–condensation of benzylic alcohol with an acetophenone also proved to be feasible (41% overall yield, Scheme 4).



Scheme 4

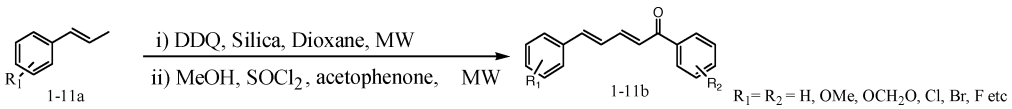
Inspired by above success, it was intriguing to explore a one-pot oxidation–condensation of various primary (1°) and secondary (2°) benzylic alcohols into corresponding chalcones, as such a strategy has recently generated much interest.[14] In this context, the use of DDQ as oxidizing agent in place of PDC proved beneficial as it prevented the over oxidation of 1° benzyl alcohol (1-naphthyl methanol) into acids while simultaneously affording an attractive approach for one-pot, two-step synthesis of chalcone (**14b**, 30% yield) from the respective benzyl alcohols (Scheme 5). The above protocol assumes significance as such a one-pot conversion of

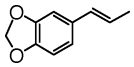
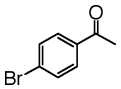
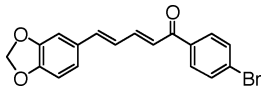
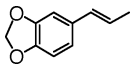
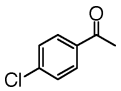
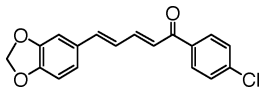
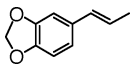
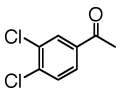
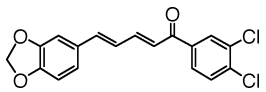
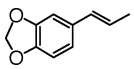
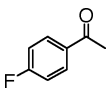
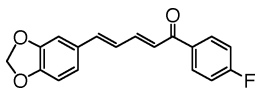
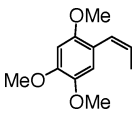
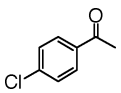
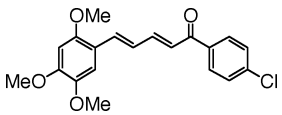
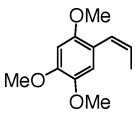
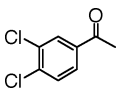
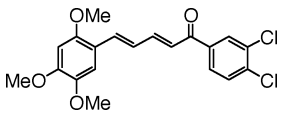
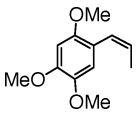
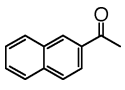
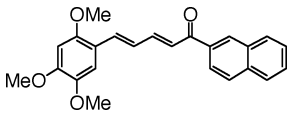
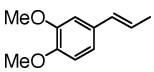
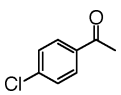
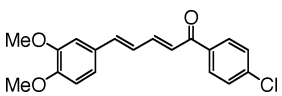
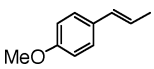
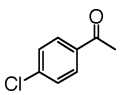
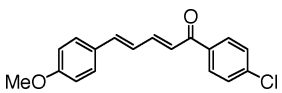
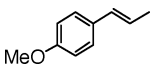
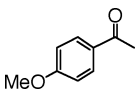
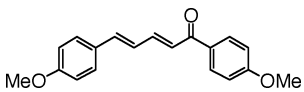
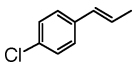
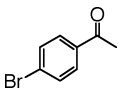
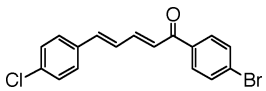


Scheme 5

benzylic alcohols into chalcones is an important component of C–C bond formation by hydrogen autotransfer strategies.[14] Having developed a tandem synthesis of 1,5-diarylpenta-2,4-dien-1-ones and chalcones *via* allylic/benzylic oxidation–condensation, it was interesting to explore if an analogous sequential allylic oxidation–esterification methodology could provide a hitherto scarce direct access to immensely important cinnamic esters from corresponding phenylpropenes. Moreover, the above proposition appeared particularly attractive as DDQ has also earlier been reported to promote esterification of cinnamaldehydes.[10c] As a proof of concept, **1a** was treated with DDQ (2.1 eq.) under MW irradiation in the presence of silica gel using dioxane as solvent. Thereafter, methanol was added to above reaction mixture and further irradiated under MW for 30 min. Gratifyingly, the above reaction upon work-up and column purification provided a product whose NMR (^1H and ^{13}C) and mass investigations confirmed it to be the corresponding methyl cinnamate (**15b**, 22% yield). Encouraged by the above result, the same reaction was also conducted by replacing silica gel with various other solid acid catalysts like Amberlyst, montmorillonite *etc.*; however, none of these proved beneficial. In order to further increase the yield of the above reaction, it was decided to add DDQ (1.8 eq.) in the second step of the reaction (esterification) as well. Interestingly, such an approach proved fruitful, as the desired **15b** was obtained in an enhanced 64% yield (Table 3, entry 15). Significantly, the above one-pot approach offers an attractive alternative to the conventional two-step protocol,[10c,11e] wherein initial column purification of cinnamaldehyde (77% yield), obtained by DDQ-assisted oxidation of phenylpropene (**1a**) followed by its esterification using MeOH/DDQ/silica gel (80% yield) provided the desired **15b** in overall 62% yield. Later on, the optimized conditions were also successfully applied on various other phenylpropenes (Table 3, entries 16–22). Interestingly, the protocol allowed the direct synthesis of diverse cinnamic esters (**15–20b**) and **21b** from methoxylated phenylpropenes (α/β-isomer) (**15–20a**) and the γ-isomer (**21a**), respectively, while the unsubstituted phenylpropene afforded the desired product in only trace amounts (Table 3, entry 22).

Table 2 Direct synthesis of aryl-substituted dienones from phenylpropenes *via* tandem allylic oxidation–condensation[a]

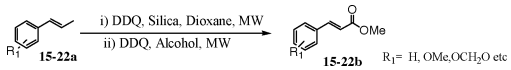


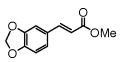
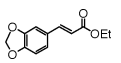
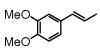
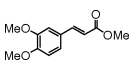
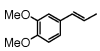
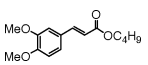
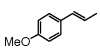
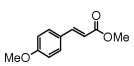
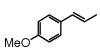
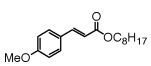
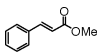
Entry	Phenylpropene	Acetophenone	Product [b]	Yield (%)[b]
1				51
2				49
3				52
4				46
5				45
6				48
7				42
8				48
9				50
10				46
11				17

[a] CEM monomode microwave. [b] Isolated yield. General conditions: phenylpropene (0.61 mmol), DDQ (1.41 mmol), silica gel (0.2 g), dioxane (6 mL) were heated under MW irradiation (90 °C, 100 W) for 25 min; followed by addition of acetophenone (0.95 mmol), methanol (5 mL), $SOCl_2$ (0.5 mL) and MW irradiation (90 °C, 100 W) for 40 min. The structures of all compounds were confirmed by NMR (^1H and ^{13}C) and HRMS analysis.

Having developed a one-pot tandem synthesis of a panel of diaryldienones and enones (chalcones and cinnamic esters), we were keen to evaluate their biological activities. In particular, we were interested in exploring the antiplasmodial[15] profiles of the above synthesized diaryldienones and enones. Such α,β-unsaturated compounds have generated immense interest as antimalarial agents since the discovery of Licochalcone,[16] a naturally occurring antimalarial chalcone (IC_{50}: 4.1 μM). However, *to the best of our knowledge, a systematic evaluation of the antimalarial activity of diaryldienones has not been previously described*,[17] even as these

Table 3 Direct synthesis of cinnamic esters from phenylpropenes *via* tandem oxidation–esterification under MW irradiation[a]



Entry	Phenylpropene	Alcohol	Product [b]	Yield (%)[b]
15		MeOH		64 (62)[c]
16		EtOH		65
17		MeOH		62
18		n-BuOH		34
19		MeOH		47
20		$CH_3(CH_2)_6CH_2OH$		51
21		MeOH	**15b**	66
22		MeOH		traces

[a] CEM monomode microwave. [b] Yield of pure isolated product (single run). General conditions: phenylpropene (0.61 mmol), DDQ (1.18 mmol), silica gel (0.2 g), dioxane (6 mL) were heated under MW irradiation (90 °C, 100 W) for 25 min; followed by addition of the respective alcohol (5 mL), DDQ (1.1 mmol) and MW irradiation (100 °C, 110 W) for 30 min. The structure of all compounds was confirmed by NMR (^{1}H and ^{13}C) analysis. [c] Overall yield of conventional two-step reaction involving column purification of reaction intermediate (cinnamaldehyde).

compounds have been evaluated for antimicrobial activities[9b,f] as well as model scaffolds in establishing structure–activity relationships (SAR) of related pharmacophores.[9a–c] Consequently, the above synthesized diaryldienones and enones were subjected to SYBR green based screening for inhibition of the growth of *Plasmodium falciparum* in blood stage culture. In order to assess the potential of these molecules to provide hope against the menace of chloroquine resistance, we have screened them against chloroquine sensitive (*Pf* 3D7) as well as chloroquine resistant (*Pf* Dd2 and *Pf* INDO) strains of the malarial parasite. Interestingly, these preliminary studies (Table 4) indicated for the first time the potential of 1,5-diarylpenta-2,4-dien-1-ones as promising lead scaffolds for antimalarial activity. Interestingly, an optimal balance in electron densities at rings **A** and **B** of the diaryldienones was found to be mandatory for enhanced antimalarial activity. Thus, **8b**, possessing 3,4-dimethoxy substitution on ring **A** (Table 4, IC_{50}: 22.5 μM) displayed better activity against *P. falciparum* (3D7 strain) in comparison to diaryldienones possessing 4-methoxy (**9b**, Table 4, IC_{50}: 88.0 μM) or 3,4-dioxymethylene (**1–4b**, Table 4, IC_{50}: >50.0 μM) substitution. However, a further increase in electron density on ring **A** (*i.e.*, 2,4,5-trimethoxy substitution, **5b**, Table 4, IC_{50}: 22.5 μM) led to over seven-fold increase in therapeutic index with retention of potency against *P. falciparum* (Table 5). Similarly, the presence of an electron withdrawing halogen group on ring **B** (**4b**, **5b**, **8b**, Table 4) generally conferred increased activity against chloroquine resistant strains and increased solubility in comparison to diaryldienones possessing an unsubstituted or methoxy-substituted ring **B** (**7b**, **10b**, Table 4). Further, the presence of multiple electron withdrawing substituents (3,4-dichloro-substituted **B** ring, **6b**, Table 4, IC_{50}: >50.0 μM) did not lead to significant activity in comparison to their monosubstituted counterparts[15a] (**5b**, Table 4, IC_{50}: 22.5 μM). On the other hand, the enones **12b** and **13b**, *i.e.*, trimethoxy-substituted chalcones (Scheme 3 and 4), displayed the most potent antimalarial activity (IC_{50} = 4.0 and 3.4 μM, respectively) which compares well with

Table 4 Antimalarial activity of diaryldienones (**1b–11b**) and enones (**12b–14b**) against *P. falciparum* (3D7, Dd2 and Indo strains)

	IC_{50} (μM)		
Compound	Pf 3d7	P*f* Dd2	P*f* INDO
1b	>50.0	74.0	73.0
2b	>50.0	73.0	64.0
3b	>50.0	>100.0	>100.0
4b	>50.0	17.0	29.0
5b	22.5	36.0	31.5
6b	>50.0	78.0	53.0
7b	>50.0	47.0	31.0
8b	22.5	25.0	26.0
9b	88.0	ND	ND
10b	>25.0	ND	>25.0
11b	>25.0	ND	>25.0
12b	4.0	6.8	10.0
13b	3.4	6.8	16.3
14b	16.5	18.2	>20.0
Chloroquine	40.0 nM	170.0 nM	500.0 nM

Table 5 Resistance and therapeutic indices of some potent dienones and enones

Compound	Resistance index		Therapeutic index	
	IC_{50}Indo/ IC_{50}3D7	IC_{50}Dd2/ IC_{50}3D7	IC_{50}HeLa/ IC_{50}3D7	IC_{50}L929/ IC_{50}3D7
5b	1.4	1.7	>4.5	1.9
8b	1.1	1.1	0.6	2.0
12b	2.5	1.7	9.0	8.3
13b	4.8	2.0	12.4	29.4
14b	>1.1	1.1	4.7	2.2
Chloroquine	12.5	4.3	>100	>100

that of Licochalcone (IC_{50} = 4.1 μM), a natural antimalarial.[16] Interestingly, the chalcone **14b** with a methoxy group on ring **B** exhibited moderate potency (IC_{50}: 16.5 μM) against *Pf* 3D7 (also see the ESI for % growth inhibition data of **1b–14b**†). Moreover, the cinnamic esters (**15b–22b**) along with starting materials like β-asarone[16] (Scheme 3, **5a**) and intermediate 2,4,5-trimethoxybenzaldehyde were found to display comparatively lower antimalarial activities (IC_{50}: >100.0 μM) than **12b** (see the ESI†).

Against a Resistance Index (IC_{50} Dd2/IC_{50} 3D7 or IC_{50} INDO/IC_{50} 3D7) of 4.3 or 12.5 for chloroquine, these indices (IC_{50} Dd2/IC_{50} 3D7) for the potent dienones and enones (*i.e.*, chalcones) (**5b**, **8b**, **12b**, **13b** and **14b**) were found to be 1.7, 1.1, 1.7, 2.0 and 1.1, respectively (Table 5).

Further, the therapeutic index of the most active compound, **13b** (IC_{50} up to 3.4 μM), was found to be up to 29.4 against two mammalian cell lines, *viz*. HeLa and fibroblast L929 (Table 5), thereby indicating that **13b** is also relatively non-toxic compared to the other compounds (**5b**, **8b**, **12b**, **14b**). The above data suggest that the selectivity is not high for those molecules that exhibit high IC_{50} values (*e.g.*, **5b**, **8b**, and **14b**) against *P. falciparum*. In contrast, molecules with low IC_{50} values (*e.g.* **12b** and **13b**) have a considerably better selectivity index. This indicates that lower potency abrogates selectivity while high potency enhances selectivity.

Conclusion

In summary, we have developed the *first direct synthesis* of biologically important diaryldienones as well as enones (chalcones and cinnamic esters) from abundantly available methoxylated phenylpropenes *via* tandem allylic oxidation–condensation or allylic oxidation–esterification sequences, respectively. Although the above one-pot strategies provided a moderate overall yield of dienones and enones from the respective phenylpropenes, these compare favorably with a majority of the conventional multistep approaches which involve tedious isolation/purification of reaction intermediates. In addition, the developed protocol offers several other inherent advantages, *viz.* use of readily available and economical substrates besides demonstrating the feasibility of developing economical antimalarial compounds from abundantly available hydrocarbon feedstocks. Importantly, the preliminary antimalarial evaluation studies of the above synthesized 1,5-diarylpenta-2,4-dien-1-ones have shown them to be promising lead candidates for developing newer antimalarial agents while one of the enones, **13b** (1-(4-chlorophenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one), was found to be a potent antimalarial compound with increased potency as compared to the well known bioactive licochalcone. Further efforts to extend the developed protocol towards heterocyclic analogues and their detailed antimalarial investigations are currently in progress.

Experimental section

General procedure

β-Asarone (*cis*-2,4,5-trimethoxyphenylpropene) and isosafrole (*trans*-3,4-dioxymethylenephenylpropene) were purified from their respective natural essential oils following our earlier reported procedure.[18] The solvents used for isolation/purification of the compounds were obtained from commercial sources (Merck) and used without further purification. DDQ, PDC and thionyl chloride were reagent grade (Merck) and used as supplied. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. HRMS-ESI spectra were determined using a micromass Q-TOF ultima spectrometer. A CEM Discover© focused microwave (2450 MHz, 300 W) was used wherever mentioned. The temperature of the reactions in microwave experiments was measured by an inbuilt infrared temperature probe that determined the temperature on the surface of the reaction flask. The sensor is attached in a feedback loop with an on-board microprocessor to control the temperature rise rate. In the case of conventional heating in an oil bath, the temperature of the reaction mixture was monitored by an inner thermometer.

Representative procedure for synthesis of 1b *via* one-pot oxidation–condensation of 1a with 1a″ using DDQ in the presence of $SOCl_2$–*MeOH* under MW irradiation

To a stirred mixture of 3,4-dioxymethylene phenylpropene (**1a**, 0.1 g, 0.61 mmol), silica gel (0.2 g) and dioxane (6 mL), DDQ (0.32 g, 1.41 mmol) were added and the reaction mixture irradiated under the focused microwave system in parts (100 W, 90 °C) for 25 min. Subsequently, 4-bromoacetophenone (0.95 mmol), methanol (5 mL) and $SOCl_2$ (0.5 mL) were added to the above reaction mixture and further irradiated under the focused microwave system (100 W, 90 °C) for 40 min. The reaction mixture was cooled, filtered and shaken well with methanol (5 mL) and vacuum evaporated. To the obtained solid, DCM (10 mL) was added and the solution was filtered over alumina. The residue obtained after evaporating DCM was further purified by column chromatography on silica gel (60–120 mesh size) using hexane–ethylacetate (9.7 : 0.3) to give **1b** (0.113 g, 51% yield).

1-(4-Bromophenyl)-5-(3,4-dioxymethylenephenyl)-penta-2,4-dien-1-one (1b, Table 2). Yellow solid, m.p. 122–125 °C, IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1652, ^{1}H NMR δ (CD_3COCD_3, 300 MHz), 7.98 (2H, d, *J* = 7.8 Hz), 7.82 (2H, d, *J* = 7.8 Hz), 7.62–7.55 (1H, m), 7.23–7.08 (5H, m), 6.91 (1H, d, *J* = 7.8 Hz), 6.07 (2H, s); ^{13}C NMR δ (75.4 MHz, $CDC1_3$), 189.6, 149.3, 148.8, 146.0, 142.6, 137.5, 132.2, 131.0, 130.3, 128.0, 125.5, 124.4, 123.8, 109.0, 106.3 and 101.9. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{18}H_{13}O_3Br$, calculated 357.0120; observed 357.0156.

The above procedure was also followed for the synthesis of various other 1,5-diarylpenta-2,4-dien-1-ones (Table 2, entries

2–11). The structures of corresponding products were confirmed by NMR (^{1}H and ^{13}C) (see the ESI for details†).

Representative procedure for synthesis of 1-(4-chlorophenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (12b) *via* one-pot oxidative cleavage–condensation of β-asarone (5a) with (i) 4-chloroacetophenone or (ii) 1-(4-chlorophenyl)ethanol under MW irradiation (Scheme 3)

To a stirred mixture of 2,4,5-trimethoxy phenylpropene (β-asarone, **5a**, 0.1 g, 0.48 mmol), acetic acid (3 mL) and dioxane (6 mL), PDC (0.36 g, 0.95 mmol) was added and the reaction mixture irradiated under the focused microwave (MW) system in parts (200 W, 150 °C) for 20 min. Subsequently, 4-chloroacetophenone (0.12 g, 0.86 mmol), methanol (5 mL) and $SOCl_2$ (0.5 mL) were added to the above reaction mixture and further irradiated under MW irradiation (100 W, 90 °C) for 40 min. The reaction mixture was cooled, filtered and shaken well with methanol (5 mL) and vacuum evaporated. The residue was purified by column chromatography on silica gel (60–120 mesh size) using hexane–ethylacetate (9.7 : 0.3) to give **12b** (0.055 g, 35% yield).

1-(4-Chlorophenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one[15a] (Scheme 3, 12b). Yellow solid, m.p. 141–142 °C, IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1653, ^{1}H NMR δ (300 MHz, $CDCl_3$); 8.12 (1H, d, J = 15.9 Hz), 7.97 (2H, d, J = 8.6 Hz), 7.49 (2H, d, J = 8.4 Hz), 7.45 (1H, d, J = 16.2 Hz), 7.13 (1H, s), 6.54 (1H, s) 3.96 (3H, s), 3.92 (6H, s); ^{13}C NMR δ (75.4 MHz, $CDCl_3$); 190.18, 155.2, 155.1, 143.7, 141.0, 139.0, 137.5, 130.2, 129.1, 120.1, 115.7, 112.0, 97.2, 57.0, 56.7 and 56.4.

In the second case (*i.e.*, use of 1-(4-chlorophenyl)ethanol in place of 4-chloroacetophenone), the procedure was the same as above for the first step. However, after the initial oxidative cleavage of **5a**, 1-(4-chlorophenyl)ethanol (0.15 g, 0.95 mmol), PDC (0.18 g, 0.47 mmol), acetic acid (3 mL) and dioxane (3 mL) were added to the same pot and the reaction mixture irradiated under MW irradiation in parts (200 W, 150 °C) for 20 min. Subsequently, methanol (5 mL) and $SOCl_2$ (0.5 mL) were added to the above reaction mixture and further irradiated under the focused microwave system (100 W, 90 °C) for 40 min. The reaction mixture was cooled, filtered and shaken well with methanol (5 mL) and vacuum evaporated. The residue was purified by column chromatography on silica gel (60–120 mesh size) using hexane–ethylacetate (9.7 : 0.3) to give **12b** (0.047 g, 30% yield) whose spectral data (^{1}H and ^{13}C NMR) matched well with that obtained above.

Representative procedure for synthesis of 1-(4-chlorophenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (13b, Scheme 4) *via* one-pot oxidation of (1-(2,3,4-trimethoxyphenyl)methanol and condensation with 4-chloroacetophenone

Synthesis of 1-(4-chlorophenyl)-3-(2,3,4-trimethoxyphenyl)-prop-2-en-1-one (13b, Scheme 4). To a stirred mixture of (1-(2,3,4-trimethoxyphenyl)methanol (0.1 g, 0.47 mmol), silica gel (0.2 g) and dioxane (6 mL), DDQ (0.139 g, 0.61 mmol) was added and the reaction mixture irradiated under the focused microwave system in parts (100 W, 90 °C) for 25 min. Subsequently, 4-chloroacetophenone (0.087 g, 0.56 mmol), methanol (5 mL) and $SOCl_2$ (0.5 mL) were added to the above reaction mixture and further irradiated under MW irradiation (100 W, 90 °C) for 40 min. The reaction mixture was cooled, filtered and shaken well with methanol (5 mL) and vacuum evaporated. The residue was purified by column chromatography on silica gel (60–120 mesh size) using hexane–ethylacetate (9.7 : 0.3) to give **13b** (0.062, 41% yield).

1-(4-Chlorophenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (13b, Scheme 4). Yellow solid, m.p. 86–89 °C, ^{1}H NMR δ (300 MHz, CD_3COCD_3); 8.13 (2H, d, J = 8.5 Hz), 8.07 (1H, d, J = 15.7 Hz), 7.76 (1H, d, J = 15.7 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.58 (2H, d, J = 8.5 Hz), 6.88 (1H, d, J = 8.8 Hz), 3.94 (3H, s), 3.91 (3H, s), 3.84 (3H, s); ^{13}C NMR δ (75.4 MHz, $CDCl_3$); 189.9, 156.5, 154.3, 142.9, 141.1, 139.3, 137.4, 130.3, 129.3, 124.1, 122.3, 121.2, 108.2, 61.8, 61.3 and 56.5. HRMS-ESI: m/z $[M + H]^+$ for $C_{18}H_{17}O_4Cl$, calculated 333.0888; observed 333.0886

Representative procedure for synthesis of chalcones from corresponding alcohols *via* one-pot oxidation–condensation

Synthesis of 1-(4-methoxyphenyl)-3-(1-naphthyl)prop-2-en-1-one (14b, Scheme 5). To a stirred mixture of (1-(naphthyl)methanol (0.1 g, 0.63 mmol), 1-(4-methoxyphenyl)ethanol (0.14 g, 0.94 mmol), silica gel (0.2 g) and dioxane (6 mL), DDQ (0.46 g, 2.02 mmol) were added and the reaction mixture irradiated under the focused microwave system in parts (100 W, 90 °C) for 25 min. Subsequently, methanol (5 mL) and $SOCl_2$ (0.5 mL) were added to the reaction mixture and further irradiated under the focused microwave system (100 W, 90 °C) for 40 min. The reaction mixture was cooled, filtered and shaken well with methanol (5 mL) and vacuum evaporated. To the obtained solid, DCM (10 mL) was added and the solution filtered over alumina. The residue obtained after evaporating the DCM was further purified by column chromatography on silica gel (60–120 mesh size) using hexane–ethylacetate (9.7 : 0.3) to give **14b** (0.07 g, 30% yield).

1-(4-Methoxyphenyl)-3-(1-naphthyl)prop-2-en-1-one[15b] (14b, Scheme 5). Yellow solid, m.p. 127–133 °C, IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1656, ^{1}H NMR δ (300 MHz, $CDCl_3$); 8.72 (1H, d, J = 15.3 Hz), 8.31 (1H, d, J = 8.4 Hz), 8.14 (2H, d, J = 7.6 Hz), 7.95–7.90 (3H, m), 7.70 (1H, d, J = 15.3 Hz), 7.65–7.50 (3H, m), 7.05 (2H, d, J = 8.4 Hz), 3.92 (3H, s); ^{13}C NMR δ (75.4 MHz, $CDCl_3$); 188.9, 163.9, 140.9, 133.7, 132.6, 131.8, 131.0, 130.9, 130.6, 128.7, 127.3, 126.7, 125.9, 125.4, 124.9, 123.9, 114.3 and 55.9.

Optimized procedure for synthesis of methyl-3-(3,4-dioxymethylenephenyl)propenoate (15b) *via* one-pot oxidation–esterification of 3,4-dioxymethylene phenylpropene (1a) using DDQ, silica gel, dioxane–methanol under MW irradiation (Table 3, entry 15)

To a stirred mixture of 3,4-dioxymethylene phenylpropene (**1a**, 0.1 g, 0.61 mmol), silica gel (0.2 g) and dioxane (6 mL), DDQ (0.27 g, 1.18 mmol) was added and the reaction mixture irradiated under the focused microwave system in parts (100 W, 90 °C) for 25 min. To the above reaction mixture methanol (5 mL) and DDQ (0.25 g, 1.10 mmol) were added and further irradiated under the focused microwave system (110 W, 100 °C) for 30 min. The reaction mixture was cooled, filtered and vacuum evaporated. To the obtained solid, DCM (10 mL) was added and the solution filtered over alumina. The residue was purified by column chromatography on silica gel (60–120 mesh size) possessing a

thin bed of alumina using hexane–ethylacetate (9.7 : 0.3) to give methyl-3-(3,4-dioxymethylenephenyl)-propenoate (**15b**, 0.081 g, 64% yield).

Methyl-3-(3,4-dioxymethylenephenyl)propenoate (15b, Table 3). White solid, m.p. 67–68 °C, ^{1}H NMR δ ($CDCl_3$, 300 MHz), 7.59 (1H, d, J = 15.9 Hz), 6.99 (1H, s), 6.95 (1H, d, J = 8.0 Hz), 6.78 (1H, d, J = 8.0 Hz), 6.26 (1H, d, J = 15.9 Hz), 5.97 (2H, s), 3.77 (3H, s); ^{13}C NMR δ (75.4 MHz, $CDC1_3$), 167.9, 150.0, 148.7, 144.9, 129.2, 124.8, 116.1, 108.9, 106.9, 101.9 and 51.9. HRMS-ESI: m/z [M + H]$^+$ for $C_{11}H_{10}O_4$, calculated 207.0651; observed 207.0673.

The above procedure was also followed for synthesis of various other cinnamic esters (Table 3, entries 16–22). The structures of the corresponding products were confirmed by NMR (^{1}H and ^{13}C) and HRMS (see the ESI for details†).

Measurement of inhibition of *P. falciparum* growth in culture

In this study, chloroquine sensitive 3D7 and chloroquine resistant Dd2 and INDO strains of *P. falciparum* were used in *in vitro* culture. Parasite strains were cultivated by the method of Trager and Jensen[19] with minor modifications. Cultures were maintained in fresh O$^+$ human erythrocytes at 4% hematocrit in complete medium (RPMI 1640 with 0.2% sodium bicarbonate, 0.5% Albumax, 45 mg L^{-1} hypoxanthine and 50 mg L^{-1} gentamicin) at 37 °C under reduced O_2 (gas mixture 5% O_2, 5% CO_2, and 90% N_2). Stock solutions of chloroquine were prepared in water (milliQ grade) and test compounds were dissolved in DMSO. All stocks were then diluted with culture medium to achieve the required concentrations (in all cases the final concentration contained 0.4% DMSO, which was found to be non-toxic to the parasite). Drugs and test compounds were then placed in 96-well flat-bottom tissue culture grade plates to yield triplicate wells with drug concentrations ranging from 0 to 10^{-4} M in a final well volume of 100 µL. Chloroquine was used as a positive control in all experiments. Parasite culture was synchronized at ring stage with 5% sorbitol. Synchronized culture was aliquoted to a drug-containing 96-well plate at 2% hematocrit and 1% parasitemia. After 48 h of incubation under standard culture conditions, plates were harvested and read by the SYBR Green I fluorescence-based method[20] using a 96-well fluorescence plate reader (Victor, Perkin Elmer), with excitation and emission wavelengths at 497 and 520 nm, respectively. The fluorescence readings were plotted against drug concentration, and IC_{50} values obtained by visual matching of the drug concentration giving 50% inhibition of growth.

Measurement of cytotoxic activity against mammalian cell lines in culture

Animal cell lines (HeLa and fibroblast L929) were used to determine drug toxicity by using MTT assay for mammalian cell viability assay as described by Mosmann [21] using HeLa and fibroblast L929 cells cultured in complete RPMI containing 10% fetal bovine serum, 0.2% sodium bicarbonate, 50 µg ml^{-1} gentamycin. Briefly, cells (10^4 cells/200 µL/well) were seeded into 96-well flat-bottom tissue-culture plates in complete culture medium. Drug solutions were added after overnight seeding and incubated for 24 h in a humidified atmosphere at 37 °C and 5% CO_2. DMSO (final concentration 10%) was added as +ve control. An aliquot of a stock solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (5 mg mL^{-1} in 1× phosphate-buffered saline) was added at 20 µL per well, and incubated for another 4 h. After spinning the plate at 1500 RPM for 5 min, supernatant was removed and 100 µL of the stop agent DMSO was added to each well. Formation of formazon, an index of growth, was read at 570 nm and IC_{50} values were determined by analysis of dose–response curves. Therapeutic index was calculated as IC_{50} mammalian cell/IC_{50} P*f*3D7.

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