

Facile Synthesis of Oxabicyclic Alkenes by Ultrasonication-Promoted Diels–Alder Cycloaddition of Furano Dienes

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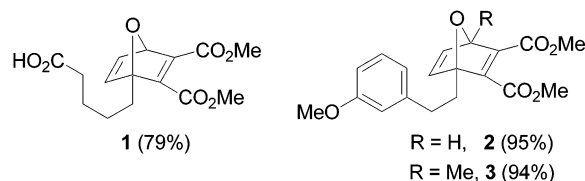
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Abstract: Ultrasonic irradiation effectively promotes the Diels–Alder reaction of substituted furans with reactive dienophiles (i.e., dimethyl acetylenedicarboxylate (DMAD) and dimethyl maleate). Regiospecific furano Diels–Alder cycloaddition of 2-vinyl furans with DMAD furnished functionalized oxabicyclic alkenes in good yield under ultrasonication condition.

Furans are generally much less reactive dienes (or dienophiles) in Diels–Alder cycloaddition reaction due to their inherent aromaticity¹ and usually facile retro-Diels–Alder reaction of the resulting adducts.² In view of the importance and great potential of Diels–Alder cycloaddition of furano derivatives as key intermediates for synthesizing structurally complex targets³ or achieving highly regio- and stereocontrolled reactions via the corresponding oxabicyclic adducts,⁴ a great deal of effort has been devoted to the development of chemical and physical means to promote the frequently difficult [4 + 2] cycloaddition of cyclic furano dienes. For example, a variety of Lewis acids⁵ were commonly used as catalysts to promote or accelerate the Diels–Alder reaction of furans. Some nonthermal forcing conditions, including high temperature and/or high pressure,⁶ and microwave irradiation⁷ have also been applied to promote cycloaddition of furans and other hetero-dienes.⁸

Although ultrasonication (sonochemical method) has been widely applied in many other synthetic reactions,⁹ there are only scattered reports¹⁰ on the Diels–Alder reaction affected by ultrasonic (US) irradiation, and very few cases^{10i,j} where the Diels–Alder reactions of furano dienes were promoted by US irradiation. In connection with our recent studies,^{4c} we report here the distinct beneficial effects of US irradiation on the Diels–Alder cycloaddition of substituted furano derivatives leading to a practical and convenient synthesis of oxabicyclic alkenes.

Although dimethyl acetylenedicarboxylate (DMAD) has been a highly reactive dienophile widely used in Diels–Alder reactions, substituted furano derivatives usually react sluggishly with DMAD under conventional thermal conditions or Lewis acid catalysis.¹¹ For example, although 2-methylfuran reacted with DMAD at 40 °C for 5 h to give the corresponding [4 + 2] cycloadduct in ca. 50% yield, the analogous adduct **1** was obtained in a small yield even in the presence of Lewis acids (i.e., BF₃·OEt₂, AlCl₃, MgBr₂, etc.) or in a sealed-tube heated to 100 °C.¹² When a (neat) mixture of 2-substituted or 2,5-disubstituted furan and DMAD was subjected to US irradiation at ambient temperature for 15 h, cycloadducts **1–3** were isolated as the sole products in good to excellent yields.



Encouraged by this initial dramatic effect of US irradiation, we next examined the 2-vinyl furano deriva-

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(1) For an account on hetero-aromaticity, see: Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777.

(2) For examples, see: (a) Woodward, R. B. *J. Am. Chem. Soc.* **1940**, *62*, 1478. (b) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893. (c) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(3) For examples, see: (a) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (b) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. J. *Am. Chem. Soc.* **1983**, *105*, 1403. (c) Schmidt, R. R.; Beitzke, C.; Forrest, A. K. *J. Chem. Soc., Chem. Commun.* **1982**, 909.

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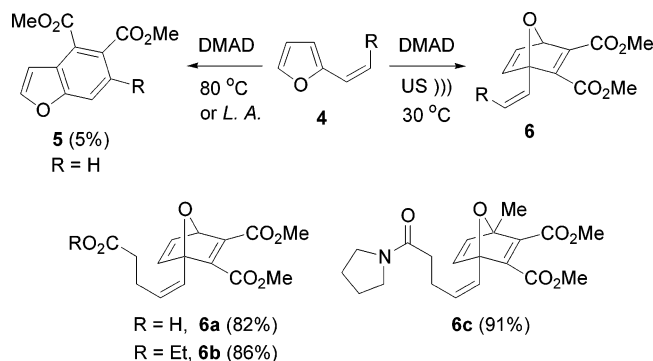
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(8) For examples, see: (a) Diaz-Ortiz, A.; De la Hoz, A.; Prieto, P.; Carrillo, J. R.; Moreno, A.; Neunhoeffer, H. *Synlett* **2001**, 236. (b) Diaz-Ortiz, A.; Carrillo, J. R.; Gomez-Escalonilla, M. J.; De la Hoz, A.; Moreno, A.; Prieto, P. *Synlett* **1998**, 1069. (c) Diaz-Ortiz, A.; Carrillo, J. R.; Diez-Barra, E.; De la Hoz, A.; Gomez-Escalonilla, M. J.; Moreno, A.; Langa, F. *Tetrahedron* **1996**, *52*, 9237. (d) Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C. O. *J. Org. Chem.* **2002**, *67*, 7904. (e) Hong, B.-C.; Shr, Y.-J.; Liao, J.-H. *Org. Lett.* **2002**, *4*, 663.

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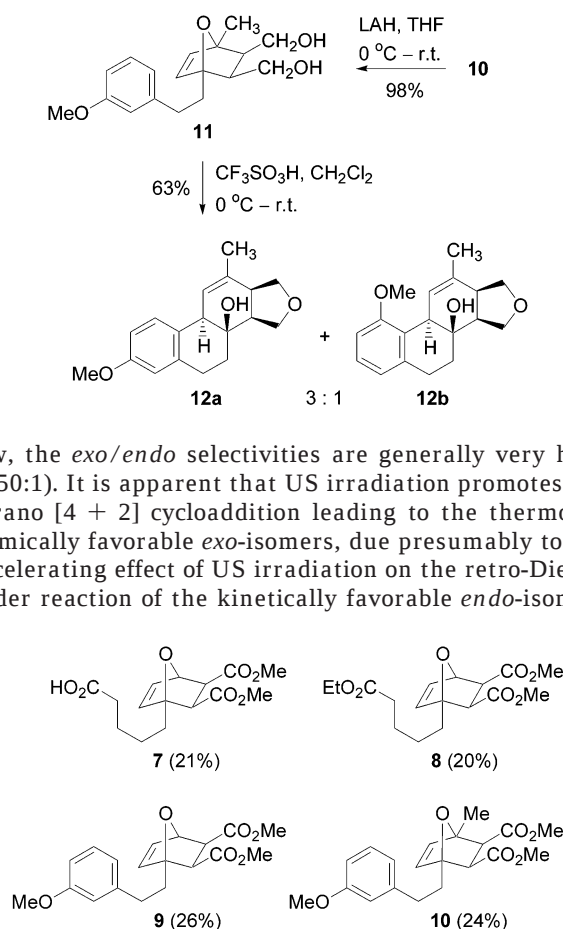
SCHEME 1



tives as dienes in the Diels–Alder reaction with DMAD, for there are two types of diene systems present, namely, the cyclic furano diene and *exo*-cyclic diene. Although a small yield (ca. 5%) of **6** (R = H) was obtained from the reaction of 2-vinyl furan **4** (R = H) and DMAD at room temperature,¹³ along with small yield (ca. 5%) of the aromatized benzofuran **5** (R = H), as previously documented by Elix and co-workers,¹⁴ the reaction of substituted 2-vinyl furan **4** (R ≠ H) with DMAD mainly led to polymerized materials, without any detectable furano diene cycloadducts under thermal or Lewis acid-catalysis (*vide supra*) conditions. Remarkably, the analogous reaction under *US irradiation conditions* furnished *solely* the cyclic furano diene cycloadducts **6a–c** from substituted 2-vinyl furan **4** in good isolated yields (Scheme 1). Thus, a highly regioselective Diels–Alder cycloadditions of 2-vinyl furans with DMAD can be achieved under US irradiation. We reason that this dramatic effect¹⁵ may be attributed to the sonochemical (kinetic) activation¹⁶ of the furan nuclei (oxa-cyclic diene) by polarization-induced electronic excitation or polarization-facilitated (single) electron transfer to the dienophile (a redox process).¹⁷

Since dimethyl maleate (DMM) is much less reactive dienophile than DMAD, the corresponding Diels–Alder reactions with furano derivatives are very slow and sluggish under thermal (sealed tube) conditions or Lewis acid catalysis, giving only a small yield of the corresponding oxabicyclic adducts, due to the facile retro-Diels–Alder process.^{4c} In contrast, the cycloaddition of DMM with 2-substituted or 2,5-disubstituted furans under US irradiation (neat, rt, 30 h) produced *solely* the corresponding [4 + 2] cycloadducts **7–10** in 20–26% yields.¹⁸ Although the conversion and isolated yields are relatively

SCHEME 2



low, the *exo/endo* selectivities are generally very high (>50:1). It is apparent that US irradiation promotes the furano [4 + 2] cycloaddition leading to the thermodynamically favorable *exo*-isomers, due presumably to the accelerating effect of US irradiation on the retro-Diels–Alder reaction of the kinetically favorable *endo*-isomer.

Reduction of the Diels–Alder adduct **10** by LiAlH₄ in THF afforded (98%) the oxabicyclic diol **11**, which then cyclized upon treatment with trifluoromethanesulfonic acid (Scheme 2) to give (63%) the 1,4-epoxy ring-opened cyclization products **12a** and **12b** (3:1), analogous to our recent report.^{4c}

In summary, the above experimental results have demonstrated the significant sonochemical effects on Diels–Alder reaction of furano dienes with reactive dienophiles in terms of the reaction yield and regio- and stereoselectivities. This convenient and practical laboratory technique provides a simple physical means for the *activation* of the relatively inert furano diene system. Although the fundamental mechanism of US activation on Diels–Alder reaction is not well understood currently and needs to be further elucidated,^{10c–g} the simple technique described herein could be generally useful in the cycloaddition of furano derivatives.

Experimental Section¹⁹

Typical Experimental Procedure for the Ultrasonication-Promoted Diels–Alder Cycloaddition of Furan. A degassed mixture of 2-[β-(*m*-methoxyphenyl)ethyl]furan (202 mg, 1.0 mmol) and DMAD (170 mg, 1.2 mmol) in a test tube was sonicated while submerged in a water bath of a common

(11) For an example, see: Alcaide, B.; Biurru, C.; Plumet, J. *Heterocycles* **1993**, 36, 1795.

(12) Cycloaddition product was severely contaminated with aromatized and other polymeric byproducts under these forcing conditions.

(13) Thermal conditions (at 80 °C) did not result in a better yield of cycloaddition product **6** but instead led to more side reactions, presumably due to the faster retro-Diels–Alder process of **6**; cf. ref 14a.

(14) (a) Davidson, W. J.; Elix, J. A. *Aust. J. Chem.* **1973**, 26, 1059. (b) Elix, J. A.; Tronson, D. *Aust. J. Chem.* **1973**, 26, 1093. For an earlier study, see also: (c) Herz, W. J. *Am. Chem. Soc.* **1946**, 68, 2732.

(15) *Cis* substituent of 2-vinyl furan **4** may further (sterically) prevent the access of *exo*-cyclic diene towards dienophile.

(16) Cf.: (a) Suslick, K. S.; Johnson, R. E. *J. Am. Chem. Soc.* **1984**, 106, 6856. (b) Diaba, F.; Lewis, I.; Grignon-Dubois, M.; Navarre, S. *J. Org. Chem.* **1996**, 61, 4830. See also ref 10d.

(17) For relevant accounts, see: (a) Woodward, R. B. *J. Am. Chem. Soc.* **1942**, 64, 3058. (b) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1944**, 66, 645.

(18) Unreacted furano derivatives can be easily recovered in good yield.

(19) For General Experimental Procedures, cf. Supporting Information of ref 4c.

laboratory ultrasonic cleaner (40 kHz, 160 W) for 15 h. The bath temperature was maintained between 25–35 °C by occasional cooling. The resulting orange gum was then purified by column chromatography on silica gel eluting with EtOAc–petroleum ether (1:8, v/v) to yield 336 mg (95%) of oxabicyclic diene **2** as a colorless oil. R_f (EtOAc–petroleum ether, 1:4) = 0.27. IR (film): $\nu_{\max}$ 3011, 2951, 1769, 1731, 1586, 1490, 1438, 1369, 1268, 1190 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 2.43(m, 2H), 2.69(m, 2H), 3.79(s, 3H), 3.80(s, 3H), 3.83(s, 3H), 5.68(d, J = 2.0 Hz, 1H), 6.73(m, 3H), 6.98(d, J = 5.2 Hz, 1H), 7.20(dd, J_1 = 1.8 Hz, J_2 = 5.0 Hz, 1H), 7.21(m, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 30.5, 30.8, 51.8, 51.9, 54.7, 83.0, 96.8, 111.0, 113.8, 120.3, 129.1, 142.6, 144.3, 144.5, 151.5, 155.4, 162.4, 164.6 ppm. LRMS (EI) m/z : 344 (M^+ , 0.1%), 312 (4), 283 (7), 202 (6), 121 (100), 81 (68). HRMS (SIMS) m/z : $[\text{M} + \text{H}]^+$ 345.1331 ($\text{C}_{19}\text{H}_{20}\text{O}_6$ requires 345.1333).

Oxabicyclic diene **3**, colorless oil. R_f (EtOAc–petroleum ether, 1:4) = 0.40. IR (film): $\nu_{\max}$ 2998, 2838, 1716, 1635, 1603, 1490, 1437, 1307, 1253, 1139, 1036 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 1.83(s, 3H), 2.46(m, 2H), 2.70(m, 2H), 3.76(s, 6H), 3.79(s, 3H), 6.71(m, 3H), 6.95(d, J = 1.6 Hz, 1H), 7.15(t, J = 7.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 15.1, 30.9, 31.0, 51.8, 51.8, 54.7, 91.8, 95.0, 111.0, 113.8, 120.4, 129.1, 142.9, 142.9, 145.9, 147.0, 153.7, 155.2, 159.3, 164.0 ppm. LRMS (EI) m/z : 358 (M^+ , 0.2%), 326 (5), 163 (94), 202 (6), 121 (58), 95 (100). HRMS (SIMS) m/z : $[\text{M} + \text{H}]^+$ 359.1494 ($\text{C}_{20}\text{H}_{22}\text{O}_6$ requires 359.1489).

Oxabicyclic triene **6b**, colorless oil. R_f (EtOAc–petroleum ether, 1:4) = 0.25. IR (film): $\nu_{\max}$ 2984, 2955, 1729, 1644, 1437, 1312, 1266, 1201, 1157, 1113 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 1.20(t, J = 7.2 Hz, 3H), 2.34(m, 2H), 2.48(m, 2H), 3.77(s, 3H), 3.82(s, 3H), 4.06(q, J = 7.2 Hz, 2H), 5.68(d, J = 2.0 Hz, 1H), 5.83(m, 2H), 7.11(d, J = 5.0 Hz, 1H), 7.18(dd, J_1 = 2.0 Hz, J_2 = 5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 14.1, 24.2, 33.7, 52.2, 52.2, 60.2, 83.5, 94.2, 121.9, 137.3, 143.6, 146.2, 149.4, 158.0, 162.4, 164.8, 172.7 ppm. LRMS (EI) m/z : 336 (M^+ , 0.6%), 310 (1), 259 (5), 194 (32), 120 (100). HRMS (SIMS) m/z : $[\text{M} + \text{H}]^+$ 337.1285 ($\text{C}_{17}\text{H}_{20}\text{O}_7$ requires 337.1282).

Oxabicyclic alkene **9**, colorless oil. R_f (EtOAc–petroleum ether, 1:4) = 0.22. IR (film): $\nu_{\max}$ 3086, 2951, 2838, 1743, 1601, 1202, 1165, 1043 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 2.13(m, 1H), 2.41(m, 1H), 2.67(m, 2H), 3.14(d, J = 10.0 Hz, 1H), 3.60(dd, J_1 = 4.4 Hz, J_2 = 10.1 Hz, 1H), 3.64(s, 3H), 3.65(s, 3H), 3.80(s, 3H), 5.13(dd, J_1 = 1.5 Hz, J_2 = 4.2 Hz, 1H), 6.47(d, J = 5.7 Hz, 1H), 6.54(dd, J_1 = 1.5 Hz, J_2 = 5.5 Hz, 1H), 6.74(m, 2H), 6.54(d, J = 7.5 Hz, 1H), 7.20(t, J = 7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 30.9, 33.5, 50.5, 51.4, 51.7, 54.9, 79.3, 91.2, 111.2, 113.8, 120.5, 129.2, 135.1, 136.7, 143.1, 159.6, 170.5, 170.9 ppm. LRMS (EI) m/z : 346 (M^+ , 0.1%), 328 (0.05), 315 (0.2), 202 (18), 121 (44), 81(100). HRMS (SIMS) m/z : $[\text{M} + \text{H}]^+$ 347.1496 ($\text{C}_{19}\text{H}_{22}\text{O}_6$ requires 347.1489).

Oxabicyclic alkene **10**, colorless oil. R_f (EtOAc–petroleum ether, 1:4) = 0.30. IR (film): $\nu_{\max}$ 2951, 2840, 1742, 1601, 1582, 1490, 1454, 1436, 1197, 1158, 1038 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 1.69(s, 3H), 2.34(m, 2H), 2.68(m, 2H), 3.61(s, 3H), 3.63(s, 3H), 3.80(s, 3H), 6.36(m, 2H), 6.72(m, 3H), 7.15(t, J = 7.8 Hz, 1H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ 18.0, 31.0, 33.8, 51.6, 52.1, 54.6, 55.0, 55.9, 87.5, 90.6, 111.2, 113.9, 120.6, 129.3, 136.7, 138.2, 143.3, 159.6, 170.9 ppm. LRMS (EI) m/z : 360 (M^+ , 0.03%), 342 (0.02), 216 (6), 113 (40), 121 (4), 95 (100). HRMS (SIMS) m/z : $[\text{M} + \text{H}]^+$ 361.1656 ($\text{C}_{20}\text{H}_{24}\text{O}_6$ requires 361.1646).

Preparation of oxabicyclic diol **11** and its cyclization.

Lithium aluminum hydride reduction^{4c} of **10** in THF gave **11** in 98% yield as a colorless oil. R_f (EtOAc–petroleum ether, 1:2) = 0.34. IR (film): $\nu_{\max}$ 3349, 2931, 1601, 1489, 1454, 1256, 1152, 1033 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 1.59(s, 3H), 2.04(m, 2H), 2.51(m, 2H), 3.26(t, J = 11.0 Hz, 2H), 3.65(d, J = 11.0 Hz, 2H), 3.75(m, 2H), 3.80(s, 3H), 6.08(s, 2H), 6.72(m, 3H), 7.15(t, J = 7.6 Hz, 1H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ 18.0, 31.0, 33.9, 51.3, 52.8, 55.0, 60.8, 60.9, 86.3, 89.4, 111.2, 114.0, 120.6, 129.3, 136.9, 138.2, 143.6, 159.6 ppm. LRMS (EI) m/z : 304 (M^+ , 0.01%), 286 (0.01), 216 (8), 121 (4), 95 (100).

To a solution of compound **11** (157 mg, 0.5 mmol) in 5 mL of CH_2Cl_2 was added $\text{CF}_3\text{SO}_3\text{H}$ (0.013 mL, 0.15 mmol) at 0 °C. The resulting mixture was stirred for 0.5 h at room temperature, quenched with saturated aqueous NaHCO_3 (5 mL), and extracted (3×50 mL) with AcOEt. The organic layer was washed with H_2O and brine, dried (MgSO_4), and concentrated, and the crude product was purified by silica gel chromatography eluting with EtOAc–petroleum ether (1:2) to yield 65 mg (48%) of **12a** and 21 mg (15%) of **12b** as colorless oils: R_f of **12a** (EtOAc–petroleum ether, 2:1) = 0.36; R_f of **12b** (EtOAc–petroleum ether, 2:1) = 0.38. **12a** IR (film): $\nu_{\max}$ 3415, 2930, 2871, 1609, 1500, 1463, 1440, 1255, 1236, 1067, 1038 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 1.81(s, 3H), 1.96(m, 3H), 2.59(m, 1H), 2.87(m, 2H), 3.32(bs, 1H), 3.51(t, J = 10.2 Hz, 1H), 3.76(s, 3H), 3.83(m, 2H), 4.05(dd, J_1 = 4.0 Hz, J_2 = 7.2 Hz, 1H), 5.73(br, 1H), 6.61(d, J = 2.6 Hz, 1H), 6.71(dd, J_1 = 2.6 Hz, J_2 = 8.4 Hz, 1H), 7.16(d, J = 8.2 Hz, 1H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ 22.4, 28.9, 29.4, 43.2, 45.5, 49.2, 55.1, 60.4, 73.9, 82.7, 112.2, 112.9, 120.4, 127.6, 131.2, 136.2, 140.7, 157.4 ppm. LRMS (EI) m/z : 286 (M^+ , 10%), 268 (1), 256 (7), 95 (100). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 287.1640 ($\text{C}_{18}\text{H}_{23}\text{O}_3$ requires 287.1643). **12b** IR (film): $\nu_{\max}$ 3402, 2930, 2872, 1580, 1464, 1438, 1248, 1060, 1022 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 1.77(s, 3H), 1.88(m, 2H), 2.05(m, 1H), 2.58(m, 1H), 2.78(m, 2H), 3.59(m, 2H), 3.83(s, 3H), 3.92(d, J = 7.2 Hz, 2H), 4.08(dd, J_1 = 4.4 Hz, J_2 = 7.4 Hz, 1H), 6.10(br, 1H), 6.68(d, J = 8.0 Hz, 2H), 7.04(t, J = 8.2 Hz, 1H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ 22.7, 29.2, 29.3, 41.9, 46.6, 49.2, 55.0, 60.5, 74.3, 83.2, 108.3, 120.7, 121.1, 126.3, 127.3, 137.1, 141.3, 157.7 ppm. LRMS (EI) m/z : 286 (M^+ , 12%), 268 (1), 256 (10), 225 (100), 84 (45). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 287.1643 ($\text{C}_{18}\text{H}_{23}\text{O}_3$ requires 287.1643).

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Supporting Information Available: Experimental procedures of preparation of substituted furans, spectral data of compounds **1**, **6a**, **6c**, **7**, and **8**, and copies of spectra (IR, ^1H and ^{13}C NMR) of compounds **1**, **6b**, **9**, **11**, **12a**, and **12b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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