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Synthesis of Poly-substituted Hydroquinolines Employing Lactic Acid as a Robust Catalyst through the Diastereoselective, One-pot Eight-component Reaction

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With the aim of developing an efficient and eco-friendly method for a diastereoselective synthesis of dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] derivatives, a one-pot pseudo-eight-components reaction between arylamines, aromatic aldehydes and Meldrum's acid was performed in the presence of lactic acid as a catalyst. The salient aspects of this protocol are operational simplicity, facile product separation, a cheap and eco-friendly catalyst, clean reaction conditions, absence of any hazardous organic solvent and moderate to high yields.

Keywords: Diastereoselective, Dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)], Pseudo-eight-components reaction, Meldrum's acid, Lactic acid

INTRODUCTION

Tetrahydroquinoline nucleus is a remarkable series of privileged N-heterocyclic scaffolds identified in a broad scope of biologically and pharmacologically active building blocks [1-4]. A number of them have biological activities such as anti-bacterial, neuroprotectant and anti-arrhythmic, *etc.* [5,6]. The fragments of tetrahydroquinoline are vital analogues for chemists generally due to their widespread distribution of natural products and medicinal agent [7-12].

In recent times, Meldrum's acid has been frequently utilized in the design of reactions with numerous constructions of carbon-carbon bonds owing to its high acidity (pKa 4.83) [13], steric rigidness and remarkable orientation to regenerate acetone [14]. Spirocyclic building blocks containing Meldrum's acid units are valued as bioactive natural products and synthetic drugs possessing a diverse range of pharmacological activities and also are the starting materials for the synthesis of exotic amino acids which are employed to improve the physical properties and biological activities of peptides, peptidomimetics, and proteins [15-19]. Accordingly, new strategies for the synthesis of a highly functionalized spiro ring system with a Meldrum's acid unit have been of a great interest [20-24].

Multicomponent reactions (MCRs) furnish an opportunity for the condensation of more than two starting materials in a one-pot function, the rapid assembly of complex molecular target skeletons via multicomponent the synchronous formation of two or more bonds, correspondent to the domino principle [25]. Outstretching a MCR-based protocol is of high urgency for the synthesis of pharmacological scaffolds due to the high adequacy of MCR in producing compounds with higher versatility and lower need to the crude chemicals [26-29].

Over the last decade, there has been augmenting emphasis on the use of biodegradable organocatalysts without any metal atom for designing multi-component reactions and the synthesis of complex molecular motifs. In this regards, the increasing of modern and versatile catalysts is favorable for chemists [30]. Lactic acid, shown in Fig. 1, is an organic scaffold with chemical formula $C_3H_6O_3$ which is classified as a α-hydroxy acid. It is constructed when glucose is broken and oxidized in human cells. Lactic acid is primarily derived from milk products, such as koumiss,

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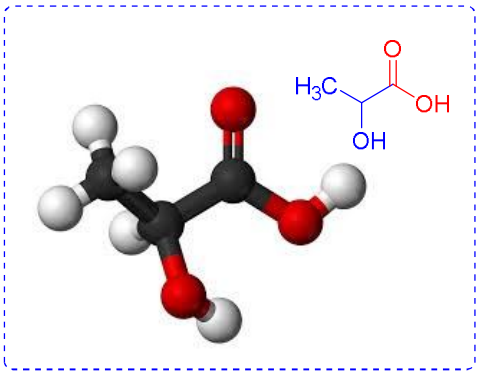
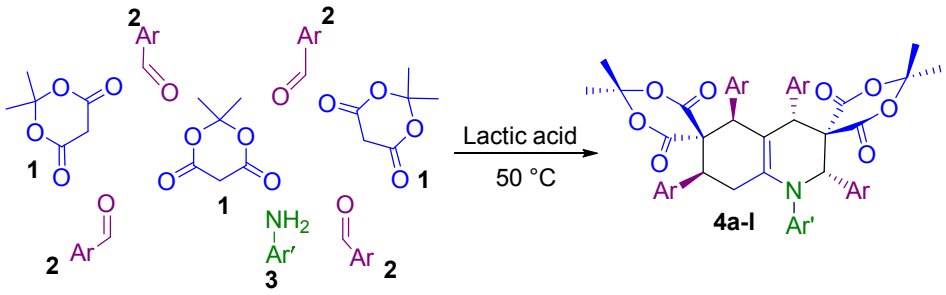


Fig. 1. Structure of lactic acid.



Scheme 1. Synthesis of dispirohydroquinolines *via* a one-pot eight-component reaction

laban, yogurt, kefir and some cottage cheeses [31].

As our continuous interest and endeavors in exploring MCRs as efficient tools in the synthesis of spiro and heterocyclic compounds [32-38], we report herein a pseudo eight-component protocol for diastereoselective synthesis of dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] derivatives using arylamines, aromatic aldehydes, and Meldrum's acid as starting materials in the presence of lactic acid as a readily available and green catalyst (Scheme 1).

RESULTS AND DISCUSSION

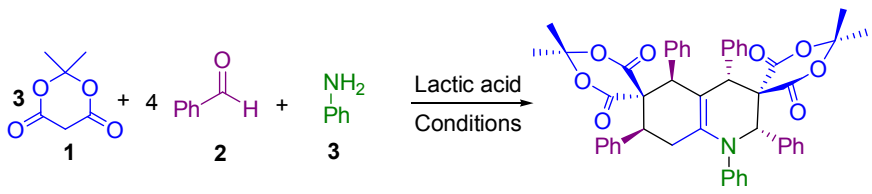
The optimization of reaction conditions was initiated by investigating the one-pot, pseudo-eight-component reaction between Meldrum's acid, benzaldehyde and aniline under lactic acid catalysis (Table 1). At first, the effect of the amount of lactic acid on the reaction was evaluated.

According to the data in Table 1, as the loading of lactic acid increased to 0.5 ml, the yield of (4a) increased to 87%. However, no increase in the yield was found as excessive lactic acid was used (Table 1, entry 4). In the next step, screening of the solvents such as MeOH and EtOH did not show the desired products in a satisfactory yield indicating that lactic acid is the most suitable reaction media.

Finally, to investigate the reaction temperature, the model reaction was carried out using 0.5 ml of the catalyst at different temperatures. It was found that 50 °C is an efficient temperature in terms of reaction time and the yield obtained (Table 1, entry 3). The product 4a was obtained in 87% yield (Table 1, entry 3) under various parameters such as the amount of catalyst, solvent and temperature.

With the optimized reaction conditions in hand, in order to further expand the substrate scope of the reaction, other aldehydes and arylamines were tested. As shown in Table 2, the reaction can be performed with both electron-

Table 1. Optimization of Reaction Conditions for the Synthesis of 4a



Entry	Temperature (°C)	Catalyst (ml)	Solvent	Time (h)	Isolated yield (%)
1	50	0/1		24	51
2	50	0/3	-	22	63
3	**50**	**0/5**	-	**18**	**87**
4	50	0/6	-	18	86
5	50	0/5	MeOH	23	67
6	50	0/5	EtOH	24	64
7	50	0/5	CH_3CN	21	72
8	r.t	0/5	-	32	76
9	40	0/5	-	29	78
10	60	0/5	-	17	82

withdrawing and electron-donating groups on the aldehyde aromatic rings and arylamines with the corresponding products in satisfied yields. The structures of some compounds were established from their IR, ^{1}H NMR and ^{13}C NMR.

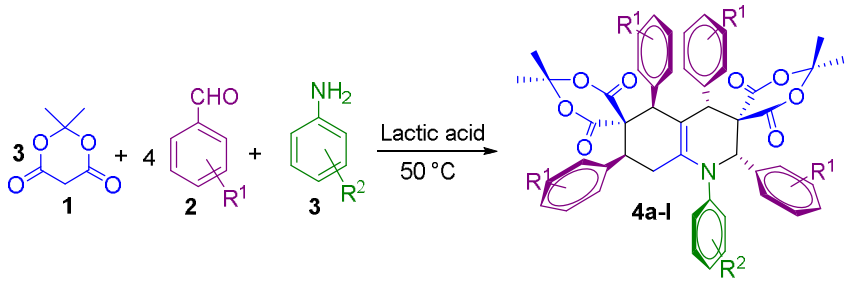
A part of the ^{1}H NMR spectrum of 4a is shown in Fig. 2. ^{1}H NMR of the compound 4a is as follows: compound 4a exhibited four singlets at δ 0.31, 0.33, 0.55 and 0.58 ppm for methyl groups of Meldrum's acid ring, a doublet of doublet at δ 2.58 ppm for H′-8′, a multiplet at chemical shift range of δ 2.64-2.71 ppm for H″-8′, a doublet of doublet at δ 3.97 ppm for H-7′, two singlets at δ 4.60 ppm and 4.63 ppm for H-4′ and H-5′, and a singlet at δ 5.21 ppm for H-2′.

In addition, the stereochemistry was determined by comparison of spectroscopic data of some products with those of authentic samples (Table 3).

A plausible mechanistic pathway for the formation of dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] is shown in Scheme 2.

Benzylidene I result from the initial Knoevenagel condensation between aldehyde 2 and Meldrum's acid 1 [39] and subsequent decomposition of intermediate afford II and acetone III [13]. Acetone III reacts with aniline 3 to provide imine IV and tautomerized to enamine V. An intermolecular reaction is carried out between enamine V and aldehyde 2 to afford the reactive Barbas dienamine VII [13,40-47]. Barbas dienamine VII undergoing an in-situ [4+2] cycloaddition would accomplish with benzylidene I as dienophiles (Diels-Alder) to give enamine VIII [44]. Consequently, IX attached to the Knoevenagel product I [48-49] could create an iminium salt X with the aldehydes 2 to afford target molecules 4 [50].

Table 2. Synthesis of Dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] Dioxane-4,6-dione)] Derivatives 4a-l



Entry	Product	R^1	R^2	Isolated yield (%)	M.p. (°C) [found]	M.p. (°C) [Ref.]
1	**4a**	H	H	87	242-245	247-249 [32]
2	**4b**	4-NO_2	4-MeO	83	242-244	246-248 [32]
3	**4c**	4-Cl	H	85	189-191	186-189 [32]
4	**4d**	2-Cl	H	79	227-228	232-234 [33]
5	**4e**	4-CN	4-Br	83	223-224	220 [36]
6	**4f**	4-OMe	4-F	81	241-245	247-248 [35]
7	**4g**	4-OMe	4-Br	83	233-235	232-235 [33]
8	**4h**	2-Me	H	79	221-222	215-218 [32]
9	**4i**	4-Me	4-OMe	86	236-237	236-239 [32]
10	**4j**	4-Me	4-F	83	245-247	242-245 [32]
11	**4k**	4-Me	4-Cl	82	232-235	238-240 [32]
12	**4l**	4-Me	4-Br	83	234-236	230-232 [32]

EXPERIMENTAL

Materials and Methods

Melting points and IR spectra of all compounds were determined using an electro thermal 9100 apparatus and FTIR-JASCO-460 plus spectrometer. The ^1H and ^{13}C NMR spectra of the known compounds were recorded on a Bruker Avance DRX-300 and 400 instrument in $CDCl_3$ as a solvent. All the chemicals were provided from chemical producer Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification.

General Procedure for the Preparation of Compounds 4a–l

A mixture of Meldrum's acid (3.0 mmol), aldehyde (4.0 mmol), aniline (1.0 mmol) and lactic acid (0.5 ml) was stirred at 50 °C for an appropriate time. After completion, as indicated by TLC, methanol was added to this mixture and the product was recrystallized from methanol to afford the pure product.

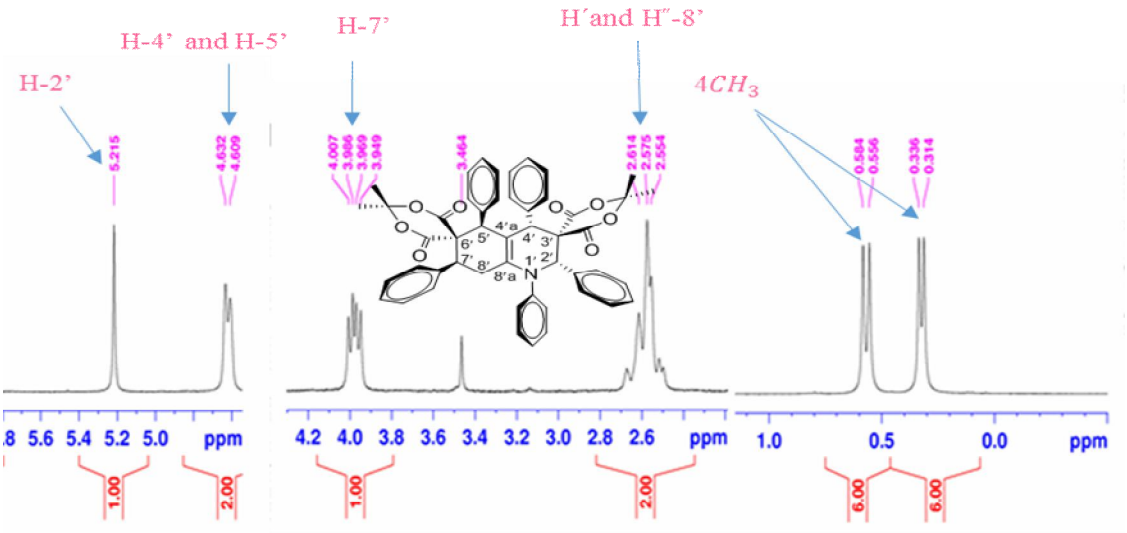


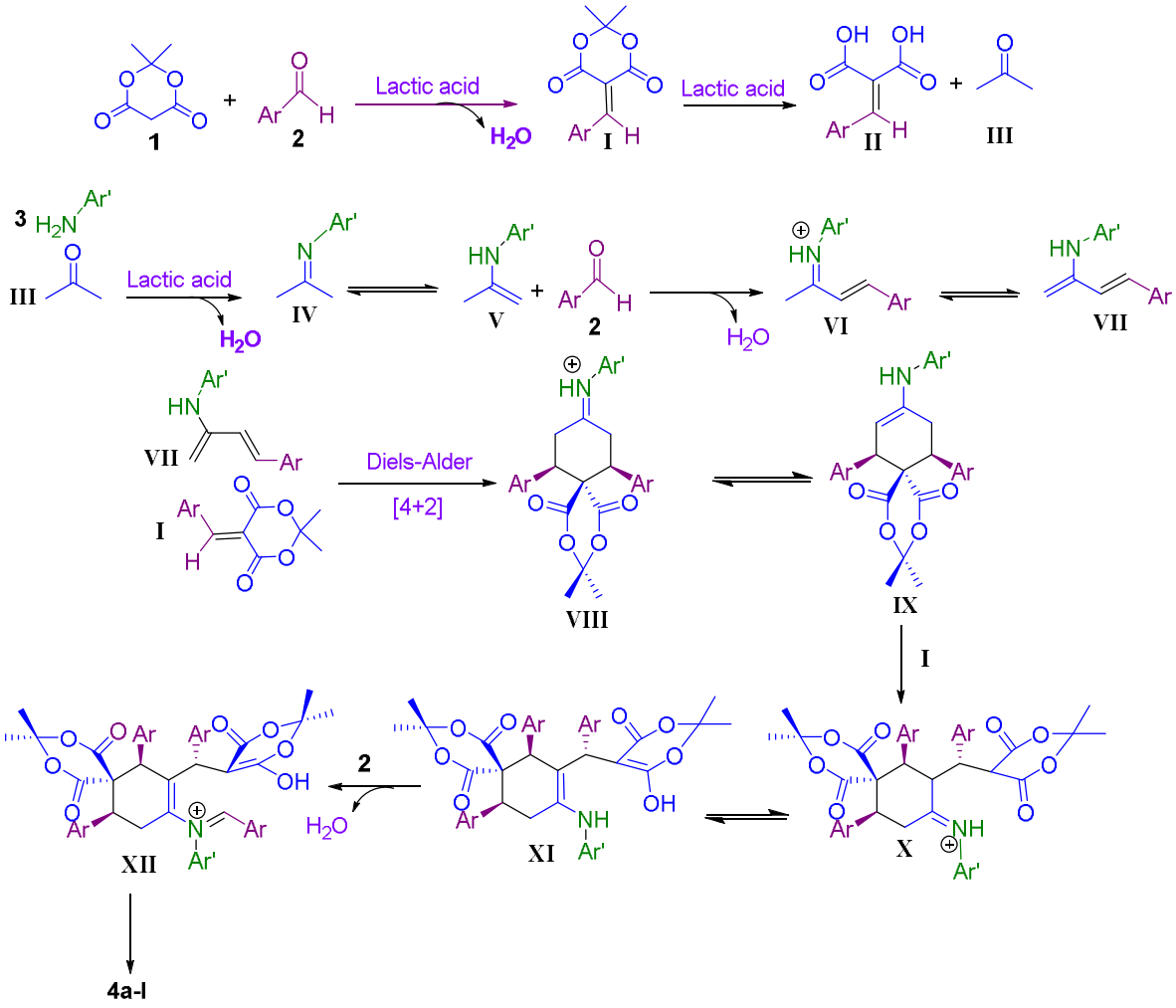
Fig. 2. [1]H NMR spectrum of 4a.

Table 3. Comparison of [1]H NMR Data

Entry	Product	H shift (found)	H shift [Ref.]
1	4a	4Me: 0.31, 0.33, 0.55 and 0.58 (4s); H´, H˝-8´: 2.64-2.71 (m); H-7´: 3.97 (dd, *J* = 6.3 Hz, *J* = 6.0 Hz); H-4´, H-5´: 4.60 and 4.63 (2s); H-2´: 5.21 (s)	4Me: 0.36, 0.38, 0.60 and 0.62 (4s); H´, H˝-8´: 2.55-2.66 (m); H-7´: 4.02 (dd, *J* = 11.6 Hz, *J* = 6.0 Hz); H-4´, H-5´: 4.65 and 4.67 (2s); H-2´: 5.26 (s) [34]
2	4j	4Me: 0.35, 0.38 0.60 and 0.63 (4s); 4ArMe: 2.15, 2.18 and 2.20 (3s); H´, H˝-8´: 2.54-2.39 (m); H-7´: 3.94 (dd, *J* = 5.7 Hz, *J* = 5.7 Hz); H-4´, H-5´: 4.50 and 4.53 (2s); H-2´: 5.08 (s)	4Me: 0.40, 0.43, 0.65 and 0.68 (4s); 4ArMe: 2.20, 2.23 and 2.25 (3s); H´, H˝-8´: 2.56-2.64 (m); H-7´: 3.94 (dd, *J* = 12.0 Hz, *J* = 5.2 Hz); H-4´, H-5´: 4.55 and 4.58 (2s); H-2´: 5.13 (s) [32]

Spectral Data of Selected Products are Represented Below

1´2´,4´,5´,7´-Petnaphenyl-1´H-dispiro[2´,4´,5´,7´,8´-tetrahydro-quinoline-5,3´,6´,5˝-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] (4a). White powder; m. p.: 242-245 °C; IR (KBr): ν 1760, 1730, 1662, 1592, 1492, 1455, 1269, 1241 cm^{-1}; 7.05-7.54 (m, 21H, H_{Ar}), 6.70 (d, 1H, *J* = 7.2 Hz, H_{Ar}), 6.65 (d, 1H, *J* = 7.2 Hz, H_{Ar}), 6.01 (t, 2H, *J* = 7.2 Hz, H_{Ar}), 5.21 (s, 1H, H-2´), 4.60 and 4.63 (2s, 2H, H-4´, H-5´), 3.97 (dd, 1H, *J* = 6.3 Hz, H-7´), 2.55-2.61 (m, 2H, H˝-8´ and H´-8´), 0.31, 0.33, 0.55 and 0.58 (4s, 12H, 4Me).



Scheme 3. Suggested mechanism for the synthesis of dispirohydroquinolines

1′-(Phenyl)-2′,4′,5′,7′-tetra(2-chlorophenyl-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydro-quinoline-5,3′,6′,5″-bis (2,2-dimethyl[1,3]dioxane-4,6-dione)] (4d). White powder; m. p.: 227-228 °C; IR (KBr): ν 1760, 1736, 1660, 1594, 1514, 1490, 1284, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.97-7.88 (m, 21H, H_{Ar}), 6.05 (s, 1H, H-2′), 4.99 and 5.06 (2s, 2H, H-4′, H-5′), 4.74 (dd, 1H, *J* = 11.2 Hz, *J* = 6.4 Hz, H-7′), 2.57-2.64 (m, 2H, H′, H″-8′), 0.63 and 0.98 (2s, 12H, 4×Me).

1′-(4-Bromophenyl)-2′,4′,5′,7′-tetra(4-cyanophenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′,6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (4e). White powder; m. p.: 223-224 °C; IR (KBr): ν 2231, 1766, 1730, 1662, 1607, 1486, 1294, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14-7.77 (m, 18H, H_{Ar}); 6.24 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz, H_{Ar}), 6.21 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz, H_{Ar}), 5.26 (s, 1H, H-2′), 4.61 and 4.64 (2s, 2H, H-4′, H-5′), 4.04 (t, 1H, *J* = 8.0 Hz, H-7′), 2.56 and 2.58 (2s, 2H, H′-8′, H″-8′), 0.44, 0.47, 0.68 and 0.69 (4s, 12H, 4Me).

1′-(4-Bromophenyl)-2′,4′,5′,7′-tetra(4-methoxy-phenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5, 3′,6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (4g). White powder; m. p.: 233-235 °C; IR (KBr): ν 1764, 1730, 1657, 1610, 1511, 1302, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.64 -7.45 (m, 16H, H_{Ar}), 6.31-6.36 (m, 2H, H_{Ar}), 6.02 (td, 2H, *J* = 8.8 Hz, *J* = 2.0 Hz, H_{Ar}), 5.10 (s, 1H, H-2′), 4.52 and 4.54 (2brs, 2H, H-4′, H-5′), 3.93 (dd, 1H, *J* = 12.0 Hz, *J* = 5.6 Hz, H-7′), 3.72 and 3.74 (2s, 12H,

4OMe), 2.54-2.63 (m, 1H, H″-8′), 2.47 (dd, 1H, *J* = 17.2 Hz, *J* = 5.6 Hz, H′-8′), 0.47, 0.50, 0.71 and 0.75 (4s, 12H, 4Me).

1′-(4-Flourophenyl)-2′,4′,5′,7′-tetra(4-methyl-phenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5, 3′,6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (4j). White solid; m. p.: 245-247 °C; IR (KBr): ν 1767, 1730, 1652, 1610, 1509, 1462, 1381, 1302, 1245, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.81-7.38 (m, 16H, H_{Ar}), 6.50 (t, 2H, *J* = 5.7 Hz, H_{Ar}), 5.91 (td, 2H, *J* = 8.0 Hz, *J* = 1.8 Hz, H_{Ar}), 5.08 (s, 1H, H-2′), 4.50 and 4.53(2s, 2H, H-4′, H-5′), 3.94 (dd, 1H, *J* = 5.7 Hz, *J* = 5.7 Hz, H-7′), 2.39-2.54 (m, 2H, H″-8′), 2.15, 2.18 and 2.20 (3s, 12H, 4ArMe), 0.35, 0.38, 0.60 and 0.63, (4s, 12H, 4Me).

CONCLUSIONS

The extension of truly efficient and environmentally friendly catalysts is one of the predominant aims in green chemistry. As outlined in this study, we have successfully elaborated a practical, convenient and environmentally benign pseudo-eight-components reaction to furnish poly-substituted hydroquinolines. The application of this strategy is in the synthesis of highly diastereoselectivity target products *via* combinations of Domino Knoevenagel, Michael, and Diels-Alder reactions in the presence of lactic acid as the catalyst and solvent. Solvent-less, operationally simple, economical, and using an eco-friendly and inexpensive catalyst are the best aspects of this protocol.

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