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A facile synthesis of highly functionalized dihydrofurans based on 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed reaction of halides with enones

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Abstract—Treatment of halides **5** with electrophilic alkenes **2** afforded the corresponding dihydrofurans **3** and **4** in the presence of 1, 4-diazabicyclo[2.2.2]octane (DABCO) with good to excellent yields and in a stereoselective manner in most cases. Moreover, the stereoisomers **3** and **4** could be easily transformed each other in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

1. Introduction

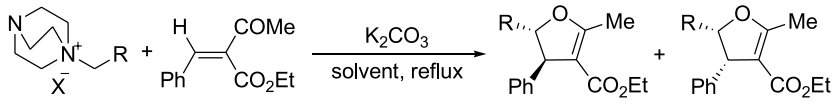
Dihydrofurans are among the most important heterocycles for the construction of a wide range of naturally occurring substances and possess a multiplicity of biological activities.[1] They are also potentially useful intermediates in organic synthesis.[2] For these reasons, the development of new and efficient methods for the synthesis of dihydrofurans remains an area of strong interest.[3]

Recently, the reactions of sulfonium[4] and arsonium[5] ylides with enones to afford dihydrofurans have been reported. However, arsonium compounds are strong hazardous materials; the reactions of sulfonium ylides gave dihydrofurans accompanying with cyclopropane byproducts. On the other hand, in the above processes, the ylide precursor was usually generated in a separate step.

In this paper, we report a novel synthetic route to form dihydrofurans via ammonium ylides[6] in one-step based on a catalytic process. Surprisingly, there was no report on this catalytic method for synthesis of dihydrofurans.

2. Results and discussion

We began our study by investigating the reactivity of preformed quaternary ammonium salts **1** with (*Z*)-ethyl-2-benzyliden-3-oxobutanoate (**2b**) under different conditions (Scheme 1). The preliminary studies demonstrated that the reaction of the ammonium ylides with the enone in the presence of anhydrous K_2CO_3 under reflux yielded dihydrofurans without the formation of cyclopropane. The results are presented in Table 1, which show that the R group of salts **1** played an important role in the stereoselectivity of the procedure. Generally, when R was a strong electron-withdrawing group, the trans-isomer was formed preferentially. As we seen, there is a higher trans-selectivity in entries 5–8 than in entries 1–4 (Table 1).



1a-d **2b** **3b, 3e, 3h, 3k** **4b,4e,4h**

Scheme 1. Reaction of salts **1** with (*Z*)-ethyl-2-benzyliden-3-oxobutanoate.

Keywords: DABCO; Ylides; Enones; Dihydrofurans; Furans.
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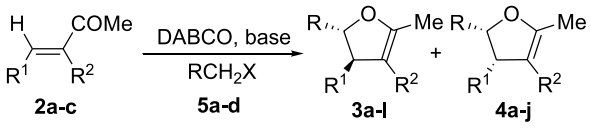
Table 1. Reaction of salts **1** with alkene **2b**[a]

Entry	Salt	X	R	Solvent	Product	Yield %[b]	Product	Yield %[b]
1	**1a**	Cl	CN	CH_2Cl_2/DMSO[c]	**3b**	67	**4b**	25
2	**1a**	Cl	CN	CH_3CN	**3b**	65	**4b**	24
3	**1b**	Cl	CO_2Et	CH_2Cl_2/DMSO[c]	**3e**	46	**4e**	37
4	**1b**	Cl	CO_2Et	CH_3CN	**3e**	47	**4e**	36
5	**1c**	Br	COPh	CH_2Cl_2/DMSO[c]	**3h**	85	**4h**	7
6	**1c**	Br	COPh	CH_3CN	**3h**	76	**4h**	6
7	**1d**	Cl	Thiophene-2-carbonyl	CH_2Cl_2/DMSO[c]	**3k**	86	None	
8	**1d**	Cl	Thiophene-2-carbonyl	CH_3CN	**3k**	75	None	

[a] Salt **1** (1.5 equiv), enone **2b** (1.0 equiv), K_2CO_3 (2.0 equiv), solvent, reflux.
[b] Isolated yield.
[c] v/v=4/1.



Scheme 2. DABCO-catalyzed reaction.

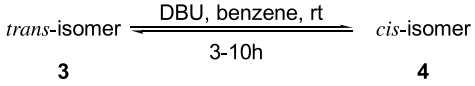
Encouraged by the above results, we then investigated a catalytic process utilizing 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst, in which the ammonium salts **1**, and hence, the ylides could be generated in situ from readily available halides **5**. The reaction worked well for a range of halides and enones (Scheme 2), and the results of which are summarized in Table 2. Chloroacetonitrile (**5a**) and ethyl chloroacetate (**5b**) gave a separable mixture of trans- and cis-dihydrofurans in good yields in CH_2Cl_2/DMSO (4:1) in the presence of K_2CO_3. The α-halo carbonyl compounds **5c** and **5d** gave mostly trans-substituted products in acetonitrile at 80 °C (Table 2). It is worth noting that no reaction took place in the absence of DABCO, which suggests that the tertiary amine is required as the catalyst in these reactions.

Although different stereoisomers were obtained in most cases, **3** and **4** could be separated from one another on silica gel with petroleum ether–ethyl acetate as eluent and the isomers pair **3** and **4** could be readily transformed each other in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[3h] in benzene (Scheme 3). The transformation could eventually reach a thermodynamic equilibrium whether a pure cis- or trans-isomer was used as the starting material (Table 3).

The dihydrofurans structure was identified by ^1H and ^{13}C NMR, MS, HRMS and IR spectral data. The five-membered heterocyclic structures of **3j** and **4j** were further confirmed by a single-crystal X-ray diffraction analysis (Figs. 1 and 2).[7,8]

The mechanism of formation of **3** and **4** could be explained by the following pathway (Scheme 4), based on the previous mechanism of Moorhoff.[9] A halide source **5** undergoes S_N2 displacement with the tertiary amine **8** to form quaternary ammonium salt **1**. Deprotonation of **1** with a mild base forms the ylide **6**, which undergoes Michael addition with **2** to afford the intermediate **7**. The intermediate **7** would readily undergo ring-closing reaction by internal S_N2 displacement of the tertiary amine **8** from the enolate oxygen to give dihydrofurans **3** and **4**. The yield of the trans-isomer is higher than that of the cis-isomer probably due to the major thermodynamic stability of the trans-isomer. This result is different from that of Fan et al.[10]

Moreover, the obtained dihydrofurans **3** and **4** could be further converted into the corresponding furans using mild



Scheme 3. Transformation.

Table 2. Synthesis of dihydrofurans

Entry	Halide	X	R	Enone	R^1	R^2	Conditions	Product	Yield %[a]	Product	Yield %[a]
1	**5a**	Cl	CN	**2a**	Ph	COMe	**A**[b]	**3a**	63	**4a**	35
2	**5a**	Cl	CN	**2b**	Ph	CO_2Et	**A**[b]	**3b**	69	**4b**	26
3	**5a**	Cl	CN	**2c**	4-Cl-C_6H_4	COMe	**A**[b]	**3c**	64	**4c**	29
4	**5b**	Cl	CO_2Et	**2a**	Ph	COMe	**A**[b]	**3d**	45	**4d**	35
5	**5b**	Cl	CO_2Et	**2b**	Ph	CO_2Et	**A**[b]	**3e**	50	**4e**	39
6	**5b**	Cl	CO_2Et	**2c**	4-Cl-C_6H_4	COMe	**A**[b]	**3f**	48	**4f**	34
7	**5c**	Br	COPh	**2a**	Ph	COMe	**B**[c]	**3g**	89	**4g**	9
8	**5c**	Br	COPh	**2b**	Ph	CO_2Et	**B**[c]	**3h**	88	**4h**	8
9	**5c**	Br	COPh	**2c**	4-Cl-C_6H_4	COMe	**B**[c]	**3i**	85	**4i**	9
10	**5d**	Cl	Thiophene-2-carbonyl	**2a**	Ph	COMe	**B**[c]	**3j**	85	**4j**	11
11	**5d**	Cl	Thiophene-2-carbonyl	**2b**	Ph	CO_2Et	**B**[c]	**3k**	88	None	
12	**5d**	Cl	Thiophene-2-carbonyl	**2c**	4-Cl-C_6H_4	COMe	**B**[c]	**3l**	80	None	

[a] Isolated yield.
[b] Enone (1.0 equiv), halide (1.0 equiv), DABCO (0.2 equiv), K_2CO_3 (1.5 equiv), CH_2Cl_2/DMSO, reflux.
[c] Enone (1.0 equiv), halide (1.0 equiv), DABCO (0.2 equiv), Na_2CO_3 (1.5 equiv), CH_3CN, 80 °C.

Table 3. Transformation of either isomer

Entry	Starting material	Product	Yield %[a]	Entry	Starting material	Product	Yield %[a]
1	**4a**	**3a**	63	11	**3a**	**4a**	34
2	**4b**	**3b**	69	12	**3b**	**4b**	26
3	**4c**	**3c**	67	13	**3c**	**4c**	29
4	**4d**	**3d**	54	14	**3d**	**4d**	44
5	**4e**	**3e**	59	15	**3e**	**4e**	39
6	**4f**	**3f**	53	16	**3f**	**4f**	41
7	**4g**	**3g**	76	17	**3g**	**4g**	18
8	**4h**	**3h**	88	18	**3h**	**4h**	7
9	**4i**	**3i**	82	19	**3i**	**4i**	14
10	**4j**	**3j**	84	20	**3j**	**4j**	11

[a] Isolated yield.

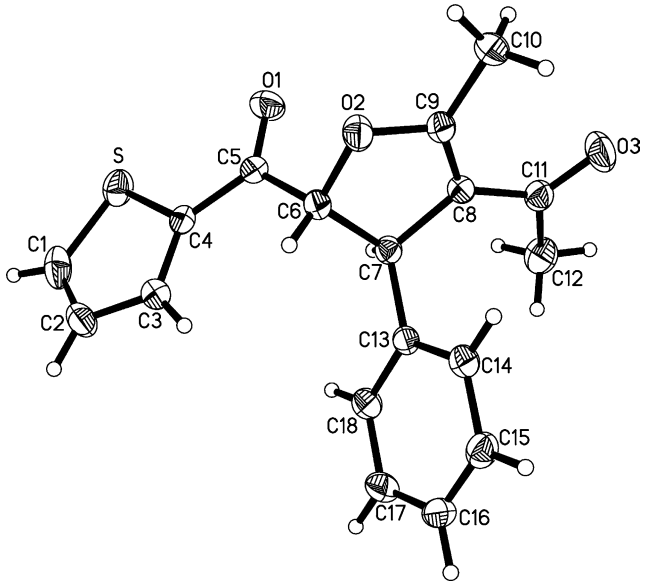


Figure 1. Molecular structure of **3j**.

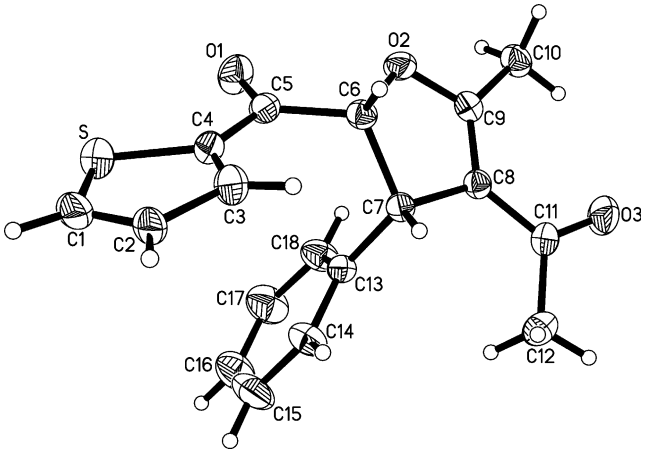
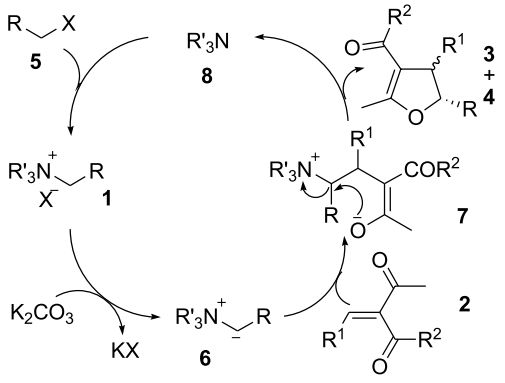
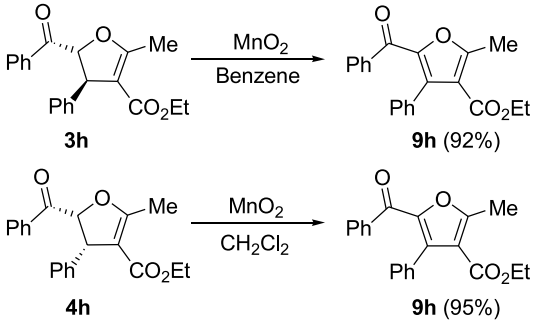


Figure 2. Molecular structure of **4j**.

oxidant, chemical manganese dioxide (CMD).[11] For example, a benzene solution of **3h** was refluxed for 48 h or a dichloromethane solution of **4h** was refluxed for 12 h in the presence of an excess of activated MnO_2 (10–15 equiv), both affording the tetrasubstituted furan **9h** in high yield (Scheme 5).



Scheme 4. Formation of dihydrofurans.



Scheme 5. Oxidation.

3. Conclusions

In this work, we have developed a facile and economical synthetic method of tetrasubstituted dihydrofurans as well as furans via the reaction of ammonium ylides in a catalytic process. Moreover, one stereoisomer of the two result dihydrofurans can be conveniently transformed to the other as required. We believe that this method would give a new viable entry to highly functionalized dihydrofurans.

4. Experimental

4.1. General

Melting points were determined on a microscopic apparatus and were uncorrected. Column chromatography was carried out on silica gel. The ^{1}H and ^{13}C NMR spectra were

recorded at 300 and 75 MHz, respectively. IR spectra were obtained using an FT-IR spectrometer and only major peaks are reported in cm^{-1}. Mass spectra were recorded by the EI method. HRMS spectra were obtained with a Bruker APEX instrument. All reagents were used directly as obtained commercially unless otherwise noted. All mixed solvent systems are reported as v/v solutions. Alkenes **2** (**2a**, **2b** and **2c**) were easily prepared using a literature procedure.[12]

4.2. Typical procedure for the preparation of ammonium salts 1[13]

DABCO (1.12 g, 10 mmol) was added to a solution of chloroacetonitrile (0.755 g, 10 mmol) in THF (50 mL). The reaction was stirred at room temperature for 1 h. After evaporating the solvent under reduced pressure, the resulting solid was washed with petroleum ether and then dissolved in a mixture of MeOH (5 mL) and PhH (5 mL). The solvents were removed under reduced pressure to afford the ammonium salt **1a** as a white solid (1.8 g, 96%).

4.3. General procedure for the reaction of ammonium salts 1 with enone 2b

The mixture of **1** (1.5 mmol), **2b** (1 mmol) and K_2CO_3 (2 mmol) in CH_3CN or in CH_2Cl_2/DMSO (v/v, 4/1) (10 mL) was stirred vigorously at refluxing temperature. Once the reaction was completed, checked by TLC analysis, the reaction was quenched with 15–20 mL of water and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). After evaporating the solvent under reduced pressure, the residue was purified on silica gel with petroleum ether–ethyl acetate (30/1–10/1) as eluent to give first the trans-isomer **3**, while further elution to yield the cis-isomer **4**.

4.4. General procedure for DABCO-catalyzed reaction of halides 5 with enones 2

DABCO (0.2 mmol) was added to a stirred solution of **5** (1 mmol) in CH_3CN or in CH_2Cl_2/DMSO (v/v, 4/1) (10 mL) at room temperature. After stirred for 30 min, the inorganic base (1.5 mmol) was added, followed by the enone **2** (1 mmol). The reaction was vigorously stirred at refluxing temperature. Once completed, checked by TLC analysis, the reaction was quenched with water (15–20 mL) and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). After evaporating the solvent under reduced pressure, the residue was purified on silica gel with petroleum ether–ethyl acetate (30/1–10/1) as eluent to give first the trans-isomer **3**, while further elution to yield the cis-isomer **4**.

4.4.1. trans-4-Acetyl-2-cyano-5-methyl-3-phenyl-2,3-dihydrofuran (3a). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.39 (m, 5H), 4.96 (d, J=4.5 Hz, 1H), 4.66 (d, J=4.2 Hz, 1H), 2.40 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8, 167.2, 139.9, 129.6, 128.7, 127.3, 117.1, 115.9, 74.9, 55.2, 29.9, 14.9. IR (KBr): 3022, 2922, 2852, 2147, 1679, 1608, 1494, 1452, 1379, 1217, 757, 703 cm^{-1}. MS (EI, 70 eV): m/z (%) 227 (M^+, 8.58), 212 (3.87), 200 (9.42), 170 (15.78), 43 (100). HRMS: m/z [M+H] calcd for $C_{14}H_{13}NO_2$: 228.1019; found: 228.1015.

4.4.2. cis-4-Acetyl-2-cyano-5-methyl-3-phenyl-2,3-dihydrofuran (4a). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.42 (m, 5H), 5.44 (d, J=10.2 Hz, 1H), 4.60 (d, J=10.2 Hz, 1H), 2.39 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 167.5, 137.4, 129.4, 129.1, 128.2, 116.0, 114.6, 74.0, 52.3, 29.8, 14.8. IR (KBr): 3022, 2922, 2218, 1676, 1606, 1495, 1381, 1216, 757, 705 cm^{-1}. MS (EI, 70 eV): m/z (%) 227 (M^+, 28.17), 212 (10.28), 200 (18.46), 170 (30.26), 43 (100). HRMS: m/z [M+H] calcd for $C_{14}H_{13}NO_2$: 228.1019; found: 228.1012.

4.4.3. trans-5-Cyano-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (3b). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.34 (m, 5H), 5.01 (d, J=4.2 Hz, 1H), 4.60 (d, J=3.9 Hz, 1H), 4.04 (q, J=7.2 Hz, 2H), 2.38 (s, 3H), 1.09 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 163.9, 140.0, 128.9, 128.0, 126.9, 117.0, 107.4, 74.5, 60.0, 54.3, 13.9, 13.8. IR (KBr): 3030, 2983, 2255, 1704, 1658, 1605, 1492, 1453, 1378, 1213, 1087, 758, 701 cm^{-1}. MS (EI, 70 eV): m/z (%) 257 (M^+, 24.57), 230 (5.66), 212 (15.06), 211 (19.74), 169 (83.64), 43 (100). HRMS: m/z [M+NH_4] calcd for $C_{15}H_{15}NO_3$: 275.1390; found: 275.1394.

4.4.4. cis-5-Cyano-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (4b). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.39 (m, 5H), 5.44 (d, J=10.2 Hz, 1H), 4.55 (d, J=10.2 Hz, 1H), 4.03 (q, J=7.2 Hz, 2H), 2.37 (s, 3H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 164.3, 137.7, 129.0, 128.6, 128.0, 114.7, 107.7, 73.8, 60.2, 51.8, 14.2, 14.0. IR (KBr): 2983, 2928, 2247, 1703, 1656, 1501, 1452, 1379, 1215, 1091, 1021, 755, 702 cm^{-1}. MS (EI, 70 eV): m/z (%) 257 (M^+, 26.33), 230 (3.75), 215 (14.25), 212 (14.15), 211 (18.12), 169 (68.66), 43 (100). HRMS: m/z [M+NH_4] calcd for $C_{15}H_{15}NO_3$: 275.1390; found: 275.1384.

4.4.5. trans-4-Acetyl-3-(4-chlorophenyl)-2-cyano-5-methyl-2,3-dihydrofuran (3c). Solid; mp 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 4.92 (d, J=4.5 Hz, 1H), 4.64 (d, J=4.5 Hz, 1H), 2.41 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 167.1, 138.3, 134.5, 129.7, 128.6, 116.8, 116.1, 74.6, 54.4, 29.8, 14.9. IR (KBr): 3030, 2921, 2844, 2263, 1679, 1632, 1608, 1491, 1381, 1216, 1091 cm^{-1}. MS (EI, 70 eV): m/z (%) 261 (M^+, 14.20), 246 (4.79), 234 (16.26), 226 (2.69), 219 (12.15), 204 (12.67), 43 (100). HRMS: m/z [M+H] calcd for $C_{14}H_{12}ClNO_2$: 262.0629; found: 262.0632.

4.4.6. cis-4-Acetyl-3-(4-chlorophenyl)-2-cyano-5-methyl-2,3-dihydrofuran (4c). Solid; mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 5.42 (d, J=9.9 Hz, 1H), 4.58 (d, J=9.9 Hz, 1H), 2.38 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 167.5, 135.9, 134.9, 129.6, 129.5, 116.1, 114.3, 73.6, 51.7, 29.7, 14.8. IR (KBr): 2924, 2247, 1677, 1629, 1605, 1491, 1381, 1213, 1090 cm^{-1}. MS (EI, 70 eV): m/z (%) 261 (M^+, 15.23), 246 (4.20), 234 (14.25), 226 (2.39),

219 (11.39), 204 (10.88), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{14}H_{12}ClNO_2$: 262.0629; found: 262.0625.

4.4.7. trans-4-Acetyl-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (3d). Solid; mp 51–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.38 (m, 5H), 4.78 (d, J=4.8 Hz, 1H), 4.49 (d, J=4.5 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.96 (s, 3H), 1.34 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 170.1, 168.8, 142.4, 129.3, 127.9, 127.4, 115.3, 86.2, 62.1, 53.5, 29.9, 15.1, 14.4. IR (KBr): 2983, 1753, 1674, 1604, 1494, 1449, 1380, 1197, 1037, 764, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 274 (M^+, 5.22), 231 (5.27), 201 (24.20), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{18}O_4$: 275.1278; found: 275.1278.

4.4.8. cis-4-Acetyl-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (4d). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.28 (m, 5H), 5.32 (d, J=10.2 Hz, 1H), 4.62 (d, J=10.2 Hz, 1H), 3.62–3.82 (m, 2H), 2.45 (s, 3H), 1.91 (s, 3H), 0.86 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 168.9, 167.6, 138.1, 128.7, 128.6, 128.1, 116.1, 83.9, 61.3, 52.1, 29.8, 15.1, 13.8. IR (KBr): 2985, 2931, 1752, 1674, 1603, 1494, 1450, 1379, 1210, 1043, 757, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 274 (M^+, 7.49), 259 (1.53), 231 (3.71), 201 (15.96), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{18}O_4$: 275.1278; found: 275.1279.

4.4.9. trans-5-Methyl-3-phenyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (3e). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.34 (m, 5H), 4.83 (d, J=4.8 Hz, 1H), 4.41 (d, J=4.5 Hz, 1H), 4.26 (q, J=6.9 Hz, 2H), 4.09 (q, J=6.9 Hz, 2H), 2.40 (s, 3H), 1.32 (t, J=7.2 Hz, 3H), 1.06 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 168.5, 165.0, 142.8, 128.8, 127.3, 106.6, 85.9, 61.9, 59.7, 52.9, 14.2. IR (KBr): 2982, 2923, 1755, 1702, 1651, 1452, 1379, 1209, 1090, 1034, 759, 700 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 304 (M^+, 23.17), 259 (16.66), 258 (28.86), 231 (29.75), 230 (78.31), 202 (27.90), 201 (28.88), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{17}H_{20}O_5$: 305.1384; found: 305.1380.

4.4.10. cis-5-Methyl-3-phenyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (4e). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.26 (m, 5H), 5.30 (d, J=10.5 Hz, 1H), 4.56 (d, J=10.5 Hz, 1H), 3.99 (q, J=7.2 Hz, 2H), 3.64–3.78 (m, 2H), 2.41 (s, 3H), 1.03 (t, J=7.2 Hz, 3H), 0.83 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 167.9, 165.0, 138.7, 128.4, 128.2, 127.7, 127.5, 107.5, 83.7, 61.2, 59.7, 51.6, 14.2, 13.7. IR (KBr): 2984, 1729, 1662, 1624, 1494, 1448, 1379, 1212, 1095, 1042, 757, 697 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 304 (M^+, 37.41), 259 (13.63), 258 (11.54), 231 (43.33), 230 (40.86), 202 (15.30), 201 (11.85), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{17}H_{20}O_5$: 305.1384; found: 305.1378.

4.4.11. trans-4-Acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (3f). Sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J=8.1 Hz, 2H), 7.18 (d, J=8.1 Hz, 2H), 4.74 (d, J=4.8 Hz, 1H), 4.48 (d, J=4.5 Hz, 1H), 4.29 (q, J=6.9 Hz, 2H), 2.44 (s, 3H), 2.00 (s, 3H), 1.32 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 169.8, 168.8, 140.9, 133.6, 129.4, 128.7, 115.4, 85.8, 62.1, 52.8, 29.7, 15.1, 14.3. IR (KBr): 2985, 2919, 1754, 1675, 1626, 1602, 1490, 1380, 1199, 1092, 1039, 832 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 308 (M^+, 10.27), 265 (10.95), 235 (47.84), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{17}ClO_4$: 309.0888; found: 309.0888.

4.4.12. cis-4-Acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (4f). Sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.4 Hz, 2H), 5.30 (d, J=10.5 Hz, 1H), 4.61 (d, J=10.5 Hz, 1H), 3.69–3.87 (m, 2H), 2.44 (s, 3H), 1.96 (s, 3H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 168.9, 167.4, 136.8, 133.9, 130.0, 128.7, 116.2, 83.6, 61.4, 51.4, 29.7, 15.1, 13.8. IR (KBr): 2986, 2936, 1753, 1719, 1675, 1599, 1490, 1381, 1210, 1092, 1043, 855 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 308 (M^+, 9.99), 293 (2.16), 265 (6.74), 235 (29.83), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{17}ClO_4$: 309.0888; found: 309.0886.

4.4.13. trans-4-Acetyl-2-benzoyl-5-methyl-3-phenyl-2,3-dihydrofuran (3g). Solid; mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.89 (m, 10H), 5.66 (d, J=4.5 Hz, 1H), 4.53 (d, J=4.5 Hz, 1H), 2.47 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ194.4, 193.5, 168.6, 142.4, 134.3, 133.7, 129.3, 129.1, 127.9, 127.8, 116.0, 89.7, 52.2, 29.8, 15.2. IR (KBr): 2921, 1693, 1671, 1601, 1490, 1382, 1224, 1069, 1017, 757, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 306 (M^+, 0.46), 263 (78.90), 201 (13.42), 105 (35.77), 77 (41.48), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{18}O_3$: 307.1329; found: 307.1332.

4.4.14. cis-4-Acetyl-2-benzoyl-5-methyl-3-phenyl-2,3-dihydrofuran (4g). Sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79–7.56 (m, 10H), 6.23 (d, J=10.2 Hz, 1H), 4.73 (d, J=10.2 Hz, 1H), 2.52 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 193.8, 169.2, 137.4, 135.9, 133.7, 128.8, 128.4, 127.9, 127.7, 116.8, 87.6, 53.2, 29.8, 15.3. IR (KBr): 2924, 1697, 1667, 1601, 1494, 1446, 1386, 1217, 1071, 1021, 755, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 306 (M^+, 2.44), 263 (42.31), 201 (18.35), 105 (64.63), 77 (46.59), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{18}O_3$: 307.1329; found: 307.1331.

4.4.15. trans-5-Benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (3h). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.85 (m, 10H), 5.73 (d, J=4.5 Hz, 1H), 4.40 (d, J=4.5 Hz, 1H), 3.96 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.04 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.7, 168.6, 165.1, 142.8, 134.2, 133.7, 129.2, 129.0, 127.8, 127.6, 107.2, 89.5, 59.7, 52.0, 14.3. IR (KBr): 3024, 2924, 2855, 1698, 1651, 1601, 1453, 1380, 1218, 1091, 757, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 336 (M^+, 9.34), 321 (9.59), 293 (17.50), 263 (34.69), 231 (22.87), 105 (100), 77 (70.78), 43 (65.56). HRMS: *m/z* [M+H] calcd for $C_{21}H_{20}O_4$: 337.1434; found: 337.1433.

4.4.16. cis-5-Benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (4h). Solid; mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81–7.55 (m, 10H), 6.20 (d, J=10.5 Hz, 1H), 4.68 (d, J=10.2 Hz, 1H), 3.99 (q, J=6.9 Hz, 2H), 2.49 (s, 3H), 1.03 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ194.1, 168.8, 165.1, 138.0, 135.9,

133.6, 128.7, 128.0, 127.9, 127.3, 108.0, 87.8, 59.8, 52.8, 14.4, 14.2. IR (KBr): 2927, 1696, 1648, 1600, 1449, 1385, 1212, 1096, 1021, 756, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 336 (M^+, 12.41), 321 (10.08), 293 (16.07), 263 (15.99), 231 (31.87), 105 (100), 77 (84.08), 43 (79.71). HRMS: *m/z* [M+H] calcd for $C_{21}H_{20}O_4$: 337.1434; found: 337.1434.

4.4.17. trans-4-Acetyl-2-benzoyl-3-(4-chloro-phenyl)-5-methyl-2,3-dihydrofuran (3i). Sticky oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.86 (m, 9H), 5.61 (d, J=4.8 Hz, 1H), 4.54 (d, J=4.5 Hz, 1H), 2.44 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.72, 193.14, 168.48, 140.92, 134.24, 133.52, 129.37, 129.14, 129.05, 128.99, 116.06, 89.20, 51.37, 29.62, 15.09. IR (KBr): 3067, 3017, 2924, 1697, 1672, 1623, 1598, 1490, 1446, 1381, 1223, 1093, 830, 756, 694 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 340 (M^+, 0.20), 297 (68.54), 235 (13.68), 105 (42.96), 77 (37.74), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{17}ClO_3$: 341.0939; found: 341.0943.

4.4.18. cis-4-Acetyl-2-benzoyl-3-(4-chloro-phenyl)-5-methyl-2,3-dihydrofuran (4i). Solid; mp 125–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.59 (m, 5H), 6.99 (d, J=8.1 Hz, 2H), 6.74 (d, J=8.4 Hz, 2H), 6.20 (d, J=10.2 Hz, 1H), 4.72 (d, J=10.2 Hz, 1H), 2.52 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 193.5, 169.2, 136.1, 135.7, 133.9, 133.6, 130.0, 128.9, 128.6, 127.9, 117.0, 87.4, 52.6, 29.7, 15.3. IR (KBr): 3015, 2924, 1698, 1671, 1623, 1597, 1489, 1446, 1384, 1214, 1088, 756, 694 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 340 (M^+, 1.67), 297 (26.85), 235 (10.66), 105 (69.69), 77 (39.45), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{17}ClO_3$: 341.0939; found: 341.0931.

4.4.19. trans-4-Acetyl-5-methyl-3-phenyl-2-(thiophene-2-carbonyl)-2,3-dihydrofuran (3j). Solid; mp 148–150 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.12–7.74 (m, 8H), 5.40 (d, J=4.8 Hz, 1H), 4.64 (d, J=4.5 Hz, 1H), 2.46 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 187.6, 168.4, 142.4, 140.5, 135.6, 134.0, 129.4, 128.6, 127.9, 127.8, 115.8, 90.5, 52.7, 29.9, 15.2. IR (KBr): 2924, 1674, 1606, 1382, 1229, 1067, 1028, 758, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 312 (M^+, 0.92), 269 (100), 201 (19.94), 111 (53.90), 43 (89.76). HRMS: *m/z* [M+H] calcd for $C_{18}H_{16}O_3S$: 313.0893; found: 313.0890.

4.4.20. cis-4-Acetyl-5-methyl-3-phenyl-2-(thiophene-2-carbonyl)-2,3-dihydrofuran (4j). Solid; mp 79–81 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.93–7.64 (m, 8H), 5.90 (d, J=10.5 Hz, 1H), 4.76 (d, J=10.5 Hz, 1H), 2.53 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 186.9, 169.0, 141.7, 137.2, 134.6, 132.8, 128.8, 128.5, 128.0, 127.8, 116.5, 88.4, 53.6, 29.8, 15.2. IR (KBr): 3104, 2924, 1670, 1602, 1515, 1383, 1219, 1068, 1031, 754, 704 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 312 (M^+, 2.50), 269 (62.00), 201 (19.31), 111 (66.74), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{18}H_{16}O_3S$: 313.0893; found: 313.0894.

4.4.21. trans-2-Methyl-4-phenyl-5-(thiophene-2-carbonyl)-4,5-dihydrofuran-3-carboxylic acid ethyl ester (3k). Sticky oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.08–7.71 (m, 8H), 5.47 (d, J=4.8 Hz, 1H), 4.53 (d, J=4.8 Hz, 1H), 3.97 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.03 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 168.2, 164.9, 142.7, 140.3, 135.3, 133.6, 128.8, 128.5, 127.6, 127.4, 107.1, 90.0, 59.6, 52.4, 14.2. IR (KBr): 3092, 3024, 2982, 2931, 1694, 1652, 1514, 1452, 1380, 1217, 1090, 1031, 756, 702 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 342 (M^+, 10.56), 327 (3.99), 299 (14.18), 269 (24.60), 231 (15.21), 111 (100), 43 (44.77). HRMS: *m/z* [M+H] calcd for $C_{19}H_{18}O_4S$: 343.0999; found: 343.0995.

4.4.22. trans-4-Acetyl-3-(4-chloro-phenyl)-5-methyl-2-(thiophene-2-carbonyl)-2,3-dihydrofuran (3l). Sticky oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.76 (m, 7H), 5.36 (d, J=4.8 Hz, 1H), 4.64 (d, J=4.8 Hz, 1H), 2.46 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 187.3, 168.4, 141.0, 140.3, 135.8, 134.1, 133.7, 129.5, 129.1, 128.7, 116.0, 90.2, 52.0, 29.8, 15.2. IR (KBr): 3097, 3015, 2911, 1672, 1625, 1599, 1514, 1490, 1380, 1228, 1090, 1022, 830 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 346 (M^+, 0.55), 303 (76.85), 235 (13.68), 111 (53.83), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{18}H_{15}ClO_3S$: 347.0503; found: 347.0505.

4.5. General procedure for the transformation of either stereoisomer

The mixture of the cis-isomer **4** (0.1 mmol) and DBU (0.01 mmol) in benzene (2 mL) was stirred at room temperature for 3 h. After evaporating the solvent under reduced pressure, the residue was purified on silica gel with petroleum ether–ethyl acetate (30/1–10/1) as eluent to give first the trans-isomer **3**, while further elution to yield the cis-isomer **4**. When the starting material was a trans-isomer, the reaction took longer.

4.6. Typical procedure for oxidation to tetrasubstituted furans[11b]

To 8 mL benzene solution of dihydrofuran **3h** (0.4 mmol) was added 0.52 g (6 mmol) of CMD, and the suspension was refluxed for 48 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified on silica gel with petroleum–ethyl acetate (20/1) as eluent to give 122.9 mg (92%) of tetrasubstituted furan **9h**.

To 5 mL dichloromethane solution of dihydrofuran **4h** (0.2 mmol) was added 174 mg (2 mmol) of CMD, and the suspension was refluxed for 12 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified on silica gel with petroleum ether–ethyl acetate (20/1) as eluent to give 63.5 mg (95%) of tetrasubstituted furan **9h**.

4.6.1. 5-Benzoyl-2-methyl-4-phenylfuran-3-carboxylic acid ethyl ester (9h). Solid; mp 75–77 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.71 (m, 10H), 4.12 (q, J=7.2 Hz, 2H), 2.74 (s, 3H), 1.06 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.5, 163.0, 162.0, 146.1, 136.9, 135.0, 132.1, 131.3, 129.8, 129.2, 127.7, 127.6, 127.2, 116.0, 60.2, 14.6, 13.6. IR (KBr): 3060, 2983, 2932, 1712, 1648, 1593, 1541, 1487, 1447, 1411, 1246, 1180, 1092, 1011, 731, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 334 (M^+, 3.66), 333 (3.09), 305 (2.57), 159 (8.16), 115 (10.39), 105

(100), 77 (66.74), 43 (45.41). HRMS: *m/z* [M+H] calcd for $C_{21}H_{18}O_4$: 335.1278; found: 335.1276.

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7. Crystal data for **3j**: $C_{18}H_{16}O_3S$, M_W=312.37, T=291(2) K, λ=0.71073 Å, monoclinic space group $P2(1)/n$, a=9.804(1) Å, b=10.474(1) Å, c=15.324(2) Å, α=90.00°, β=102.860(2)°, γ=90.00°, V=1534.0(3) Å^3, Z=4, D_c=1.353 mg/m^3, μ=0.221 mm^{-1}, $F(000)$=656, crystal size 0.38×0.29×0.21 mm, independent reflections 2860 [R(int)=0.0142], reflections collected 7885, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.105, final R indices [$I>2\sigma(I)$] R_1=0.0373, wR_2=0.1067, R indices (all data) R_1=0.0427, wR_2=0.1092, extinction coefficient 0.0117(18), largest diff. peak and hole 0.243 and −0.424 e Å^{-3}. Crystallographic data for **3j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-268616. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].
8. Crystal data for **4j**: $C_{18}H_{16}O_3S$, M_W=312.37, T=288(2) K, λ=0.71073 Å, triclinic space group P-1, a=6.407(1) Å, b=11.386(2) Å, c=11.936(2) Å, α=88.60(1)°, β=75.35(1)°, γ=75.53(1)°, V=815.05(21) Å^3, Z=2, D_c=1.273 mg/m^3, μ=0.208 mm^{-1}, $F(000)$=328, crystal size 0.46×0.34×0.26 mm, independent reflections 3025 [R(int)=0.0084], reflections collected 3432, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.073, final R indices [$I>2\sigma(I)$] R_1=0.0540, wR_2=0.1669, R indices (all data) R_1=0.0761, wR_2=0.1814, extinction coefficient 0.013(6), largest diff. peak and hole 0.340 and −0.509 e Å^{-3}. Crystallographic data for **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-268617. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].
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