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α-Nitro carbonyl compounds in the synthesis of 2,3-dihydrofurans

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ABSTRACT

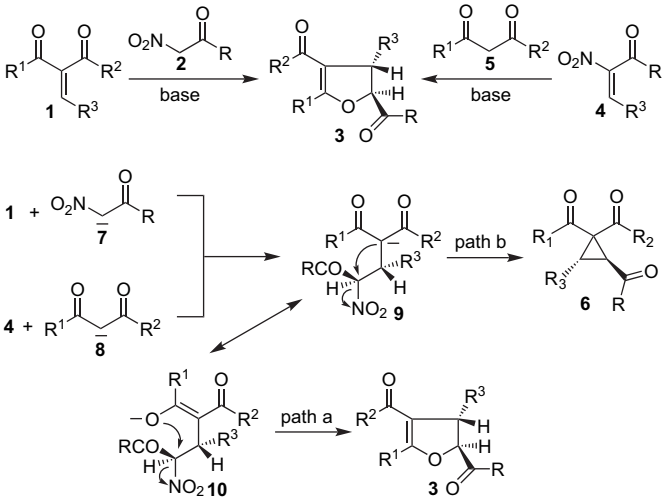
A new method for the synthesis of 2,3-dihydrofurans from readily available starting enones and α-nitro carbonyl compounds has been developed. This protocol can provide a novel and effective methodology for the preparation of 2,3-dihydrofurans in a stereoselective fashion. With 1,4-dien-3-ones, 2,3-dihydrofurans and cyclohexenecarboxylates were produced and high chemoselectivity was observed in different solvents.

1. Introduction

Dihydrofurans are the most important heterocycles commonly found in a large variety of naturally occurring substances.[1] The development of new and efficient methods for their synthesis remains an area of current interest and a whole series of new synthetic methods have appeared in literature.[2–5] Among synthetic methodologies toward dihydrofurans, non-ionic as well as ionic procedures have been exploited. Radical[2] or carbenoid[3] additions to olefins have been utilized as non-ionic procedures. Among ionic reaction conditions, dihydrofuran syntheses via tandem nucleophilic reaction of 1,3-dicarbonyl compounds[4] or ylides[5] with enones have been reported. Aliphatic nitro compounds can be considered as versatile building blocks in organic synthesis, both the activating effect of the nitro group and its facile transformation into various functionalities have extended the importance of nitro compounds in the preparation of complex molecules.[6] Although a number of methods are available as cited above, the search for newer methods for dihydrofuran synthesis is continuously being pursued. In this paper, we report a new method for the synthesis of 2,3-dihydrofuran via nitronate anions.

2. Results and discussion

The reaction between 3-benzylidene-2,4-pentanedione (**1a**) and ethyl nitroacetate (**2a**) was first examined (Scheme 1). Treatment of **1a** with triethylamine and **2a** in acetonitrile at 60 °C gave



Scheme 1.

2,3-dihydrofuran **3a** as the only product in 93% yield (Table 1, entry 1). The structure of **3a** is clearly assigned as trans compounds by the analysis of the vicinal coupling constant of the two methine protons ($J_{2,3}$=4.7 Hz) and by the analogy with earlier reported paper.[2g,4c,5b–d] On the basis of this finding, a plausible reaction mechanism is shown in Scheme 1. Deprotonation of **2a** forms nitronate anion **7a** and then a Michael addition of **7a** to enone **1a** affords the enolate anion **10a**. Finally, the intramolecular nucleophilic O-alkylation[7] of **10a** gave the cycloadduct **3a** (path a). In this reaction, no cyclopropane **6a** derived from the intramolecular nucleophilic

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Table 1
Reaction between 3-benzylidene-2,4-pentanedione (**1a**) and ethyl nitroacetate (**2a**)

Entry	Solvent	Base	Reaction time (h)	Product (yield (%))[a]
1	CH_3CN	Et_3N	2	**3a** (93)
2	EtOH	Et_3N	2	**3a** (92)
3	CH_3NO_2	Et_3N	2	**3a** (92)
4	$CHCl_3$	Et_3N	17	**3a** (89)
5	C_6H_6	Et_3N	23	**3a** (87)
6	CH_3CN	K_2CO_3	2	**3a** (94)
7	CH_3CN	DABCO	2	**3a** (95)

[a] Isolated yield.

C-alkylation[8] of **9a** could be found (path b). During the ring closure, the two large neighboring groups preferably formed trans conformation for the sake of stereohindrance. In attempt to investigate the range of solvents compatible with this reaction, enone **1a** and ethyl nitroacetate (**2a**) were chosen as model compounds and this reaction was performed in various solvents. The results are summarized in Table 1 (entries 2–5). The change of solvent to ethanol, nitromethane, chloroform, or benzene gave similar result. In chloroform and benzene, it proceeds in a much slower reaction rate. We also used different bases for this reaction. In acetonitrile, replacement of triethylamine with other bases also led to a similar reaction yield (entries 6 and 7). On the basis of these results, by choosing acetonitrile as solvent and triethylamine as base, we applied this method to other enones **1b** and **1c** (Table 2, entries 3 and 5). The reaction worked well and 2,3-dihydrofurans **3c** and **3e** were formed in 96% and 99% yields, respectively. With α-nitroacetophenone (**2b**), the corresponding 2,3-dihydrofuran **3** was also produced in good yield (entries 2, 4, and 6). This method proved to be of general applicability on enone **1** and α-nitro carbonyl compound **2**. In all cases, 2,3-dihydrofuran **3** was obtained in good to excellent yield.

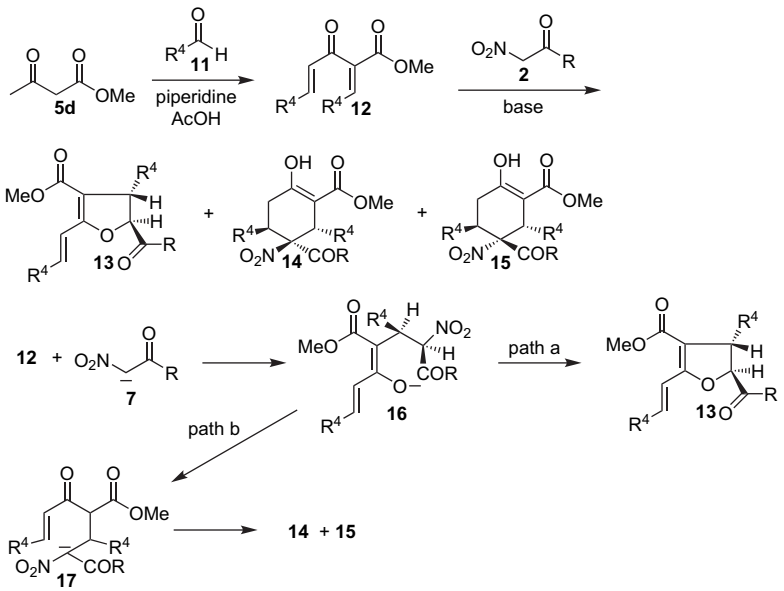
Table 2
Synthesis of 2,3-dihydrofurans[a]

Entry	Enone	Carbonyl compound	Reaction time (h)	Product (yield (%))[b]
1	**1a**: R^1=Me, R^2=Me, R^3=Ph	**2a**: R=OEt	2	**3a** (93)
2	**1a**: R^1=Me, R^2=Me, R^3=Ph	**2b**: R=Ph	5	**3b** (88)
3	**1b**: R^1=Me, R^2=OMe, R^3=*p*-Tol	**2a**: R=OEt	2	**3c** (96)
4	**1b**: R^1=Me, R^2=OMe, R^3=*p*-Tol	**2b**: R=Ph	5	**3d** (89)
5	**1c**: R^1=Ph, R^2=OEt, R^3=Ph	**2a**: R=OEt	4	**3e** (99)
6	**1c**: R^1=Ph, R^2=OEt, R^3=Ph	**2b**: R=Ph	4	**3f** (89)
7	**4a**: R^3=Ph, R=OEt	**5a**: R^1=Me, R^2=Me	4	**3a** (92)
8	**4a**: R^3=Ph, R=OEt	**5b**: R^1=Ph, R^2=OEt	4	**3e** (97)
9	**4b**: R^3=Ph, R=Ph	**5b**: R^1=Ph, R^2=OEt	4	**3f** (84)
10	**4b**: R^3=Ph, R=Ph	**5a**: R^1=Me, R^2=Me	4	**3b** (82)

[a] All reactions were performed at 60 °C in CH_3CN with Et_3N as base.
[b] Isolated yield.

According to the proposed reaction mechanism shown above, we believe that enolate **10** can also be formed via the Michael addition of enolate **8** (generated by the deprotonation of **5**) to enone **4** and subsequently 2,3-dihydrofuran **3** can be produced. We then studied the reaction between **4** and **5** for the synthesis of 2,3-dihydrofuran **3**. In agreement with this expectation, when **4a** was heated with **5a** and triethylamine in acetonitrile, **3a** was obtained in 92% yield (Table 2, entry 7). Other examples are also summarized in Table 2 (entries 8–10) and 2,3-dihydrofurans were obtained effectively.

Next, we investigate this reaction with 1,4-dien-3-ones **12**. The starting 2*E*,4*E*-dienones were prepared effectively by the reaction of methyl acetoacetate (**5d**) with appropriate aromatic aldehydes **11** under Knoevenagel conditions followed by the recrystallization of the product mixture (Scheme 2). The reaction yields of dienones **12** are listed in Table 3. This dienone **12** was formed presumably via the Knoevenagel condensation of **5d** with **11** followed by the aldol condensation of the resulting Knoevenagel condensation product with another **11**. The structure of **12** was revealed by ^1H and ^{13}C NMR analyses. In addition, the stereochemistry of **12b** was further assigned by single crystal X-ray diffraction analysis (Fig. 1).[9] When dienone **12a** was reacted with ethyl nitroacetate (**2a**) and triethylamine in acetonitrile, in addition to the expected 2,3-dihydrofuran **13a** (25%), cyclohexenecarboxylates **14a** and **15a** were also produced in 42% and 19% yield, respectively (Table 4, entry 1). 2,3-Dihydrofuran **13a** was formed via the O-alkylation of **16a** similar to that for **3a** (Scheme 2, path a). Cyclohexenecarboxylates **14a** and **15a** were produced via the intramolecular Michael addition of nitronate anion **17a**, generated by the proton shift of **16a** (Scheme 2, path b). It is well known that the O-alkylation of an enolate anion is usually favored by the use of polar aprotic solvents.[10] We believed that **13a** could be obtained in a higher selectivity when this reaction was performed in DMF or DMSO. Indeed, when **12a** was reacted with **2a** and triethylamine in DMF, the **13a**/**14a**+**15a** ratio rose to 71:16 (entry 2). In DMSO, a similar result was obtained (entry 3).



Scheme 2.

Table 3
Synthesis of 1,4-dien-3-ones **12**

Entry	Benzaldehyde	Product (yield (%))[a]
1	**11a**: R^1=*p*-ClC_6H_4	**12a** (46)
2	**11b**: R^1=Ph	**12b** (55)
3	**11c**: R^1=*p*-Tol	**12c** (52)

[a] Isolated yield.

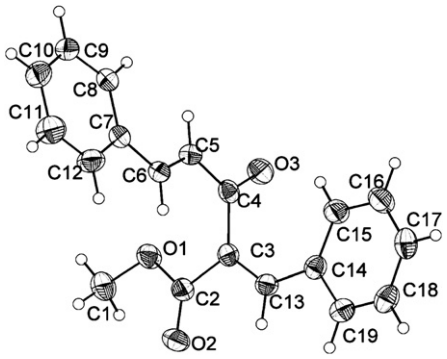


Figure 1. The molecular structure of **12b**.

With potassium carbonate, **13a** was obtained as the only product in 83% yield (entry 4). Since K_2CO_3/DMF is the most effective condition for the formation of **13a**, so the scope of this reaction was explored with a variety of dienone **12** and α-nitro carbonyl compound **2** using K_2CO_3/DMF conditions and a series of 2,3-dihydrofuran derivatives were synthesized in good yields. All of these results are summarized in Table 4 (entries 5–9). We have continued to study the reaction between **12** and ethyl nitroacetate (**2a**) in nonpolar solvent. Reaction of dienone **12a** with ethyl nitroacetate (**2a**) and triethylamine in benzene only resulted in the formation of cyclohexenecarboxylates **14a** and **15a** in 55% and 13% yield, respectively, and no 2,3-dihydrofuran **13a** could be found (entry 10). In chloroform, the reaction yield for **14a** and **15a** are 69% and 11%, respectively (entry 11). This high chemoselectivity is presumably due to the stronger coordination of triethylammonium cation with the oxygen atom of nitronate anion **16a** in chloroform than that in DMF—the intramolecular O-alkylation rate of **16a** is retarded (path a) and the Michael addition of nitronate anion **17a** becomes the major route (path b). In protic solvent (EtOH), this reaction also gave only the cyclohexenecarboxylate products but in a lower **14a**/**15a** ratio (entry 12). The structures of **14a** and **15a** were established by the ^{1}H NMR, ^{13}C NMR, and X-ray analyses (Figs. 2 and 3).[9] Under $Et_3N/CHCl_3$ conditions, with dienones **12b** and **12c**, cyclohexenecarboxylate derivatives were obtained in good yields and the results are listed in Table 4 (entries 13 and 14).

In conclusion, we have developed a new reaction for the synthesis of 2,3-dihydrofurans from readily available starting enones and α-nitro carbonyl compounds. This protocol can provide a novel and effective methodology for the preparation of 2,3-dihydrofurans in a stereoselective fashion. The reaction is applicable to a range of enones and α-nitro carbonyl compounds with a variety of versatile functional groups. With 1,4-dien-3-ones, 2,3-dihydrofurans and cyclohexenecarboxylates were produced and high chemoselectivity was observed in different solvents.

3. Experimental

3.1. General

Melting points are uncorrected. The NMR spectra were recorded on a Brucker AVANCE 300, AMX-400, or AVANCE 500 spectrometer. Chemical shifts are reported in parts per million relative to TMS as internal reference. Elemental analyses were performed with Heraeus CHN-Rapid Analyzer. HRMS were recorded on a JEOL JMS-SX 102A mass spectrometer. X-ray diffraction structure analyses were performed with a Nonius Kappa CCD diffractometer. Structure analysis was made by using SHELXTL program on a personal computer. Analytical thin-layer chromatography was performed with precoated silica gel 60 F-254 plates (0.25 mm thick) and visualized by UV light. The reaction mixture was purified by column chromatography over silica gel (70–230 mesh).

3.2. Typical procedure for the reactions between enones 1 and α-nitro carbonyl compounds 2 to produce 2,3-dihydrofurans 3

A solution of 3-benzylidene-2,4-pentanedione (**1a**, 167 mg, 0.89 mmol), ethyl nitroacetate (**2a**, 177 mg, 1.33 mmol), and triethylamine (134 mg, 1.33 mmol) in CH_3CN (6 mL) was heated at 60 °C for 2 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g, eluted with 8:1 hexane/EtOAc) followed by crystallization (hexane/EtOAc) to give **3a** (226 mg, 93%).

Table 4
Reactions of 1,4-dien-3-ones **12**

Entry	Dienone	Nitro carbonyl compound	Solvent	Base	Reaction time (h)	Product (yield (%))[a]		
1	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	CH_3CN	Et_3N	4	**13a** (25)[b]	**14a** (42)	**15a** (19)[b]
2	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	DMF	Et_3N	2	**13a** (71)[b]	**14a** (12)	**15a** (4)[b]
3	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	DMSO	Et_3N	2	**13a** (67)[b]	**14a** (12)	**15a** (5)[b]
4	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	DMF	K_2CO_3	2	**13a** (83)		
5	**12b**: R^1=Ph	**2a**: R=OEt	DMF	K_2CO_3	2	**13b** (79)		
6	**12c**: R^1=*p*-Tol	**2a**: R=OEt	DMF	K_2CO_3	2	**13c** (87)		
7	**12b**: R^1=Ph	**2b**: R=Ph	DMF	K_2CO_3	2	**13d** (89)		
8	**12b**: R^1=Ph	**2c**: R=$(CH_2)_2$Ph	DMF	K_2CO_3	2	**13e** (91)		
9	**12b**: R^1=Ph	**2d**: R=$N(Et)_2$	DMF	K_2CO_3	2	**13f** (81)		
10	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	C_6H_6	Et_3N	14		**14a** (55)	**15a** (13)
11	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	$CHCl_3$	Et_3N	14		**14a** (69)	**15a** (11)
12	**12a**: R^1=*p*-ClC_6H_4	**2a**: R=OEt	EtOH	Et_3N	14		**14a** (57)	**15a** (24)
13	**12b**: R^1=Ph	**2a**: R=OEt	$CHCl_3$	Et_3N	14		**14b** (66)[c]	**15b** (15)[c]
14	**12c**: R^1=*p*-Tol	**2a**: R=OEt	$CHCl_3$	Et_3N	14		**14c** (72)[c]	**15c** (13)[c]

[a] Isolated yield.
[b] Deduced from the NMR integration of the product mixture of **13a** and **15a**.[11]
[c] Deduced from the NMR integration of the product mixture of **14** and **15**.[12]

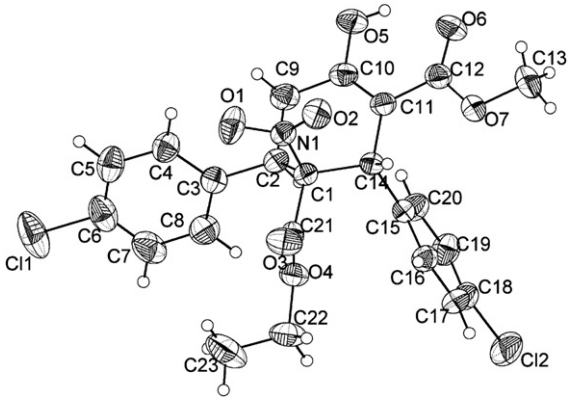


Figure 2. The molecular structure of **14a**.

*3.2.1. trans-4-Acetyl-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester **3a***

White crystals; mp 65–66 °C; IR ($CHCl_3$) 2990, 1740, 1670, 1495, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J=7.3 Hz, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.44 (d, J=1.2 Hz, 3H, CH_3), 4.23–4.35 (m, 2H, OCH_2), 4.45–4.51 (m, 1H, CH), 4.78 (d, J=5.0 Hz, 1H, OCH), 7.21–7.38 (m, 5H, ArH); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.1 (q), 14.9 (q), 29.6 (q), 53.2 (d), 61.9 (t), 86.0 (d), 115.1 (s), 127.2 (2×d), 127.6 (d), 129.1(2×d), 142.2 (s), 168.6 (s), 169.9 (s), 194.3 (s). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.01; H, 6.59.

*3.2.2. trans-1-(5-Benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-yl)ethanone **3b***

White crystals; mp 139–140 °C; IR ($CHCl_3$) 3005, 1670, 1600, 1450, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.54 (d, J=4.7 Hz, 1H, CH), 5.65 (d, J=4.7 Hz, 1H, OCH), 7.25 (d, J=7.8 Hz, 2H, ArH), 7.29–7.42 (m, 3H, ArH), 7.47 (t, J=7.6 Hz, 2H, ArH), 7.62 (t, J=7.6 Hz, 1H, ArH), 7.88 (d, J=7.6 Hz, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.9 (q), 29.6 (q), 51.9 (d), 89.4 (d), 115.8 (s), 127.6 (2×d), 127.7 (d), 128.8 (2×d), 129.09 (2×d), 129.13 (2×d), 133.4 (s), 134.0 (d), 142.2 (s), 168.4(s), 193.3 (s), 194.2 (s). Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.36; H, 5.92.

*3.2.3. trans-5-Methyl-3-(p-tolyl)-2,3-dihydrofuran-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester **3c***

Colorless oil; IR ($CHCl_3$) 2990, 1745, 1690, 1650, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.40 (d, J=1.2 Hz, 3H, CH_3), 3.57 (s, 3H, OCH_3), 4.22–4.31 (m, 2H, OCH_2), 4.35–4.40 (m, 1H, CH), 4.79 (d, J=4.7 Hz, 1H, OCH), 7.06–7.18 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (q), 21.1 (q), 50.9 (q), 52.2 (d), 61.7 (t), 85.9 (d), 106.1 (s), 126.8 (2×d), 129.4 (2×d), 136.9 (s), 139.5 (s), 165.4 (s), 168.6 (s), 170.0 (s); HRMS calcd for $C_{17}H_{20}O_5$: m/e 304.1311; found: m/e 304.1320.

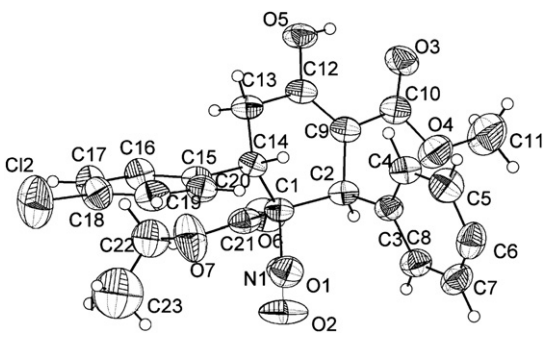


Figure 3. The molecular structure of **15a**.

*3.2.4. trans-5-Benzoyl-2-methyl-4-(p-tolyl)-4,5-dihydrofuran-3-carboxylic acid methyl ester **3d***

White needles; mp 108–109 °C; IR ($CHCl_3$) 2955, 1690, 1650, 1440, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 4.36–4.39 (m, 1H, CH), 5.69 (d, J=4.4 Hz, 1H, OCH), 7.15 (d, J=8.2 Hz, 2H, ArH), 7.17 (d, J=8.2 Hz, 2H, ArH), 7.46 (t, J=7.5 Hz, 2H, ArH), 7.61 (t, J=7.5 Hz, 1H, ArH), 7.85 (d, J=7.5 Hz, 2H, ArH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 14.1 (q), 21.1 (q), 50.8 (q), 51.3 (d), 89.5 (d), 106.7 (s), 127.3 (2×d), 128.8 (2×d), 129.0 (2×d), 129.5 (2×d), 133.4 (s), 133.9 (d), 137.0 (s), 139.4 (s), 165.3 (s), 168.5 (s), 193.5 (s). Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 74.98; H, 6.07.

*3.2.5. trans-3,5-Diphenyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester **3e***

Colorless oil; IR ($CHCl_3$) 2985, 1740, 1690, 1450, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J=7.1 Hz, 3H, CH_3), 1.36 (t, J=7.2 Hz, 3H, CH_3), 3.99 (q, J=7.1 Hz, 2H, OCH_2), 4.26–4.37 (m, 2H, OCH_2), 4.61 (d, J=4.1 Hz, 1H, CH), 4.96 (d, J=4.1 Hz, 1H, OCH), 7.24–7.39 (m, 5H, ArH), 7.39–7.52 (m, 3H, ArH), 7.92–7.99 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8 (q), 14.2 (q), 54.0 (d), 59.9 (t), 61.8 (t), 84.9 (d), 106.6 (s), 127.1 (2×d), 127.4 (d), 127.7 (2×d), 128.8 (2×d), 129.1 (s), 129.8 (2×d), 130.9 (d), 142.5 (s), 164.0 (s), 165.4 (s), 170.2 (s); HRMS calcd for $C_{22}H_{22}O_5$: m/e 366.1467; found: m/e 366.1477.

*3.2.6. trans-5-Benzoyl-2,4-diphenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester **3f***

White crystals; mp 115–116 °C; IR ($CHCl_3$) 2990, 1680, 1630, 1450, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=7.1 Hz, 3H, CH_3), 3.89–3.97 (m, 2H, OCH_2), 4.65 (d, J=4.3 Hz, 1H, CH), 5.82 (d, J=4.3 Hz, 1H, OCH), 7.29–7.50 (m, 10H, ArH), 7.59–7.65 (m, 1H, ArH), 7.89–7.94 (m, 2H, ArH), 7.95–8.01 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8 (q), 53.0 (d), 59.8 (t), 88.5 (d), 107.0 (s), 127.5 (d), 127.6 (2×d), 127.7 (2×d), 128.8 (2×d), 128.9 (2×d), 129.0 (2×d), 129.3 (s), 129.9 (2×d), 130.8 (d), 133.4 (s), 133.9 (d), 142.4 (s), 164.0 (s), 165.5 (s), 193.5 (s). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.41; H, 5.56.

3.3. Typical procedure for the synthesis of 1,4-dien-3-ones 12

A solution of methyl acetoacetate (**5d**, 1.03 g, 8.88 mmol), benzaldehyde (**11a**, 4.97 g, 35.5 mmol), piperidine (305 mg, 3.59 mmol), and 306 mg (5.1 mmol) of acetic acid (306 mg, 5.1 mmol) in benzene (20 mL) was heated under reflux for 24 h with azotropic removal of water using a Dean–Stark trap. The reaction mixture was diluted with EtOAc (300 mL), washed with H_2O (3×100 mL), aqueous saturated sodium bicarbonate (3×100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (40 g, eluted with 10:1 hexane/EtOAc) followed by recrystallization (hexane/EtOAc) to give **12a** (1.46 g, 46%).

*3.3.1. (2E,4E)-2-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-3-oxo-4-pentenoic acid methyl ester **12a***

White powder; mp 126–127 °C; IR (KBr) 1715, 1640, 1255, 1195, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 6.80 (d, J=16.8 Hz, 1H, CH), 7.29 (d, J=8.6 Hz, 2H, ArH), 7.34 (d, J=8.6 Hz, 2H, ArH), 7.36 (d, J=8.6 Hz, 2H, ArH), 7.41 (d, J=8.6 Hz, 2H, ArH), 7.42 (d, J=16.8 Hz, 1H, CH), 7.86 (s, 1H, CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.7 (q), 127.0 (d), 129.1 (2×d), 129.2 (2×d), 129.7 (2×d), 131.2 (s), 131.3 (2×d), 131.6 (s), 132.4 (s), 136.7 (s), 137.1 (s), 141.2 (d), 145.0 (d), 165.1 (s), 194.9 (s). Anal. Calcd for $C_{19}H_{14}Cl_2O_3$: C, 63.18; H, 3.91. Found: C, 62.84; H, 3.87.

*3.3.2. (2E,4E)-2-Benzylidene-3-oxo-5-phenyl-4-pentenoic acid methyl ester **12b***

White powder; mp 102–103 °C; IR (KBr) 1715, 1645, 1255, 1200, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 6.84 (d,

J=16.3 Hz, 1H, CH), 7.28–7.51 (m, 11H, ArH+CH), 7.92 (s, 1H, CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.4 (q), 126.7 (d), 128.4 (2×d), 128.7 (2×d), 128.8 (2×d), 130.0 (2×d), 130.3 (d), 130.8 (d), 131.0 (s), 132.6 (s), 133.8 (s), 142.4 (d), 146.4 (d), 165.3 (s), 195.4 (s). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.01; H, 5.51.

3.3.3. (2E,4E)-2-(4-Methylbenzylidene)-5-(4-methylphenyl)-3-oxo-4-pentenoic acid methyl ester ***12c***

White crystals; mp 119–120 °C; IR (KBr) 1715, 1640, 1260, 1200, 815 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.81 (d, J=16.2 Hz, 1H, CH), 7.10 (d, J=8.1 Hz, 2H, ArH), 7.16 (d, J=8.1 Hz, 2H, ArH), 7.34 (d, J=8.1 Hz, 2H, ArH), 7.37 (d, J=8.1 Hz, 2H, ArH), 7.46 (d, J=16.2 Hz, 1H, CH), 7.88 (s, 1H, CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.4 (q), 21.5 (q), 52.5 (q), 126.0 (d), 128.6 (2×d), 129.5 (2×d), 129.6 (2×d), 130.0 (s), 130.1 (s), 130.3 (2×d), 131.4 (s), 141.0 (s), 141.6 (s), 142.5 (d), 146.5 (d), 165.7 (s), 196.0 (s). Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.69; H, 6.29.

3.4. Typical procedure for the reactions between dienones 12 and α-nitro carbonyl compounds 2 in DMF to produce 2,3-dihydrofurans 13

A mixture of dienone (**12a**, 127 mg, 0.35 mmol), ethyl nitroacetate (**2a**, 92 mg, 0.69 mmol), and potassium carbonate (114 mg, 0.83 mmol) in DMF (6 mL) was heated at 60 °C for 2 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g, eluted with 15:1 hexane/EtOAc) followed by crystallization (hexane/EtOAc) to give **13a** (130 mg, 83%).

3.4.1. trans-5-[(E)-4-Chlorostyryl]-3-(4-chlorophenyl)-2,3-dihydrofuran-2,4-dicarboxylic acid 2-ethyl 4-methyl ester ***13a***

White crystals; mp 132–133 °C; IR (KBr) 1695, 1635, 1205, 1045, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.2 Hz, 3H, CH_3), 3.63 (s, 3H, OCH_3), 4.24–4.36 (m, 2H, OCH_2), 4.50 (d, J=4.4 Hz, 1H, CH), 4.86 (d, J=4.4 Hz, 1H, CH), 7.20 (d, J=8.5 Hz, 2H, ArH), 7.31 (d, J=8.5 Hz, 2H, ArH), 7.35 (d, J=8.4 Hz, 2H, ArH), 7.40 (d, J=16.3 Hz, 1H, CH), 7.51 (d, J=8.4 Hz, 2H, ArH), 7.64 (d, J=16.3 Hz, 1H, CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (q), 51.2 (q), 52.4 (d), 61.9 (t), 85.2 (d), 107.3 (s), 115.7 (d), 128.5 (2×d), 128.94 (2×d), 128.97 (2×d), 129.04 (2×d), 133.2 (s), 134.2 (s), 135.3 (s), 137.1 (d), 140.7 (s), 163.7 (s), 164.7 (s), 169.7 (s). Anal. Calcd for $C_{23}H_{20}Cl_2O_5$: C, 61.76; H, 4.51. Found: C, 61.57; H, 4.53.

3.4.2. trans-3-Phenyl-5-[(E)-styryl]-2,3-dihydrofuran-2,4-dicarboxylic acid 2-ethyl 4-methyl ester ***13b***

White needles; mp 126–127 °C; IR (KBr) 1695, 1630, 1205, 1040, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.1 Hz, 3H, CH_3), 3.62 (s, 3H, OCH_3), 4.26–4.36 (m, 2H, OCH_2), 4.52 (d, J=4.3 Hz, 1H, CH), 4.92 (d, J=4.3 Hz, 1H, CH), 7.23–7.41 (m, 8H, ArH), 7.46 (d, J=16.2 Hz, 1H, CH), 7.59 (d, J=7.0 Hz, 2H, ArH), 7.69 (d, J=16.2 Hz, 1H, CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.2 (q), 51.2 (q), 53.0 (d), 61.8 (t), 85.4 (d), 107.2 (s), 115.4 (d), 127.1 (2×d), 127.4 (d), 127.8 (2×d), 128.77 (2×d), 128.79 (2×d), 129.4 (d), 135.8 (s), 138.3 (d), 142.3 (s), 163.9 (s), 165.0 (s), 170.1 (s). Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 72.88; H, 5.87.

3.4.3. trans-5-[(E)-4-Methylstyryl]-3-(4-methylphenyl)-2,3-dihydrofuran-2,4-dicarboxylic acid 2-ethyl 4-methyl ester ***13c***

White needles; mp 120–121 °C; IR (KBr) 1695, 1630, 1205, 1045, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 4.24–4.33 (m, 2H, OCH_2), 4.48 (d, J=4.3 Hz, 1H, CH), 4.88 (d, J=4.3 Hz, 1H, CH), 7.13 (d, J=8.5 Hz, 2H, ArH), 7.17 (d, J=8.5 Hz, 2H, ArH), 7.18 (d, J=8.1 Hz, 2H, ArH), 7.42 (d, J=16.2 Hz, 1H, CH), 7.48 (d, J=8.1 Hz, 2H, ArH), 7.64 (d, J=16.2 Hz, 1H, CH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.2 (q), 21.1 (q), 21.4 (q), 51.1 (q), 52.7 (d), 61.7 (t), 85.5 (d), 106.9 (s), 114.5 (d), 127.0 (2×d), 127.8 (2×d), 129.45 (2×d), 129.51 (2×d), 133.1 (s), 136.9 (s), 138.2 (d), 139.5 (s), 139.7 (s), 164.0 (s), 165.1 (s), 170.2 (s). Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.91; H, 6.44.

3.4.4. trans-5-Benzoyl-4-phenyl-2-[(E)-styryl]-4,5-dihydrofuran-3-carboxylic acid methyl ester ***13d***

White needles; mp 180–181 °C; IR (KBr) 1695, 1635, 1215, 1040, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (s, 3H, OCH_3), 4.56 (d, J=4.3 Hz, 1H, CH), 5.78 (d, J=4.3 Hz, 1H, CH), 7.27–7.40 (m, 8H, ArH), 7.46 (d, J=16.4 Hz, 1H, CH), 7.48 (d, J=7.8 Hz, 2H, ArH), 7.58 (d, J=7.2 Hz, 2H, ArH), 7.62 (d, J=7.2 Hz, 1H, ArH), 7.71 (d, J=16.4 Hz, 1H, CH), 7.91 (d, J=7.2 Hz, 2H, ArH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 51.1 (q), 52.0 (d), 89.0 (d), 107.9 (s), 115.5 (d), 127.5 (3×d), 127.8 (2×d), 128.7 (2×d), 128.8 (2×d), 128.9 (2×d), 129.0 (2×d), 129.4 (d), 133.6 (s), 133.9 (d), 135.8 (s), 138.3 (d), 142.3 (s), 163.7 (s), 164.9 (s), 193.7 (s). Anal. Calcd for $C_{27}H_{22}O_4$: C, 79.01; H, 5.40. Found: C, 78.98; H, 5.41.

3.4.5. trans-4-Phenyl-5-(3-phenylpropanoyl)-2-[(E)-styryl]-4,5-dihydrofuran-3-carboxylic acid methyl ester ***13e***

White needles; mp 116–117 °C; IR (KBr) 1700, 1635, 1225, 1045, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85–3.06 (m, 4H, 2×CH_2), 3.60 (s, 3H, OCH_3), 4.41 (d, J=4.3 Hz, 1H, CH), 4.80 (d, J=4.3 Hz, 1H, CH), 7.16–7.43 (m, 14H, ArH+CH), 7.56–7.61 (m, 2H, ArH), 7.71 (d, J=16.3 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.2 (t), 40.1 (t), 51.2 (q), 51.7 (d), 91.9 (d), 107.8 (s), 115.5 (d), 126.3 (d), 127.2 (2×d), 127.3 (d), 127.8 (2×d), 128.4 (2×d), 128.6 (2×d), 128.79 (2×d), 128.82 (2×d), 129.6 (d), 135.6 (s), 138.0 (d), 140.6 (s), 142.4 (s), 163.2 (s), 164.9 (s), 207.7 (s). Anal. Calcd for $C_{29}H_{26}O_4$: C, 79.43; H, 5.98. Found: C, 79.37; H, 5.95.

3.4.6. trans-5-(Diethylcarbamoyl)-4-phenyl-2-[(E)-styryl]-4,5-dihydrofuran-3-carboxylic acid methyl ester ***13f***

White needles; mp 154–155 °C; IR (KBr) 1695, 1635, 1215, 1045, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J=7.0 Hz, 6H, 2×CH_3), 3.23–3.41 (m, 3H, NCH_2+NCH), 3.53 (dq, J=13.9, 7.0 Hz, 1H, NCH), 3.59 (s, 3H, OCH_3), 4.77 (d, J=5.1 Hz, 1H, CH), 5.15 (d, J=5.1 Hz, 1H, CH), 7.23–7.36 (m, 7H, ArH+CH), 7.38 (d, J=8.0 Hz, 2H, ArH), 7.56 (d, J=8.0 Hz, 2H, ArH), 7.69 (d, J=16.3 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.8 (q), 14.4 (q), 40.5 (t), 41.4 (t), 51.0 (q), 52.3 (d), 85.5 (d), 108.6 (s), 115.8 (d), 127.2 (d), 127.5 (2×d), 127.7 (2×d), 128.7 (4×d), 129.2 (d), 135.9 (s), 137.5 (d), 142.8 (s), 163.1 (s), 165.1 (s), 167.5 (s). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.97; H, 6.75; N, 3.38.

3.5. Typical procedure for the reactions between dienones 12 and ethyl nitroacetate (2a) in $CHCl_3$ to produce cyclohexenecarboxylates 14 and 15[12]

A solution of dienone **12a** (130 mg, 0.36 mmol), ethyl nitroacetate (**2a**, 74 mg, 0.56 mmol), and triethylamine (75 mg, 0.74 mmol) in $CHCl_3$ (6 mL) was heated at 60 °C for 14 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g, eluted with 15:1 hexane/EtOAc) to give **14a** (123 mg, 69%) and **15a** (20 mg, 11%).

3.5.1. rel-(1S,2S,6R)-2,6-Bis(4-chlorophenyl)-4-hydroxy-1-nitrocyclohex-3-ene-1,3-dicarboxylic acid 1-ethyl 3-methyl ester ***14a***

White crystals; mp 191–192 °C; IR (KBr) 1750, 1660, 1220, 1095, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.1 Hz, 3H, CH_3), 2.78 (dd, J=19.6, 7.8 Hz, 1H, CH), 2.83 (d, J=19.6, 11.2 Hz, 1H, CH),

3.60 (s, 3H, OCH_3), 3.80 (q, J=7.1 Hz, 2H, OCH_2), 3.98 (dd, J=11.2, 7.8 Hz, 1H, CH), 4.85 (s, 1H, CH), 7.15 (d, J=8.3 Hz, 2H, ArH), 7.17 (d, J=8.3 Hz, 2H, ArH), 7.23 (d, J=8.3 Hz, 2H, ArH), 7.32 (d, J=8.3 Hz, 2H, ArH), 12.31 (s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.3 (q), 32.5 (t), 39.5 (d), 46.4 (d), 51.9 (q), 62.6 (t), 97.4 (s), 98.1 (s), 127.8 (2×d), 128.6 (2×d), 130.6 (2×d), 131.7 (2×d), 134.0 (s), 134.1 (s), 134.6 (s), 136.8 (s), 163.8 (s), 169.1 (s), 170.9 (s). Anal. Calcd for $C_{23}H_{21}Cl_2NO_7$: C, 55.88; H, 4.28; N, 2.83. Found: C, 55.70; H, 4.28; N, 2.74.

3.5.2. *rel-(1S,2S,6R)-4-Hydroxy-1-nitro-2,6-diphenylcyclohex-3-ene-1,3-dicarboxylic acid 1-ethyl 3-methyl ester* ***14b***

White crystals; mp 145–146 °C; IR (KBr) 1755, 1670, 1220, 1035, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J=7.1 Hz, 3H, CH_3), 2.82 (dd, J=19.3, 7.0 Hz, 1H, CH), 2.89 (dd, J=19.3, 11.9 Hz, 1H, CH), 3.59 (s, 3H, OCH_3), 3.64–3.80 (m, 2H, OCH_2), 4.10 (dd, J=11.9, 7.0 Hz, 1H, CH), 4.88 (s, 1H, CH), 7.18–7.27 (m, 7H, ArH), 7.30–7.39 (m, 3H, ArH), 12.32 (s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.2 (q), 32.9 (t), 40.1 (d), 47.2 (d), 51.8 (q), 62.3 (t), 98.0 (s), 98.5 (s), 127.7 (2×d), 128.0 (d), 128.1 (d), 128.4 (2×d), 129.4 (2×d), 130.4 (2×d), 136.5 (s), 138.4 (s), 164.2 (s), 169.3 (s), 171.2 (s). Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.78; H, 5.43; N, 3.23.

3.5.3. *rel-(1S,2S,6R)-4-Hydroxy-2,6-bis(4-methylphenyl)-1-nitrocyclohex-3-ene-1,3-dicarboxylic acid 1-ethyl 3-methyl ester* ***14c***

White crystals; mp 158–159 °C; IR (KBr) 1745, 1645, 1220, 1040, 815 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.77 (dd, J=19.2, 6.9 Hz, 1H, CH), 2.85 (dd, J=19.2, 12.0 Hz, 1H, CH), 3.59 (s, 3H, OCH_3), 3.75 (q, J=7.2 Hz, 2H, OCH_2), 4.06 (dd, J=12.0, 6.9 Hz, 1H, CH), 4.81 (s, 1H, CH), 7.04 (d, J=8.4 Hz, 2H, ArH), 7.09 (d, J=8.4 Hz, 2H, ArH), 7.10 (d, J=8.4 Hz, 2H, ArH), 7.13 (d, J=8.4 Hz, 2H, ArH), 12.29 (s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.3 (q), 21.0 (q), 21.1 (q), 32.9 (t), 39.6 (d), 46.8 (d), 51.8 (q), 62.2 (t), 98.0 (s), 98.6 (s), 128.3 (2×d), 129.0 (2×d), 129.3 (2×d), 130.2 (2×d), 133.4 (s), 135.3 (s), 137.7 (s), 137.8 (s), 164.1 (s), 169.2 (s), 171.3 (s). Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.14; H, 6.01; N, 3.11.

3.5.4. *rel-(1R,2S,6R)-2,6-Bis(4-chlorophenyl)-4-hydroxy-1-nitrocyclohex-3-ene-1,3-dicarboxylic acid 1-ethyl 3-methyl ester* ***15a***

White crystals; mp 214–215 °C; IR (KBr) 1755, 1660, 1225, 1070, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J=7.1 Hz, 3H, CH_3), 2.85 (dd, J=19.5, 11.1 Hz, 1H, CH), 2.88 (dd, J=19.5, 7.9 Hz, 1H, CH), 3.61 (s, 3H, OCH_3), 4.00 (dd, J=11.1, 7.9 Hz, 1H, CH), 4.21 (dq, J=10.8, 7.1 Hz, 1H, OCH), 4.37 (dq, J=10.8, 7.1 Hz, 1H, OCH), 4.80 (s, 1H, CH), 7.11 (d, J=8.6 Hz, 2H, ArH), 7.18 (d, J=8.6 Hz, 2H, ArH), 7.22 (d, J=8.6 Hz, 2H, ArH), 7.30 (d, J=8.6 Hz, 2H, ArH), 12.33 (s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.6 (q), 34.3 (t), 39.3 (d), 46.8 (d), 52.1 (q), 63.1 (t), 97.9 (s), 98.8 (s), 127.8 (2×d), 128.8 (2×d), 130.4 (2×d), 132.1 (2×d), 134.0 (s), 134.1 (s), 134.5 (s), 136.1 (s), 164.8 (s), 169.1 (s), 170.9 (s). Anal. Calcd for $C_{23}H_{21}Cl_2NO_7$: C, 55.88; H, 4.28; N, 2.83. Found: C, 55.76; H, 4.24; N, 2.78.

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9. *Crystal data for* ***12b***: $C_{19}H_{16}O_3$, M=292.32, T=200(2) K, λ=0.71073 Å, triclinic, space group $P\bar{1}$, a=8.8923(2) Å, b=9.3625(2) Å, c=10.0929(3) Å, α=112.8270(10)°, β=92.8430(10)°, γ=100.4750(10)°, V=754.84(3) Å^3, Z=2, D_c=1.286 mg/m^3, μ=0.086 mm^{-1}, F(000)=308, crystal size 0.75×0.65×0.35 mm^3, reflections collected 10,206, independent reflections 2759 [R (int)=0.0732], refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 0.983, final R indices [$I>2\sigma(I)$] R_1=0.0505, wR_2=0.1453, R indices (all data) R_1=0.0611, wR_2=0.1693, largest diff. peak and hole 0.368 and −0.420 e Å^{-3}. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 679631.
Crystal data for ***14a***: $C_{23}H_{21}Cl_2NO_7$, M=494.31, T=296(2) K, λ=0.71073 Å, triclinic, space group $P\bar{1}$, a=9.577(2) Å, b=10.459(3) Å, c=13.331(3) Å, α=92.318(7)°, β=109.428(6)°, γ=114.004(6)°, V=1126.3(5) Å^3, Z=2, D_c=1.458 mg/m^3, μ=0.334 mm^{-1}, F(000)=512, crystal size 0.46×0.32×0.12 mm^3, reflections collected 7857, independent reflections 3846 [R (int)=0.0270], refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 0.661, final R indices [$I>2\sigma(I)$] R_1=0.0440, wR_2=0.1262, R indices (all data) R_1=0.0677, wR_2=0.1741, largest diff. peak and hole 0.676 and −0.422 e Å^{-3}. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 679632.
Crystal data for ***15a***: $C_{23}H_{21}Cl_2NO_7$, M=494.31, T=296(2) K, λ=0.71073 Å, monoclinic, space group $P2_1/n$, a=13.0209(15) Å, b=9.5917(10) Å, c=19.436(2) Å, α=90°, β=105.880(1)°, γ=90°, V=2334.7(4) Å^3, Z=4, D_c=1.406 mg/m^3, μ=0.322 mm^{-1}, F(000)=1024, crystal size 0.72×0.26×0.20 mm^3, reflections collected 15,546, independent reflections 4127 [R (int)=0.0446], refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 0.979, final R indices [$I>2\sigma(I)$] R_1=0.0547, wR_2=0.1480, R indices (all data) R_1=0.0919, wR_2=0.1807, largest diff. peak and hole 0.529 and −0.308 e Å^{-3}. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 679633. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
10. leNoble, W. J.; Morris, H. F. *J. Org. Chem.* **1969**, *34*, 1969.
11. Dihydrofuran **13a** and cyclohexenecarboxylate **15a** are inseparable on column chromatography.
12. Cyclohexenecarboxylates **14b**/**15b** and **14c**/**15c** cannot be separated by column chromatography; however, the major product **14b** or **14c** can be obtained in pure form by crystallization from the isomeric product mixture.