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One-Pot Stereoselective Synthesis of Tricyclic Bislactones from 2-Pyrones and 2-Methoxyfuran

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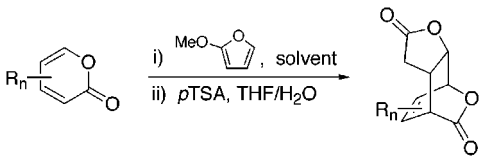
ABSTRACT



A one-pot synthesis of the title compounds via highly chemo-, regio-, and stereoselective Diels−Alder reactions of 2-pyrones with 2-methoxyfuran is described.

A large number of natural products of biological importance possess the γ-butyrolactone moiety as an integral part of their structure.[1] Due to this, there are continued interests in the synthesis of the butyrolactone skeleton.[2] Most recently, during our studies on the Diels−Alder reactions of masked *o*-benzoquinones (MOBs) with furans,[3,4] we have shown MOBs to be efficient intermediates for the stereoselective synthesis of highly functionalized tricyclic γ-lactones.[4] In addition, the δ-lactone moiety is featured in many natural products such as pheromones, and food flavors, and also attracts many synthetic approaches.[5] In this Letter, we report the hitherto unknown synthesis of highly functionalized tricyclic bislactones from readily available 2-pyrones and 2-methoxyfuran.

Owing to their partial aromatic nature, 2-pyrones participate in Diels−Alder reactions less readily than most cyclic conjugated homodienes.[6] In general, they need high temperatures and pressures to ensure that these cycloadditions are taking palce. The cycloadducts formed from olefinic dienophiles, if isolable, could serve as a source of highly functionalized and stereochemically rich compounds.[6a] However, the initially formed bicyclic lactones often undergo CO_2 extrusion leading to dihydrobenzene products under the reaction conditions. Utilization of electronically matching partners is one of the strategies used to perform the cycloaddition at lower temperatures, thus avoiding the extrusion of CO_2 from the bicyclolactones. We envisioned the structural similarity between MOB and 2-pyrone (Figure 1) and the facile cycloadditions of MOBs with 2-methoxyfuran.[4] Thus, if 2-pyrones undergo facile Diels−Alder cycloadditions with 2-methoxyfuran to furnish isolable adducts, easy access to highly functionalized tricyclic bislactones could be achieved.

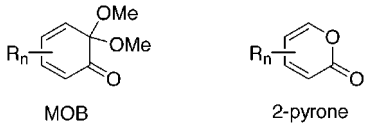


Figure 1. Cyclic conjugated dienones.

(1) Petit, G. R.; Grag, G. M.; Ode, R. H. *Biosynthetic Products for Cancer Therapy*; Plenum: New York, 1977−1979; Vol. 1−3.

(2) (a) Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157. (c) Collins, I. *Contemp. Org. Synth.* **1997**, *4*, 281; **1996**, *3*, 295.

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(4) Rao, P. D.; Chen, C.-H.; Liao, C.-C. *Chem. Commun.* **1999**, 713.

(5) (a) Mulzer, J. In *Comprehensive Organic Functional Group Transformations*; Katrizky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier: Oxford, 1995; Vol. 5, p 121. (b) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423.

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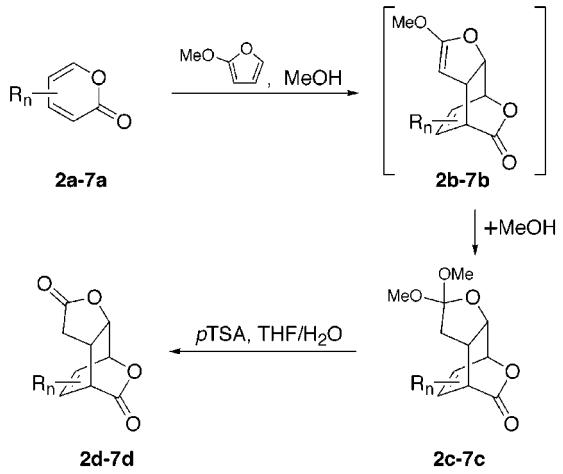
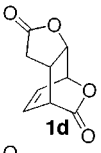
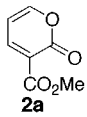
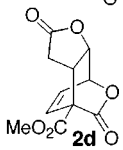
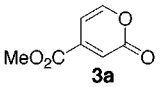
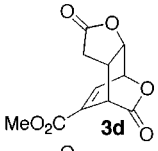
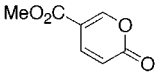
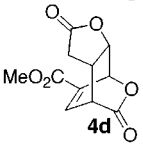
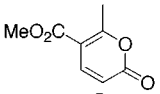
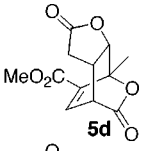
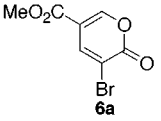
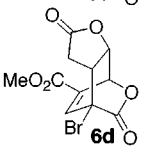
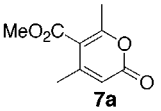
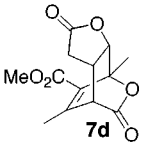
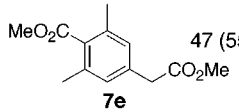
Accordingly, we have carried out the reaction of 2-pyrone **1a** with 2-methoxyfuran in refluxing MeOH. Unfortunately, no product was obtained; instead, the starting material was recovered. However, when the reaction was performed at 90 °C in 1,4-dioxane, the corresponding bislactone **1d** was isolated in moderate yield. 2-Pyrones[7−12] **2a**−**7a** and 2-methoxyfuran underwent cycloadditions in MeOH at ambient temperatures to afford ortho esters of type **2c**−**7c**, which resulted from the addition of MeOH to the initially formed cyclic ketene acetals **2b**−**7b** are not stable enough to be purified by column chromatography. However, they were hydrolyzed to the corresponding bislactones **2d**−**7d**[13] (Scheme 1, Table 1).

Scheme 1



The structures of all the products were established by their IR, ^{1}H and ^{13}C NMR, DEPT, and low- and high-resolution mass spectral analyses. For the majority of the bislactones, a satisfactory elemental analysis was obtained. The formation of a single ortho ester was confirmed by analysis of the ^{1}H NMR (400 MHz) spectra of each crude reaction mixture. The regiochemistry of these cycloaddition reactions was determined by ^{1}H−^{1}H decoupling NMR experiments on the bislactones in each case. The stereochemical assignments of these products are based on the observed long-range coupling between the vinylic proton and the nearest methine proton of the γ-butyrolactone moiety in **1d**−**6d**. The *anti* configuration of the γ-butyrolactone moiety to the carbonyl group of δ-lactone in **7d** was confirmed by the single-crystal X-ray diffraction method (Figure 2). The regio- and stereoselec-

Table 1. Tricyclic Bislactones from 2-Pyrones and 2-Methoxyfuran[a]

entry	2-pyrone	temp[b]	time[b]	product	yield[c](%)
1	 **1a**	reflux	3 d	–	–[d]
2	**1a**	90 °C[e]	3 d	 **1d**	39 (56)
3	 **2a**	rt	8 h	 **2d**	80
4	 **3a**	reflux	10 h	 **3d**	53
5	 **4a**	rt	10 h	 **4d**	82
6	 **5a**	reflux	24 h	 **5d**	60
7	 **6a**	rt	10 h	 **6d**	71
8	 **7a**	rt	7 d	 **7d**	55 (91)
9	**7a**	reflux	50 h	 **7e**	47 (55)

[a] All reactions were performed in MeOH unless specified (also see ref 13). [b] For cycloaddition step. [c] Yields are of isolated products and are unoptimized. Yields in parentheses are based on consumed pyrone. [d] Starting material was recovered. [e] Reaction was carried out in 1,4-dioxane.

(6) For reviews, see: (a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. (b) Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3. (c) Kalinin, V. N.; Shilova, O. S. *Russ. Chem. Rev.* **1994**, *63*, 661. (d) Woodard, B. T.; Posner, G. H. Recent advances in Diels−Alder cycloadditions of 2-pyrones. In *Advances in Cycloaddition*; JAI Press: Greenwich, 1999; Vol. 5, p 47.

(7) The 2-pyrones **3a**,[8] **4a**,[9] **5a**,[10] **6a**,[11] and **8a**[12] were prepared according to literature procedures.

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(12) Wiley, R. H.; Hart, A. *J. Am. Chem. Soc.* **1954**, *76*, 1942.

(13) **General procedure:** A solution of pyrones **1a**−**7a** (1 mM) and 2-methoxyfuran (2 mM for entries 3 and 7; 4 mM for entry 5; and 5 mM for the remaining entries) in the solvent (5 mL) was stirred at ambient temperature over the period mentioned in Table 1. The solvent was then removed from the reaction mixture. The residue was subjected to column chromatography for entries 2 and 9 to furnish **1d** and **7e**, respectively. For enties 3−8, the crude residue was dissolved in THF (5 mL), *p*-TsOH (100 mg) and water (2 drops) were added, and the solution was stirred for 4 h at room temperature. The solution thus obtained was concentrated under reduced pressure and purified by flash column chromatography on silica gel using ethyl acetate in hexanes as eluent to afford bislactones **2d**−**7d**.

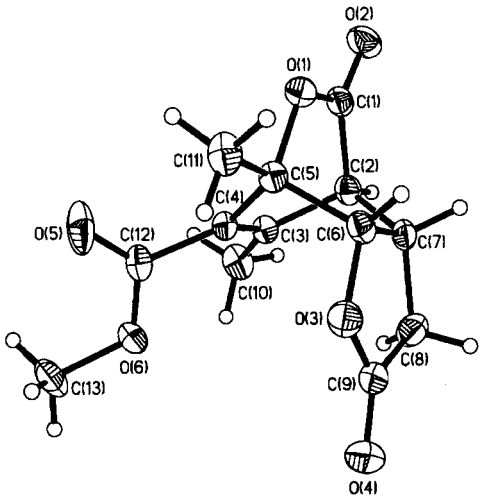

Figure 2. ORTEP plot of the crystal structure of **7d** (numbering is arbitrary).

tivities were similar to those of the products derived from MOBs and 2-methoxyfuran.[4]

By comparison of the reaction temperature and the reaction time given in Table 1, the methoxycarbonyl group (CO_2-Me), which is an electron-withdrawing substituent, enhances the rates of Diels−Alder cycloadditions. 2-Pyrones with the CO_2Me group at position 3 or 5 (**2a** and **4a**, entries 3 and 5) react faster than the 4-substituted 2-pyrone (**3a**, entry 4). It is interesting to note that no reaction was observed for 6-methoxycarbonyl-2-pyrone (**8a**, Figure 3) with 2-methoxyfuran even at reflux temperatures in MeOH or 1,4-dioxane. This fact of decreasing rate is presumably due to a steric effect. Similarly, methyl substitution at position 6 of 5-methoxycarbonyl-2-pyrone retards the reaction (entries 5 and 6). Again, 3,6-dimethyl-5-methoxycarbonyl-2-pyrone (**7a**) reacts much slower than **4a**. 2-Pyrone **7a** afforded bislactone **7d** at room temperature, but yielded **7e** in refluxing MeOH (entries 8 and 9). Similar results were reported[14] for the cycloaddition reactions of **7a** with other electron-rich dienophiles. By comparison with the parent 2-pyrone (**1a**, entry 2), in contrast, **9a** and **10a** (Figure 3) possessing electron-releasing groups gave no cycloadducts, which presumably is due to both steric and electronic effects. It is

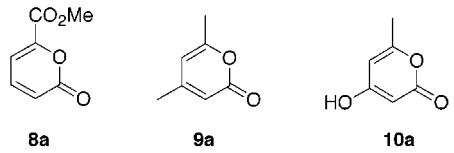

Figure 3. Unreactive 6-substituted 2-pyrones.

worth mentioning that the reactions of 5-alkoxycarbonyl-2-pyrone with 3,4-dimethoxy- and 3,4-(bis)benzyloxyfurans produced the corresponding [4 + 2] cycloadducts nonstereoselectively.[16] Interestingly, in our present study, 2-methoxyfuran underwent facile Diels−Alder cycloadditions with 2-pyrones with high regio- and stereoselectivities.

Semiempirical calculations (AM1 and PM3) suggest that the interaction between the HOMO of 2-methoxyfuran and LUMO of the 2-pyrones contributes mainly in the cycloaddition reactions, indicating that these are inverse-electron demand Diels−Alder cycloadditions. Although there are a priori many possible modes of [4 + 2] cycloadditions, in each case the unsubstituted double bond of the 2-methoxyfuran ring participated as a dienophile in the reaction, showing that the cycloaddition is highly chemoselective. Steric factors appear to be responsible for these results on the basis of our calculations (AM1) on transition-state energies. The transition state shown in Figure 4, through

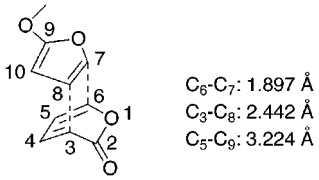

Figure 4. Transition state for the cycloaddition of 2-pyrone and 2-methoxyfuran.

which cycloaddition occurs to form the initial adduct **1b**, has the lowest energy out of eight possible transition states. These calculations are in full agreement with our observed chemo-, regio-, and stereoselectivities. In addition, the coefficients of the frontier molecular orbitals obtained from the semiempirical calculations also support the procured regioselectivity. The extremely high stereoselectivity observed in these cycloadditions may be explained by invoking secondary orbital interactions. The fact that in all the cases only the bislactones resulting from *endo* addition were produced clearly shows that these reactions follow all the ground rules of Diels−Alder reactions.[15] In the transition state, the distance between C_6 and C_7 is shorter than that of C_3 and C_8, indicating that the formation of the C_6−C_7 bond is taking place prior to the formation of the C_3−C_8 bond (Figure 4). Consequently, a substituent at the C_6 position of the 2-pyrone causes a steric effect for the in coming dienophile, preventing cycloaddition as evidenced in the reactions of 2-pyrones **8a**−**10a** with 2-methoxyfuran.

In summary, we have demonstrated that 2-pyrones and 2-methoxyfuran react under mild conditions in one pot to generate structurally complex and potentially useful bislactones. Nucleophilic ring opening of these bislactones will

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allow easy access to tetrasubstituted cyclohexenes with established stereochemistry at all four contiguous stereocenters. Work toward this direction is underway.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support and Drs. R. K. Peddinti and P. Dharma Rao for helpful discussions. We also thank Professor Yu Wang of the Department of Chemistry, National Taiwan University for the X-ray diffraction studies.

Supporting Information Available: ^{1}H and ^{13}C NMR and DEPT spectra for compounds **1d**−**7d** and X-ray crystallographic data for compound **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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