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Diastereoselective intramolecular Diels–Alder reactions of masked *o*-benzoquinones: a short entry to highly functionalized tricyclic [*m*.2.2.0] ring systems

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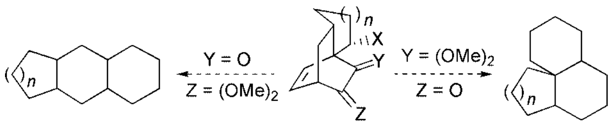
Masked *o*-benzoquinones bearing a chiral center in the carbon-tether with a terminal olefin underwent diastereoselective intramolecular Diels–Alder reactions resulting in highly functionalized tricyclic ring systems.

The intramolecular Diels–Alder (IMDA) reaction is a powerful tool for the rapid construction of highly substituted polycyclic carbon skeletons.[1] Milder reaction conditions and superior reactivity and selectivities are often experienced as a result of the entropy factor in IMDA reactions in comparison to bimolecular Diels–Alder reactions. Recently, we have reported the IMDA reactions of masked *o*-benzoquinones (MOBs)[2] and masked *p*-benzoquinones (MPBs)[3] producing functionalized ring systems. Herein, we report our preliminary results regarding the diastereoselective IMDA reactions of MOBs bearing a chiral centre in the carbon-tether with a terminal olefin leading to highly functionalized tricyclic ring systems.

Masked *o*-benzoquinones,[4] a highly reactive class of 6,6-dialkoxycyclohexa-2,4-dienones, can be easily generated *in situ* by the oxidation of the corresponding 2-methoxyphenols with hypervalent iodine reagents in MeOH. The *in situ* generated MOBs undergo facile Diels–Alder reactions with a wide variety of dienophiles.[5] When the oxidation was carried out in the presence of an alkenol, MOBs undergo IMDA reactions *via* a tandem oxidative acetalization process.[2] It was envisioned that if MOBs bearing a chiral center in the alkenyl-tether undergo intramolecular cycloaddition, easy access to highly substituted tricyclic ring systems that are precursors for several linear and angular tricyclic skeletons (Scheme 1), could be achieved.

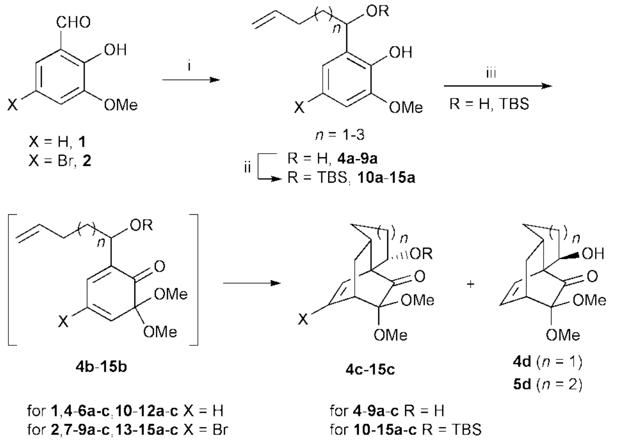
The substrates required for this strategy were prepared from benzaldehydes **1**, **2** and **3**. The Grignard reaction of **1** and **2** with alkenylmagnesium reagents of varying chain length afforded 2-methoxyphenols **4a**–**9a**, having a chiral center in the alkenyl-tether, in 80–92% yield. The oxidation of **4a** in MeOH to the corresponding MOB **4b** *via* the slow addition of diacetoxyiodobenzene (DAIB) at room temperature (Method A) did not give satisfactory results. However, the slow addition of DAIB to a methanolic solution of **4a** (n = 1) at reflux temperature (Method B) afforded IMDA adducts **4c** and **4d** of five-membered ring annulation *via* transiently generated **4b**, in 51 and 6% chemical yield, respectively, resulting from *endo*-addition, in addition to 17% of a mixture of dimers (Scheme 2, Table 1).† Similar results were obtained when the chain length was increased by one carbon (n = 2) (entry 2). However, when the reaction conditions were extended to **6a** (n = 3), only a mixture of dimers of MOB **6b** were obtained. To prevent the dimerization,[6,7] we have examined the reaction of 4-bromophenols **7a** and **8a** with DAIB in MeOH at room temperature, which furnished the single diastereomers **7c** and **8c** resulting from IMDA reaction of MOBs **7b** and **8b** in very good yields (entries 4 and 5). The reaction of bromophenol **9a** (n = 3) proceeded slowly and afforded only 4% of the seven-membered ring annulated cycloadduct **9c** in 12 h.



Scheme 1

To ascertain whether the protection of the hydroxy function at the tetrahedral carbon of **4a**–**9a** has influenced the stereochemical outcome of the reaction, we have prepared their *tert*-butyldimethylsilyl derivatives **10a**–**15a** and evaluated the IMDA reaction of MOBs **10b**–**15b** (Scheme 2). Gratifyingly, the 2-methoxyphenols **10a**, **11a** and **13a**–**15a** furnished a single diastereomer in each case with an improved chemical yield. The reaction of phenol **12a** at either room temperature or reflux temperature failed to produce the cycloadduct. These results are summarized in Table 1.

Given the success in the IMDA reactions of *in situ* generated MOBs, it seemed to us that a related process could be used for the more stable MOBs to synthesize the tricyclic ring skeletons. To test this proposition, phenols **16a**–**18a** were synthesized from **3**. From our previous work, it was found that MOBs bearing substituents at C-5 are quite stable and could be isolated.[7] Likewise, **16a**–**18a** were oxidized with DAIB in MeOH to the MOBs **16b**–**18b** in excellent to quantitative yields (Scheme 3). Interestingly, the IMDA reaction of **16b** (n = 1) proceeded in toluene at reflux temperature to furnish the *endo*-diastereomeric adducts **16c**,**d** in 38 and 15%, respectively, in addition to 19% of *exo*-isomer **16e**. Nevertheless, the **17b** reacted intramolecularly in THF at reflux temperature to afford six-membered ring annulated adducts **17c** and **17d** in 93 and 4% yield, respectively, with complete *endo*-selectivity, albeit with longer reaction time. Similarly, **18b** (n = 3) when heated at reflux in mesitylene for 24 h, produced IMDA adducts **18c** and **18d** in rather poor yields. The MOB **19b** formed from TBS protected phenol **19a**, upon reflux in toluene produced quantitatively *endo*-**19c** and *exo*-**19e** in 3 : 2 ratio. In contrast, a single



Scheme 2 *Reagents and conditions*: (i) $CH_2CH(CH_2)_{n+1}$ MgBr, THF, rt (80–92%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C (89–100%); (iii) DAIB, MeOH (Methods A and B).

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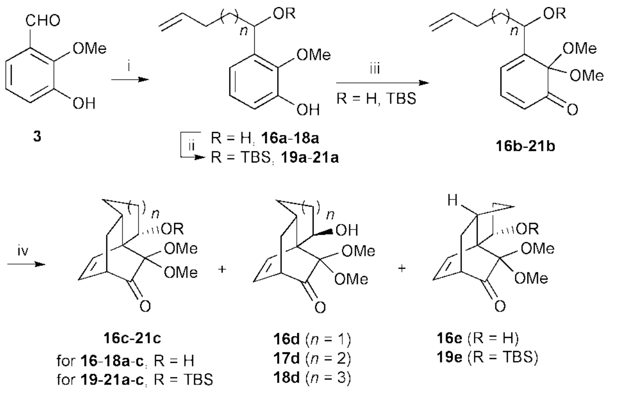
Table 1 IMDA reactions of MOBs **4b**–**21b** generated from phenols **4a**–**21a**

Entry	Phenol	Method/ time[a]	MOB	Time[b]	DA adduct(s) (Yield %)[c]
1	**4a** (X = H, R = H, n = 1)	B/2 h	**4b**	0.5 h	**4c** (51), **4d** (6)
2	**5a** (X = H, R = H, n = 2)	B/2 h	**5b**	0.5 h	**5c** (46), **5d** (2)
3	**6a** (X = H, R = H, n = 3)	B/2 h	**6b**	0.5 h	**6c** —
4	**7a** (X = Br, R = H, n = 1)	A/1.5 h	**7b**	3.5 h	**7c** (80)
5	**8a** (X = Br, R = H, n = 2)	A/1 h	**8b**	1 h	**8c** (71)
6	**9a** (X = Br, R = H, n = 3)	A/2 h	**9b**	12 h	**9c** (4)
7	**10a** (X = H, R = TBS, n = 1)	B/1.5 h	**10b**	1 h	**10c** (53)
8	**11a** (X = H, R = TBS, n = 2)	B/2 h	**11b**	0.5 h	**11c** (73)
9	**12a** (X = H, R = TBS, n = 3)	B/2 h	**12b**	0.5 h	**12c** —
10	**13a** (X = Br, R = TBS, n = 1)	A/1 h	**13b**	1.5 h	**13c** (90)
11	**14a** (X = Br, R = TBS, n = 2)	A/1 h	**14b**	2 h	**14c** (95)
12	**15a** (X = Br, R = TBS, n = 3)	B/2 h	**15b**	1 h	**15c** (15)
13	**16a** (R = H, n = 1)	C	**16b**	7.5 h	**16c** (38), **16d** (15), **16e** (19)
14	**17a** (R = H, n = 2)	C	**17b**	6 d	**17c** (93), **17d** (4)
15	**18a** (R = H, n = 3)	C	**18b**	24 h	**18c** (12), **18d** (3)
16	**19a** (R = TBS, n = 1)	C	**19b**	4 h	**19c** (60), **19e** (40)
17	**20a** (R = TBS, n = 2)	C	**20b**	20 h	**20c** (98)
18	**21a** (R = TBS, n = 3)	C	**21b**	18 h	**21c** (10)

[a] Time during which DAIB was added. DAIB in MeOH was added to the phenol in MeOH at either rt (Method A) or reflux temperature (Method B). In Method C, MOB was isolated and the IMDA reaction was carried out at reflux temperature in a solvent (toluene for entries 13, 16 and 17; THF for entry 14; and mesitylene for entries 15 and 18). [b] The reaction time after the addition of DAIB in entries 1–12. [c] Yields are of pure and isolated adducts.



Scheme 3 *Reagents and conditions*: (i) $CH_2CH(CH_2)_{n+1}$ MgBr, THF, rt (71–77%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C (89–99%); (iii) DAIB, MeOH, rt; (iv) solvent, reflux (Method C).

endo-diastereomer **20c** was produced in near quantitative yield from MOB **20b** (Scheme 3, Table 1).

The stereoselectivity of the cycloadduct of each successful case is completely analogous to the first example (entry 1), with the major, or sole, diastereomer arising from an approach in which all three rings adopt conformations of *endo*-mode with α-OH or α-OTBS in the transition state. The stereochemistries of **5c′** (3,5-dinitrobenzoate of **5c**), **7c**, **16c** and **16e′** (3,5-dinitrobenzoate of **16e**) were confirmed from their X-ray structures‡ and that of the other adducts were confirmed by chemical correlation and/or by comparing ^{1}H NMR data.

The IMDA reactions of the MOBs with 4-Br substitution proceeded in a highly diastereoselective manner leading to a single *endo*-, α-OR isomer. With one exception (**19b**), all the MOBs having OTBS functionality at the chiral center provided a single diastereomer (*endo*-, α-OTBS). The reduced reactivity of IMDA reactions with increased tether length as reflected in seven-membered ring annulations (n = 3) has been previously recorded.[8] However, the yields of these reactions (n = 3) were partially improved (**6c**: 28; **9c**: 25; **15c**: 59%) by the pyrolysis of the crude mixture which contains dimers, obtained after oxidation in mesitylene.

In summary, we have demonstrated here that masked *o*-benzoquinones bearing a chiral center in the carbon-tether underwent IMDA reactions to provide densely substituted tricyclic ring systems. Transformation of these adducts to linear and angular tricyclic skeletons, and the asymmetric version of the present protocol are under active investigation.

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Notes and references

† All the new compounds were charaterized by IR, ^{1}H (400 MHz), and ^{13}C NMR (100 MHz), DEPT, and low and high resolution MS analyses.

‡ *Crystal data for **5c′***: $C_{21}H_{22}N_2O_9$, M = 446.41, triclinic, a = 6.3649(3), b = 9.8499(4), c = 17.6830(7) Å, α = 82.19, β = 85.9730(10), γ = 72.0600(10)°, V = 1044.45(8) Å^3, T = 293(2) K, space group $P1$, Z = 2, μ(Mo-Kα) = 0.112 mm^{-1}. 10153 reflections collected, independent reflections 4527 (R_{int} = 0.0384), final R indices [$I > 2\sigma(I)$] $R1$ = 0.0523, $wR2$ = 0.1102. CCDC 160765. See http://www.rsc.org/suppdata/cc/b1/b103440p/

*Crystal data for **7c***: $C_{13}H_{17}BrO_4$, M = 317.18, triclinic, a = 7.9569(2), b = 12.4857(4), c = 14.1058(3) Å, α = 82.922(1), β = 83.764(1), γ = 77.597(1)°, V = 1353.35(6) Å^3, T = 295(2) K, space group $P1$, Z = 4, μ(Mo-Kα) = 3.041 mm^{-1}. 13761 reflections collected, independent reflections 5460 (R_{int} = 0.0324), final R indices [$I > 2\sigma(I)$] $R1$ = 0.0488, $wR2$ = 0.1096. CCDC 160763.

*Crystal data for **16c***: $C_{13}H_{18}O_4$, M = 238.27, monoclinic, a = 6.7251(2), b = 24.8959(4), c = 7.5943(3) Å, α = 90, β = 109.260(2), γ = 90°, V = 1200.33(6) Å^3, T = 295(2) K, space group Cc, Z = 4, μ(Mo-Kα) = 0.097 mm^{-1}. 3372 reflections collected, independent reflections 2080 (R_{int} = 0.0187), final R indices [$I > 2\sigma(I)$] $R1$ = 0.0412, $wR2$ = 0.1070. CCDC 160762.

*Crystal data for **16e′***: $C_{20}H_{20}N_2O_9$, M = 432.38, monoclinic, a = 20.8010(1), b = 12.5757(2), c = 15.9854(2) Å, α = 90, β = 112.123(1), γ = 90°, V = 3873.72(8) Å^3, T = 295(2) K, space group $P2_1/c$, Z = 8, μ(Mo-Kα) = 0.119 mm^{-1}. 18200 reflections collected, independent reflections 7835 (R_{int} = 0.0254), final R indices [$I > 2\sigma(I)$] $R1$ = 0.0502, $wR2$ = 0.1174. CCDC 160764.

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