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Highly Diastereoselective and Asymmetric Diels–Alder Reactions of Masked *o*-Benzoquinones with Chiral Racemic and Homochiral Furans. Synthesis of Optically Active Tricyclic γ-Lactones

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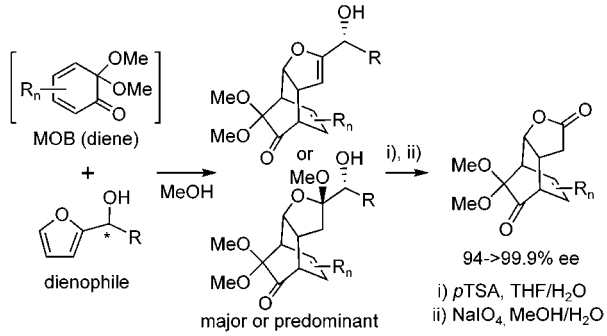
ABSTRACT



The first examples of highly diastereoselective and asymmetric Diels–Alder cycloadditions of in situ generated masked *o*-benzoquinones (MOBs) with chiral racemic and homochiral furans bearing a chiral center in the α-position leading to highly functionalized diastereomeric/enantioselective tricyclic heterocycles and chiral tricyclic γ-lactones are described.

The Diels−Alder reaction is one of the most versatile and synthetically useful reactions due to its inherent potential to generate up to four new stereogenic centers besides forming two new C−C bonds in a single synthetic operation.[1] Among the enantioselective variants, chiral auxiliary-based reactions[2] have occupied a prominent position, though the catalytic reactions[3] have been rapidly emerging. In continuation of our work on the utilization of masked *o*-benzoquinones (MOBs)[4] for the synthesis of various structurally diverse organic compounds[5] via the Diels−Alder protocol, herein we describe the first examples of diastereoselective[6] and asymmetric Diels−Alder reactions of MOBs with chiral racemic and homochiral furans.

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Masked *o*-benzoquinones are indeed highly reactive and versatile building blocks in organic synthesis. A wide variety of highly substituted ring systems such as bicyclo[2.2.2]-octenones, oxatricycles, triquinanes, and bicyclo[4.2.2]-decenones that are useful substructures in the construction of several natural products have been synthesized from simple 2-methoxyphenols via the Diels−Alder methodology of transiently generated MOBs.[4] By utilizing this strategy, very recently, the total synthesis of racemic magellanine—a highly condensed molecular architecture with six contiguous stereogenic centers—has been accomplished.[5c] Despite their remarkable synthetic potential, no report is yet available on the asymmetric variation of MOB Diels−Alder protocol leading to optically active subunits. Recently, we found that the reactions between MOBs and furans proceed in a highly regio- and stereoselective manner and furans apparently play the role of dienophiles.[7] It was envisioned that if chiral racemic and homochiral furans bearing a chiral center in its α-substitution undergo cycloaddition with MOBs, easy access to highly functionalized diastereomeric/enantioselective tricyclic heterocycles and chiral racemic/nonracemic tricyclic γ-lactones[8] could be achieved. Accordingly, we have carried out the reactions of 2-methoxyphenols **7** with chiral racemic and homochiral furan derivatives **1**−**6**.

At the outset, we studied the impact of the bulkiness of substituent R of the furan derivatives (±)-**1**−**5**[9] on the extent of diastereoselective outcome in the Diels−Alder reaction of MOB **8a** generated in situ by the diacetoxyiodobenzene (DAIB)-mediated oxidation of acetovanillone (**7a**) in methanol (Scheme 1, Table 1, entries 1−5). All the reactions (method A) proceeded efficiently, reached completion in 1 h, and afforded the cycloadducts in good yields.[10] Although moderate selectivities were observed in the reactions of racemic **1** and **2** (R = Me, Et), the furans (±)-**3**−**5** (R = *i*Pr, *t*Bu, Ph) underwent cycloaddition with excellent diastereoselectivities.

We next turned our attention to determining the scope of 2-methoxyphenols that are suitable substrates for this new diastereoselective process. The reaction of MOB **8b** derived from methyl vanillate (**7b**) with racemic **3** and **4** afforded the major adducts **11b** and **12b** in 78% and 75% isolated yield, respectively, and the diastereomeric ratio was found to be 98:2 by HPLC analysis of the reaction mixture (entries 6 and 7). Similar selectivities were noticed in the reaction of methyl syringate (**7c**) with racemic furans **3** and **4**.[11] The reduced chemical yields are due to the formation of considerable amounts of the dimer of the MOB **8c** under the reaction conditions. The Diels−Alder reactions of relatively less reactive 4-Br- and 4-acetal-substituted MOBs

Scheme 1

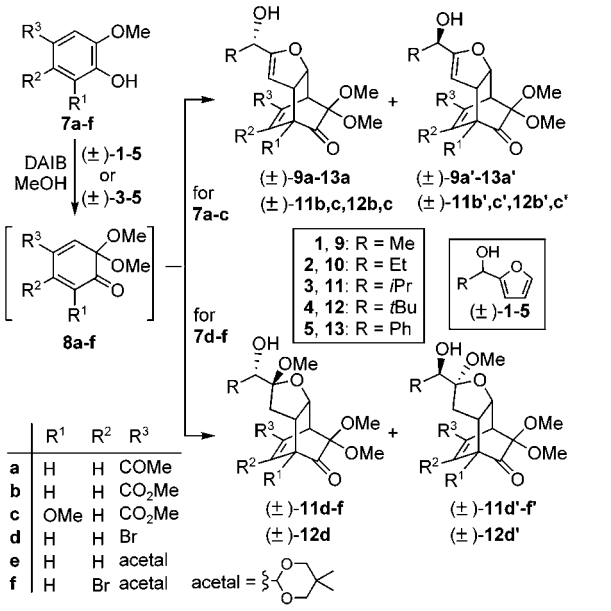

Table 1. Diastereoselective Diels−Alder Reactions of MOBs **8** Derived from 2-Methoxyphenols **7** with Furans (±)-**1**−**5**[a]

entry	phenol/ MOB	furan/ R	*T*[b]/ °C	time[c]/ h	adduct/ % yield[d]	% de[e]
1	**7a**/**8a**	**1**/Me	rt	1	**9a** + **9a′**/70[f]	43[g]
2	**7a**/**8a**	**2**/Et	rt	1	**10a** + **10a′**/73[f]	50[g]
3	**7a**/**8a**	**3**/*i*Pr	rt	1	**11a**/79	99
4	**7a**/**8a**	**4**/*t*Bu	rt	1	**12a**/73	98
5	**7a**/**8a**	**5**/Ph	rt	1	**13a**/74	93
6	**7b**/**8b**	**3**/*i*Pr	rt	0.8	**11b**/78	96
7	**7b**/**8b**	**4**/*t*Bu	rt	0.8	**12b**/75	96
8	**7c**/**8c**	**3**/*i*Pr	80	1	**11c**/55	92
9	**7c**/**8c**	**4**/*t*Bu	80	1	**12c**/52	92
10	**7d**/**8d**	**3**/*i*Pr	60	18	**11d**/47	97
11	**7d**/**8d**	**4**/*t*Bu	60	20	**12d**/48	96
12	**7e**/**8e**	**3**/*i*Pr	80	48	**11e**/42	92
13	**7f**/**8f**	**3**/*i*Pr	80	24	**11f**/46	90

[a] Reactions performed according to method A (entries 1−9) or method B (entries 10−13). [b] Oil bath temperature for the DA reaction. [c] For entries 1−9, time during which DAIB/MeOH was added; for entries 10−13, DA reaction time. [d] Of pure and isolated adduct(s). A considerable amount of the corresponding dimer was also obtained in entries 8−13. [e] Determined by HPLC analysis of the crude sample using an Si-60 column unless otherwise noted. [f] Combined yield of major and minor diastereomers. [g] Determined by ^{1}H NMR (400 MHz) analysis of the crude sample.

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(8) For natural products bearing butyrolactone moiety which exhibit interesting and useful biological activities, see: Pettit, G. R.; Grag, G. M.; Ode, R. H. *Biosynthetic Products for Cancer Theraphy*; Plenum: New York, 1977−1979; Vols. I−III.

(9) Racemic furans **1**,[9a] **2**,[9a] **3**,[9b] **4**,[9c] and **5**[9b] were synthesized according to literature procedures. (a) West, F. G.; Gunawardena, U. *J. Org. Chem.* **1993**, *58*, 2402−2406. (b) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 7007−7014. (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232.

(10) **Method A.** In a representative procedure, to a mixture of a 2-methoxyphenol **7** (0.5 mmol) and a furan derivative (**1**−**6**, 1.5 mmol) in MeOH (3 mL) was added DAIB (0.75 mmol) in MeOH (2 mL) during 1 h under stirring at room temperature. After 10 min of stirring, MeOH was removed under reduced pressure and the adducts were separated by silica gel column chromatography.

8d−**f** require higher temperatures and longer reaction times (entries 10−13). Under these conditions, the products **11d**−**f** and **12d** resulted from the addition of methanol to the initially formed cycloadducts were isolated. In these cases, excellent diastereoselectivities are realized, although the chemical yields of **11d**−**f** and **12d** are moderate owing to the formation of dimers of MOBs (Figure 1). Notably, all the MOBs

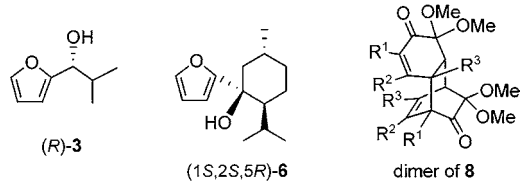


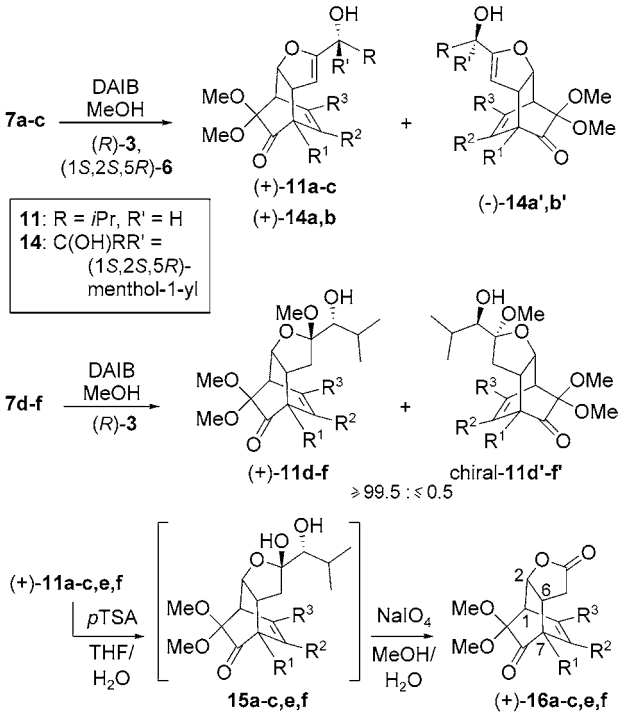
Figure 1. Chiral furan derivatives and dimers of MOBs.

employed in this study undergo cycloaddition with (±)-**3** and (±)-**4** with excellent diastereoselectivity (90−99%).

Having achieved success in the diastereoselective Diels−Alder reactions of MOBs with chiral racemic furan derivatives, we have then carried out the asymmetric reactions of **7a**−**f** with homochiral furans **3**[12a] and **6**[12b] (Figure 1). The reaction of **7a** with (*R*)-**3** provided the adduct (+)-**11a** with excellent diastereoselectivity (Scheme 2, Table 2). However, the furan derivative (1*S*,2*S*,5*R*)-**6** derived from (−)-menthone produced (+)-**14a** in 83% diastereoselectivity. The isopropyl-bearing furan derivative (*R*)-**3** gave better results in the reactions with **7b**,**c**. The reactions of **7c**−**f** with (*R*)-**3** proceeded in a parallel fashion in comparison to (±)-**3**; nevertheless, improved chemical yields and diastereoselectivities were observed. The diastereomers (+)-**11a**−**c**,**e**,**f** were treated with *p*TSA in THF/water to provide hemiacetals **15**, which were subsequently oxidized to the corresponding lactones (+)-**16a**−**c**,**e**,**f** in excellent enantiomeric excesses (Scheme 2, Table 3).

The assigned absolute stereochemistry of the major adducts (+)-**11**−(+)-**14** (Scheme 2, Table 2) is based on their circular dichroism spectra and the single-crystal X-ray structures[13a,b] of (+)-**11a** and (+)-**11d** (Supporting Information). The relative stereochemistry of the racemic adducts **9**−**13** (Table

Scheme 2



1) was established by comparing their spectral data with those of optically pure compounds (Table 2). The relative stereochemistry of (±)-**13a** was further confirmed from its single-crystal X-ray structure.[13c] Further, the sense of asymmetric induction observed in these reactions is consistent as indicated by the circular dichroism spectra of the lactones (+)-**16a**−**c**,**e**,**f** (Scheme 2) revealing that all of them possess the same absolute stereochemistry (1*R*,2*R*,6*R*,7*S* for **16a**,**b**,**e**,**f**

Table 2. Diastereoselective Diels−Alder Reactions of MOBs **8** Derived from 2-Methoxyphenols **7** with Chiral Furans (*R*)-**3** and (1*S*,2*S*,5*R*)-**6**[a]

entry	phenol/ MOB	furan	*T*[b]/ °C	time[c]/ h	adduct/ % yield[d]	% de[e]
1	**7a**/**8a**	(*R*)-**3**	rt	1	(+)-**11a**/77	98
2	**7a**/**8a**	(1*S*,2*S*,5*R*)-**6**	rt	1	(+)-**14a**/65, (−)-**14a′**/6	83[f]
3	**7b**/**8b**	(*R*)-**3**	rt	0.8	(+)-**11b**/74	96
4	**7b**/**8b**	(1*S*,2*S*,5*R*)-**6**	rt	0.8	(+)-**14b**/56, (−)-**14b′**/16	56[f]
5	**7c**/**8c**	(*R*)-**3**	80	1	(+)-**11c**/60	99
6	**7d**/**8d**	(*R*)-**3**	60	18	(+)-**11d**/45	99
7	**7e**/**8e**	(*R*)-**3**	80	48	(+)-**11e**/44	>99.9
8	**7f**/**8f**	(*R*)-**3**	80	24	(+)-**11f**/47	99

[a] Reactions performed according to method A (entries 1−5) or method B (entries 6−8). [b] Oil bath temperature for the DA reaction. [c] For entries 1−5, time during which DAIB/MeOH was added; for entries 6−8, DA reaction time. [d] Of pure and isolated adduct(s), unless otherwise noted. A considerable amount of the corresponding dimer was also obtained in entries 5−8. [e] Determined by HPLC analysis of the crude sample using an Si-60 column unless otherwise noted. [f] Determined by ^{1}H NMR (400 MHz) analysis of the crude sample.

(11) **Method B.** In a representative procedure, to a 2-methoxyphenol **7** (0.5 mmol) in MeOH (3 mL) was added DAIB (0.75 mmol) in MeOH (2 mL) in one portion under stirring at 0 °C. After 10 min of stirring at 0 °C, MeOH was removed by rotary evaporator, the residue was washed with brine solution and extracted with ethyl acetate, and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Thus obtained crude MOB **8** was taken in MeOH (3 mL), to this was added a furan derivative (**3** or **4**, 1.5 mmol) in MeOH (3 mL), and the resulting mixture stirred at the appropriate temperature (see Tables 1 and 2). After completion of the reaction (see Tables 1 and 2 for reaction time), MeOH was removed under reduced pressure and the adducts were separated by silica gel (neutralized with triethylamine) column chromatography.

(12) Homochiral furan derivatives (*R*)-**3**,[12a] (*R*)-**5**,[12a] and (1*S*,2*S*,5*R*)-**6**[12b] were synthesized according to literature procedures: (a) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085−2091. (b) Dinesh, C. U.; Kumar, P.; Reddy, R. S.; Pandey, B.; Puranik, V. G. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2961−2970.

(13) (a) (+)-**11a**: CCDC 199010. (b) (+)-**11d**: CCDC 199012. (c) (±)-**13a**: CCDC 199011.

Table 3. Hydrolysis and Oxidation of Diels−Alder Adducts (+)-**11** to Chiral Tricyclic Lactones (+)-**16**

entry	cycloadduct	oxidation time[a]/h	lactone/% yield	% ee[b]
1	(+)-**11a**	2	(+)-**16a**/94	98
2	(+)-**11b**	3	(+)-**16b**/80	94
3	(+)-**11c**	8	(+)-**16c**/88	>99.9
4	(+)-**11e**	10	(+)-**16e**/84	98
5	(+)-**11f**	17	(+)-**16f**/89	>99.9

[a] Time for the oxidation step. [b] Determined by HPLC analysis of the crude sample using a Chiralcel-OD column.

and 1*R*,2*R*,6*S*,7*S* for **16c**; the latter differs in *R*,*S*-nomenclature at the chiral center C-6 as the result of the sequence rules).

It is noteworthy that all the Diels−Alder reactions proceeded with complete site-selectivity with the participation of unsubstituted double bond in the reaction. Furthermore, all the cycloadditions described in this study proceed in highly regio- and stereoselective manner, thus providing ortho,endo-adducts exclusively. The complete ortho (C=C bond of the heterocyclic moiety is adjacent and anti to carbonyl function) regioselectivity resulted from the initial bond formation between the most electron-rich carbon-2 of furan derivative and the electron-deficient carbon-5 of MOB.[4,14] The endo nature of the transition state brings the chiral center into play (Figure 2). The furan derivatives direct

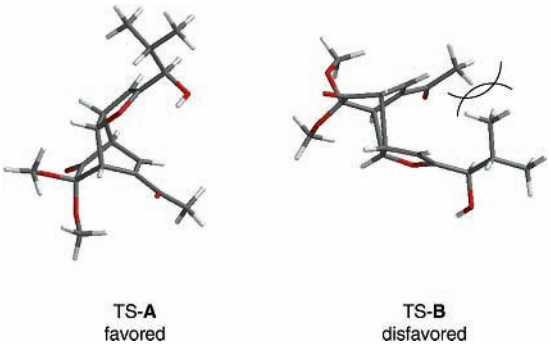


Figure 2. Transition-state structures TS-A and TS-B for the reaction of **8a** and **3**.

the facial selectivity in the present Diels−Alder reactions. The observed high diastereoslectivities can be understood by the inspection of molecular models. Furthermore, the calculations of two endo transition-state structures for the reaction of **8a** and **3** at PM3 level suggest that the diene approaches the dienophile from the more open surface (TS-**A**, favorable), where the isopropyl group orients away from the reaction site leading to major adduct **11a**. The approach that forms TS-**B** is disfavored due to steric interactions and leads to minor diastereomer **11a′** (Figure 2). The sterically small R groups in the dienophile such as **1** (Me) or **2** (Et) cannot induce better facial discrimination during the reaction and thus produce moderate diastereoselectivities (entries 1 and 2, Table 1). The electronic variations in the MOB (**8d**−**f**) influence the subsequent methanol addition to the cycloadducts **11** and **12**. Although there are a priori 16 possible modes of [4 + 2] cycloadditions, the reactions of (*R*)-**3** provided exclusively a single isomer in several cases. It is interesting to note that apparent repulsion of furan oxygen atom and hydroxyl function of the side chain (2-substitution on the furan moiety) leads to an anti arrangement of these atoms that can also be observed in the crystal structure of the adduct (+)-**11a** (Figure 3). The same is true in the case of crystal structures (+)-**11d** and (±)-**13a**.

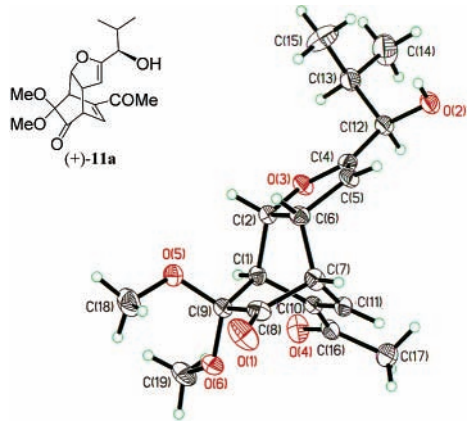


Figure 3. ORTEP diagram of the crystal structure of the adduct (+)-**11a**.

In conclusion, we have documented the first diastereoselective and asymmetric Diels−Alder protocol of masked *o*-benzoquinones leading to highly functionalized and novel tricyclic ring systems with four stereogenic centers from simple starting materials. The cycloadditions proceed under mild conditions with high selectivities and excellent asymmetric induction. The immense potential of this Diels−Alder strategy is realized via a two-pot, four-step synthesis of several enantioselective tricyclic lactones from easily accessible guaiacol derivatives and furan derivative (*R*)-**3**. Further insight into this Diels−Alder methodology is under current investigation and will be reported in due course.

Acknowledgment. Financial support from the National Science Council of Republic of China is gratefully acknowledged. R.K.P. thanks the NSC for a postdoctoral fellowship.

Supporting Information Available: Tables of selected ^{1}H NMR chemical shifts and coupling constants, CD curves, copies of ^{1}H and ^{13}C NMR and DEPT spectra, and HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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