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One-pot stereoselective synthesis of tricyclic γ-lactones from 2-methoxyfuran and 2-methoxyphenols

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A one-pot synthesis of the title compounds is achieved *via* highly facile Diels–Alder reactions of 2-methoxyfuran with masked *o*-benzoquinones.

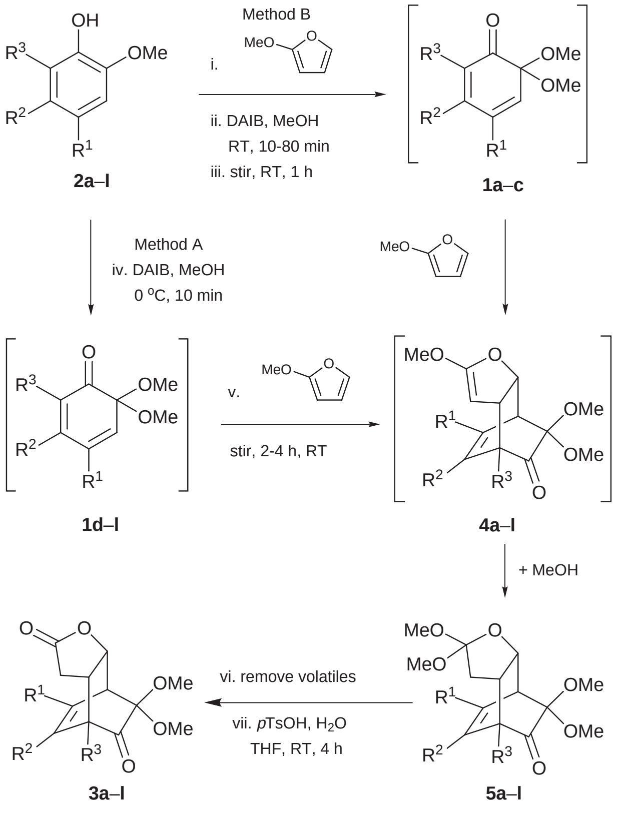
The butyrolactone moiety features in a large number of natural products which exhibit interesting and useful biological activities.[1] Moreover, the butyrolactone moiety is an immediate precursor of the α-methylene-γ-butyrolactone substructure which also features in many pharmacologically important natural products.[1,2] During the synthesis of natural products, construction of a β,γ-fused butyrolactone skeleton is generally achieved in a linear fashion using various precursors that contribute at least two carbons to the butyrolactone moiety.[2,3] In contrast, there are no efficient methods that can directly and stereoselectively introduce a β,γ-fused butyrolactone unit into a carbocycle in an intermolecular reaction using a four-carbon unit.[4] In this regard, the intermolecular Diels–Alder reactions of 5-alk-1-enylfuran-2(3*H*)-one with maleic anhydride, vinyl sulfones and α-chloroacrylonitrile and intramolecular cycloaddition reactions of 5-alkadienylfuran-2(5*H*)-one are noteworthy.[5]

Masked *o*-benzoquinones (MOBs) are a type of cyclohexa-2,4-dienones with a high propensity to dimerize.[6] Our laboratory has succeeded in developing efficient procedures for their generation and in identifying their immense synthetic potential especially as dienes in Diels–Alder reactions. Their inter- and intra-molecular Diels–Alder reactions have been shown to be quite useful in the synthesis of various polysubstituted cyclohexanes, *cis*-decalins, bicyclo[2.2.2]octenones, bicyclo[4.2.2]-decenones, linear and angular triquinanes.[7,8] Although furans have been widely used as dienes in Diels–Alder reactions,[9] their dienophilic behavior was observed only in a few specially activated cases.[10] Recently we have clearly shown that furan as well as some of its derivatives can function efficiently as dienophiles in their Diels–Alder reactions with selected MOBs.[11] It occurred to us that if 2-alkoxyfurans can also function as dienophiles, the reactions would provide an easy means for the direct and stereoselective synthesis of β,γ-fused butyrolactones. Accordingly, Diels–Alder reactions of 2-methoxyfuran with several MOBs were examined. We herein report that 2-methoxyfuran reacts as a dienophile with MOBs **1a–l** generated from 2-methoxyphenols **2a–l** to provide an easy access to highly functionalized tricyclic γ-lactones **3a–l** in excellent yields (Scheme 1, Table 1).

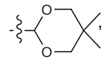
Addition of 2-methoxyfuran to a freshly prepared MOB **1** in MeOH at 0 °C (Method A) or gradual addition of (diacetoxy)-iodobenzene (DAIB) to a mixture of 2-methoxyphenol **2** and 2-methoxyfuran in MeOH at room temperature (Method B) affords ortho esters of the type **5**. These cyclic ortho esters, which should have resulted from the addition of MeOH to the initially formed cyclic ketene acetals **4**, are not stable to purification by column chromatography and are not characterized. Instead they were hydrolyzed to afford the tricyclic lactones **3a–l** in excellent yields.[12] The reactions of MOBs **1a–c** produced considerable amounts of dimers when they were generated in the absence of 2-methoxyfuran. Consequently, phenols **2a–c** were oxidized in the presence of 2-methoxyfuran to suppress dimerization.

The gross structures of all the lactones were determined by their IR, ^{1}H and ^{13}C NMR, DEPT, low- and high-resolution mass spectral analyses. All these lactones provided satisfactory elemental analyses. The ^{1}H NMR (400 MHz) spectra of the crude reaction mixtures showed the formation of a single lactone in every case indicating the high regio- and stereoselectivity of the initial cycloaddition reactions. The regiochemistry of these cycloaddition reactions was determined by ^{1}H–^{1}H decoupling NMR experiments on the corresponding lactones in each case and is in agreement with our earlier results.[11]

The assigned stereochemistry of the lactones was deduced from the observed long-range coupling between vinylic hydrogens and the nearest ring junction hydrogens in all the cases where vinylic hydrogens exist. In the cases of **3h** and **3j**, it was assigned as shown by analogy with our earlier results where the



For **1**–**5**

a: $R^1 = R^2 = R^3 = H$
b: $R^1 = R^2 = H$, $R^3 = Me$
c: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OMe$
d: $R^1 = CO_2Me$, $R^2 = R^3 = H$
e: $R^1 = COMe$, $R^2 = H$, $R^3 = H$
f: $R^1 = R^3 = H$, $R^2 = CO_2Me$
g: $R^1 = Me$, $R^2 = R^3 = H$
h: $R^1 = Me$, $R^2 = Br$, $R^3 = H$
i: $R^1 = R^3 = H$, $R^2 = Me$
j: $R^1 = Br$, $R^2 = Me$, $R^3 = H$
k: $R^1 = Br$, $R^2 = H$, $R^3 = Me$
l: $R^1 =$  , $R^2 = R^3 = H$

Scheme 1

Table 1 Synthesis of tricyclic γ-lactones

Entry	Phenol	MOB	Method[a]	Lactone/ Yield (%)[b]
1	**2a**	**1a**	B	**3a**/80
2	**2b**	**1b**	B[c]	**3b**/44[d]
3	**2c**	**1c**	B	**3c**/80
4	**2d**	**1d**	A	**3d**/89
5	**2e**	**1e**	A	**3e**/90
6	**2f**	**1f**	A	**3f**/86
7	**2g**	**1g**	A	**3g**/88
8	**2h**	**1h**	A	**3h**/94
9	**2i**	**1i**	A	**3i**/78
10	**2j**	**1j**	A	**3j**/95
11	**2k**	**1k**	A	**3k**/93
12	**2l**	**1l**	A	**3l**/90

[a] See ref. 12. [b] Yields are of isolated lactones and are not optimized. [c] DAIB was added during 80 min. [d] Dimer of **1b** was also produced in 30% yield.

anti configuration of furan moiety to the keto group was confirmed by X-ray diffraction analysis.[11] The fact that in all the cases the *endo* adducts were produced exclusively shows that these cycloaddition reactions obey all the ground rules of Diels–Alder reactions.[13]

It is important to mention that 2-methoxyfuran was earlier shown to act as dienophile in its high pressure cycloaddition reactions with tropone albeit with moderate efficiency and poor stereoselectivity.[14] On the other hand, 2-alkoxy- and 2-silyloxyfurans have been often used as dienes and nucleophiles.[9,15] Interestingly, 2-methoxyfuran underwent facile cycloaddition with MOBs bearing electron-withdrawing as well as electron-donating substituents unlike other furan derivatives which reacted with only MOBs bearing electron-withdrawing substituents in our earlier studies.[11]

In conclusion, the present reactions make use of readily available 2-methoxyfuran and 2-methoxyphenols and produce highly complex and potentially useful multifunctional molecules in excellent yields *via* a simple one-pot process. Most importantly, these reactions resulted in the development of a novel and efficient methodology for the direct and stereoselective introduction of a β,γ-fused γ-butyrolactone moiety using 2-methoxyfuran as a masked but-3-enolide.

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12 Method A: *General procedure for 2-methoxyphenols* **2d-l**: A solution of phenol **2** (1 mM) in MeOH (10 mL) was cooled to 0 °C and DAIB (1.1 mM) was added as solid in one portion. After 10 min of stirring at 0 °C, 2-methoxyfuran (5 mM) was added and the cooling bath was removed. The reaction mixture was stirred at room temperature for 2–4 h (2 h for **2d**–**f** and 4 h for **2g**–**l**) and then MeOH and other volatile materials were removed under reduced pressure. The residue was dissolved in THF and *p*-TsOH (100 mg) and water (3 drops) were added. The resulting solution was stirred for 4 h at room temperature and the volatiles were then removed under reduced pressure. The residue was purified by column chromatography on silica gel using 40% ethyl acetate in hexanes as eluent to obtain lactone **3** as a colorless solid. Method B: *General procedure for 2-methoxyphenols* **2a**-**c**: To a mixture of 2-methoxyphenol (1 mM) and 2-methoxyfuran (5 mM) in MeOH (4 mL) was added a solution of DAIB (1.2 mM) in MeOH (6 mL) during a period of time (10 min for **2a** and **2c** and 80 min for **2b**) using a syringe pump at room temperature. After stirring for a further 1 h, MeOH and other volatile materials were removed under reduced pressure and the residue was subjected to hydrolysis as described in method A.

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