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Intramolecular Diels–Alder reactions of masked *p*-benzoquinones: a novel methodology for the synthesis of highly functionalized *cis*-decalins

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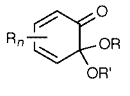
Tethering of dienols to hydroquinones under Mitsunobu conditions followed by oxidation with diacetoxyiodobenzene in methanol resulted in the development of highly functionalized *cis*-decalins *via* intramolecular Diels–Alder reactions of *in situ* generated masked *p*-benzoquinones.

Because of their widespread occurrence in a large variety of natural products of biological importance, decalins remain a focus of attention for synthetic organic chemists.[1–3] Functionalized decalins with proper stereochemistry are possible intermediates for several terpenoids possessing biological activity. Not surprisingly, there has been a great deal of interest in developing methodologies for their synthesis, as evidenced by the growing number of reports in this area.[4–8] Most recently, we have shown that masked *o*-benzoquinones (MOBs), *i.e.*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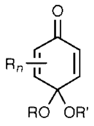
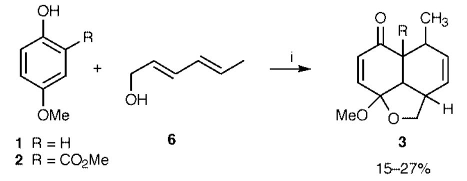

MPB

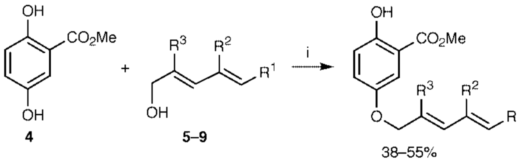
6,6-dialkoxycyclohexa-2,4-dienones, are efficient intermediates for the stereoselective synthesis of highly functionalized *cis*-decalins.[9] Herein, we report a novel method for the synthesis of highly functionalized decalins *via* the intramolecular Diels–Alder (IMDA) reactions of *in situ* generated masked *p*-benzoquinones (MPBs), a class of cross-conjugated cyclohexadienones. To the best of our knowledge this is the first detailed study of IMDA reactions of MPBs.[10]

Over the past ten years we have been investigating the inter- and intra-molecular Diels–Alder reactions of MOBs[11] and their synthetic potential has been exploited.[12] In contrast to the case of MOBs, the Diels–Alder chemistry of MPBs is less explored.[13] This may be due to the fact that the lesser reactivity of MPBs often requires harsh reaction conditions like high pressure[13a] or high temperature[13c,d] with prolonged reaction times. We envisioned that this problem could possibly be overcome by performing these reactions in an intramolecular fashion[14] *via* the *in situ* generation of MPBs by oxidizing *p*-methoxyphenols with diacetoxyiodobenzene (DAIB) in the presence of a dienol in a tandem oxidative acetalization process that would furnish stereoselective and highly functionalized *cis*-decalins.

As a prelude to this objective, we have carried out the reactions of *p*-methoxyphenols **1** and **2** with 10 equiv. of sorbic alcohol (**6**) in the presence of DAIB in different solvents, such as THF, CF_3CH_2OH and CH_2Cl_2. We have isolated the adducts **3** formed *via* IMDA reaction of *in situ* generated MPBs in rather poor yields (Scheme 1). Although the reasons for the lower reactivity of **1** and **2** with **6** are not known at this point, it is apparent that, unlike 2-methoxyphenols,[11b] 4-methoxyphenols cannot undergo facile tandem IMDA reactions. Consequently, we have switched our attention to tethering[15] the diene moiety to the hydroquinones *via* Mitsunobu reaction with dienols prior to oxidation by DAIB. For this purpose, we have performed the reactions of hydroquinone **4** and dienols **5–6** under Mitsunobu conditions to obtain the products in 38–55% yields (Scheme 2).



Scheme 1 *Reagents and conditions*: i, DAIB, solvent, room temp., 2 h.

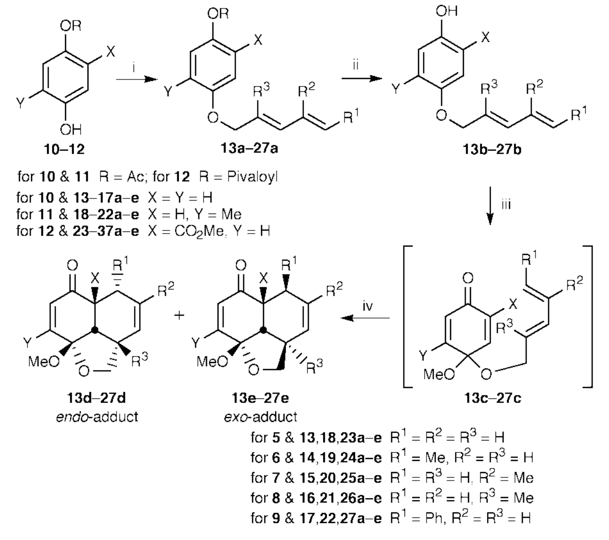


Scheme 2 *Reagents and conditions*: i, PPh_3, DEAD, THF.

Attempts to improve the yields by changing the reaction conditions were not successful. The use of DIAD in place of DEAD produced slightly better yields. However, we have conveniently produced the required phenols **13b–27b** by choosing selectively protected hydroquinones **10–12** as starting materials for Mitsunobu reaction followed by saponification in very good yields (Scheme 3, Table 1).

Masked *p*-benzoquinones **13c–27c** generated *via* oxidation of phenols **13b–27b** (0.5 mM) in MeOH (50 ml) using DAIB (0.75 mM) as oxidant underwent intramolecular cyclization at room temperature (Method A), or at reflux temperature in benzene (Method B) or in toluene (Method C) to afford the cycloadducts **13d,e–27d,e** in 78–90% yield (Scheme 3). Table 2 illustrates typical results of the IMDA reactions of MPBs.

The gross structures of all the IMDA adducts were determined by their IR, ^1H and ^{13}C NMR, DEPT, low- and high-resolution mass spectral analyses. The stereochemistries of



Scheme 3 *Reagents and conditions*: i, PPh_3, DIAD, THF, **5–9**; ii, K_2CO_3, MeOH, 0 °C; iii, DAIB, MeOH; iv, Methods A–C.

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Table 1 Synthesis of phenols **13b**–**27b**

Phenols **10**–**12**	Dienols **5**–**9**	Dienyl ethers **13a**–**27a** (% yield)	Phenols **13b**–**27b** (% yield)
10	**5**	**13a** (82)	**13b** (98)
	6	**14a** (86)	**14b** (98)
	7	**15a** (84)	**15b** (97)
	8	**16a** (87)	**16b** (99)
	9	**17a** (78)	**17b** (99)
11	**5**	**18a** (87)	**18b** (81)
	6	**19a** (85)	**19b** (85)
	7	**20a** (85)	**20b** (85)
	8	**21a** (83)	**21b** (88)
	9	**22a** (74)	**22b** (76)
12	**5**	**23a** (85)	**23b** (98)
	6	**24a** (83)	**24b** (96)
	7	**25a** (85)	**25b** (97)
	8	**26a** (83)	**26b** (97)
	9	**27a** (75)	**27b** (99)

Table 2 IMDA reactions of MPBs **13c**–**27c** generated from phenols **13b**–**27b**

Entry	Phenol	MPB	Method[a]	DA adduct	Yield (%)	*endo* : *exo*[b]
1	**13b**	**13c**	B	**13d** + **e**	88	1 : 1
2	**14b**	**14c**	A	**14d**	90	1 : 0
3	**15b**	**15c**	B	**15d** + **e**	85	3 : 1
4	**16b**	**16c**	C	**16d**	80	1 : 0
5	**17b**	**17c**	A	**17d**	78	1 : 0
6	**18b**	**18c**	B	**18d** + **e**	85	1 : 1
7	**19b**	**19c**	A	**19d**	84	1 : 0
8	**20b**	**20c**	B	**20d** + **e**	88	2.5 : 1
9	**21b**	**21c**	C	**21d**	79	1 : 0
10	**22b**	**22c**	A	**22d**	79	1 : 0
11	**23b**	**23c**	A	**23d** + **e**	83	1 : 1
12	**24b**	**24c**	A	**24d** + **e**	87	1.2 : 1
13	**25b**	**25c**	A	**25d** + **e**	88	2.5 : 1
14	**26b**	**26c**	C[c]	**26d**	83	1 : 0
15	**27b**	**27c**	A	**27d** + **e**	82	1 : 1

[a] All MPBs were generated at 0 °C and after usual workup, the crude residue was used as such for Methods B and C. Method A: room temp., 15 min; Method B: benzene, reflux, 4 h; Method C: toluene, reflux, 40 h. [b] Determined by ^{1}H NMR. [c] Reaction time: 18 h.

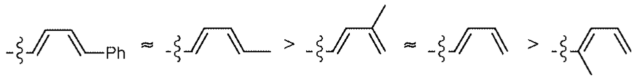

Fig. 1 Reactivity series for the diene moiety.

endo-adducts **14d**, **16d**, **17d**, **19d**, **21d**, **22d** and **26d** were established by NOE studies. The *endo*-adduct **25d** and the *exo*-adduct **25e** were separated from their mixture **25d** + **e** by recrystallizing from hexane–Et_2O to afford the former as an oil and the latter as crystals, and their stereochemistry was deduced from NOE studies. The stereochemistry of **25e** was further confirmed from its single crystal X-ray structure.[16] The *endo* and *exo* ratios of cycloadducts from entries 1, 3, 6, 8, 11–13 and 15 were determined from their ^{1}H NMR (400 MHz) spectra.

In the IMDA reactions of unsymmetrical MPBs **18c**–**22c** and **23c**–**27c**, the double bond with less electron density, *i.e.* the unsubstituted double bond in **18c**–**22c** and the CO_2Me-substituted double bond in **23c**–**27c**, behaved as a dienophile. The IMDA reactions of MPBs **23c**–**27c** bearing an additional electron-withdrawing group (CO_2Me) (entries 11–15) are faster than those of **13c**–**22c** (entries 1–10), where such a group is not present. The two sets of MPBs **13c**–**22c** and **23c**–**27c** show comparable reactivities. It appears that the reactivity pattern mainly depends on the tethered diene unit and could be explained on the basis of the position of the substituents attached to the diene moiety,[17] as shown in Fig. 1.

In most of the cases studied, the *endo*-adduct was obtained as either the sole product or the predominant product. The transformation of transoid to cisoid conformation of the diene units in MPBs **16c**, **21c** and **26c** (R^1 = R^2 = H, R^3 = Me) required for Diels–Alder reaction needs more energy as reflected by the reaction conditions employed (entries 4, 9 and 14). Owing to the disfavored interactions in their *exo*-transition states (Fig. 2), *endo*-adducts **16d**, **21d** and **26d** were formed exclusively in these reactions.

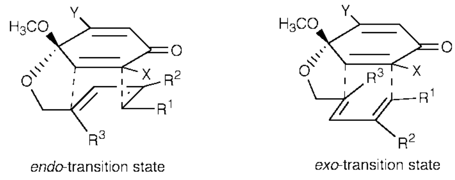

Fig. 2 Diels–Alder transition states.

In summary, we have shown for the first time that masked *p*-benzoquinones tethered to a diene moiety undergo efficient intramolecular cyclization to produce highly functionalized *cis*-decalins in very good yields. Our methodology provides an easy access to a series of stereoselective *cis*-decalins attached to five-membered oxygen heterocycles which may otherwise be difficult to synthesize. Further applications of MPBs in organic synthesis are under investigation in our laboratory.

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