Stereoselective synthesis of highly functionalized *cis*-decalins from masked *o*-benzoquinones

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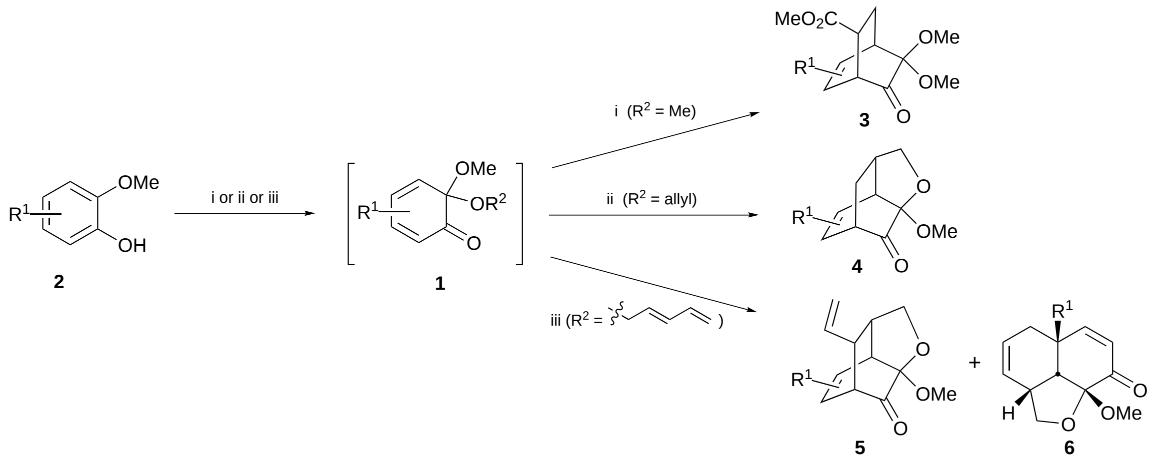
Highly functionalized *cis*-decalins are prepared from commercially available 2-methoxyphenols and acyclic 1,3-dienes.

The decalin skeleton features in a large variety of natural products with interesting biological properties, *e.g.* kaurenes, aphidicolanes, quassinoids and azadirachtins.[1,2] A functionalized decalin has often been the starting point for the synthesis of the above mentioned classes of terpenoids. Owing to this, there is continued interest in the stereoselective synthesis of decalins, as is amply evidenced by the recent flurry of reports by various groups including ours.[3,4] Herein we report a novel method for the preparation of highly functionalized decalins from commercially available 2-methoxyphenols and acyclic 1,3-dienes.

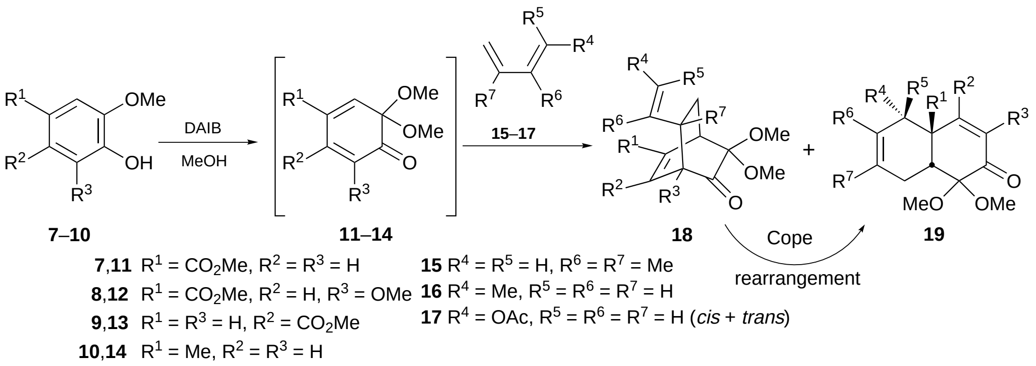
Masked *o*-benzoquinones, *i.e.*, 6,6-dialkoxycyclohexa-2,4-dienones **1**, when compared to their counterparts derived from *p*-benzoquinones,[5] are a relatively underutilized class of compounds. Prior to our studies, there have been only sporadic reports on their chemistry.[6,7] The main reason for this could be their high propensity to dimerize. In most cases, they were isolated in poor yields as dimers. For the last ten years we have been interested in exploiting the synthetic potential of this neglected class of compounds. We have already shown that the masked *o*-benzoquinones **1**, generated *in situ* by the oxidation of 2-methoxyphenols **2** with (diacetoxy)iodobenzene (DAIB) or [bis(trifluoroacetoxy)]iodobenzene (BTIB) in presence of a dienophile in MeOH, an allyl alcohol in CH_2Cl_2 or a 2,4-dienol in THF, undergo Diels–Alder reactions to provide compounds of the types **3**, **4**, and **5** and **6**, respectively (Scheme 1).[4,8]

Masked *o*-benzoquinones, or cyclohexa-2,4-dienones in general, are commonly used as dienes.[7,9] We and others have recently found that they can also act as dienophiles in an intramolecular sense when forced by their structures.[4,10] We now report that masked *o*-benzoquinones **11**–**14**, generated *in situ* from phenols **7**–**10**, exhibit sufficient dienophilicity to react even with unactivated acyclic dienes such as 2,3-dimethylbutadiene **15**, *trans*-piperylene **16** and 1-acetoxybutadiene **17** to provide highly substituted *cis*-decalins with very high regio- and stereo-selectivity (Scheme 2). To the best of our knowledge, these findings are unprecedented.

Phenols **7**–**10** were oxidized by slow addition of a solution of DAIB in MeOH in presence of an excess of a diene in MeOH at



Scheme 1 *Reagents and conditions*: i, DAIB, methyl acrylate, MeOH; ii, DAIB, allyl alcohol, CH_2Cl_2; iii, BTIB, 2,4-dienol, THF



7,**11** $R^1 = CO_2Me, R^2 = R^3 = H$
8,**12** $R^1 = CO_2Me, R^2 = H, R^3 = OMe$
9,**13** $R^1 = R^3 = H, R^2 = CO_2Me$
10,**14** $R^1 = Me, R^2 = R^3 = H$
15 $R^4 = R^5 = H, R^6 = R^7 = Me$
16 $R^4 = Me, R^5 = R^6 = R^7 = H$
17 $R^4 = OAc, R^5 = R^6 = R^7 = H$ (*cis* + *trans*)

Scheme 2

Table 1 Stereoselective synthesis of *cis*-decalins **19**

			Diels–Alder reaction					Cope rearrangement of **18**[d]			
Entry	Phenol	Diene	*T*/°C[a]	*t*/h[b]	Ratio **18** : **19**	Yield of **18**[c] (%)	Yield of **19**[c] (%)	*T*/°C	*t*/h	Yield of **19**[c] (%)	Total yield of **19**[c] (%)
a	**7**	**15**	80	3	1 : 2	29	53	220	24	95	91
b	**7**	**16**	50	3	2 : 1	55	25	200	50	91[e]	—
c	**7**	**17**	80	0.1	2 : 1	62	34	200	40	87	88
d	**8**	**15**	80	3	0 : 1	—	81	—	—	—	81
e	**8**	**16**	50	3	6 : 1	64	11	200	24	85[e]	—
f	**8**	**17**	80	0.5	4 : 1	61	16	200	40	91	71
g	**9**	**15**	80	3	4 : 1	56	14	220	24	86	62
h	**9**	**16**	50	3	1 : 0	81	—	200	50	87[e]	—
i	**9**	**17**	80	0.5	5 : 1	64	14	180	40	89	71
j	**10**	**15**	80	6	3 : 1	34	12	220	24	98	45
k	**10**	**16**	50	6	—	40[f]	—				
l	**10**	**17**	50	6	—	60[f]	—				

[a] Oil bath. [b] During which DAIB is added. [c] Yields are of isolated products and unoptimized. [d] Reaction conditions: **18** + $HC(OMe)_3$ (1 equiv.), mesitylene, heat. [e] Based on consumed starting material. [f] An inseparable mixture of bicyclo[2.2.2]octenones is obtained.

appropriate temperature to obtain compounds **18** and **19**.† In all the cases, the bicyclo[2.2.2]octenone derivatives **18a–j** underwent Cope rearrangement, smoothly providing *cis*-decalins **19** in very high yields.† The total yields of decalins are quite high and hence a new efficient method for the stereoselective preparation of *cis*-decalins has been developed. Although many isomers are possible, we generally isolate only two products, except in case of phenol **10**, showing that these reactions are highly regio- and stereo-selective and obey the ground rules of the Diels–Alder reaction.

The *cis*-decalins **19** could result from either direct Diels–Alder reactions, in which masked *o*-benzoquinones behave as dienophiles, or from tandem processes involving Diels–Alder reactions, in which masked *o*-benzoquinones act as dienes and the resultant vinylbicyclo[2.2.2]octenones **18** then undergo Cope rearrangement. In order to ascertain the actual pathway, the bicyclo[2.2.2]octenones **18e** and **18g** were subjected to heating in MeOH containing AcOH and the corresponding diene in the appropriate proportions for 3 h. In the case of **18e**, the crude reaction mixture was found to contain compounds **18e** and **19e** in a 97 : 3 ratio *via* ^1H NMR spectroscopy. On the other hand, compound **18g** remained unchanged. We therefore believe that the decalins **19** are generally primary products. Nevertheless the aforementioned tandem process can not be completely ruled out.

All the compounds were characterized by ^1H and ^{13}C NMR, IR and mass spectral analysis. The structural assignments of bicyclo[2.2.2]octenones **18** are based on the fact that they isomerize to *cis*-decalins **19** smoothly. The stereochemical assignments of the decalins are based on NOE studies and coupling constants. Closely related compounds can be obtained *via* the reaction of *o*-benzoquinones with acyclic dienes, but the senstive α-dicarbonyl moiety makes these compounds less attractive. Moreover, they aromatize to naphthalene derivatives very easily.[11]

It is quite clear from Table 1 that the masked *o*-benzoquinones can be good dienophiles. Apparently, it is difficult to predict whether a masked *o*-benzoquinone would behave as a diene or a dienophile in its reactions with added dienes. It is obviously linked to the structure of added diene and the nature and/or the position of the substituents present on the masked *o*-benzoquinone. For example, the methoxycarbonyl group on masked *o*-benzoquinone **13** diminishes the dienophilicity due to cross conjugation, which reinforces the diene character. Similarly, the methyl group on masked *o*-benzoquinone **14** increases the diene character, possibly *via* hyperconjugation.

Masked *o*-benzoquinone **11** is undoubtedly the best, exhibiting optimum reactivity and very high selectivity in all respects. On the other hand, **14** showed very poor selectivity, providing mixtures of bicyclo[2.2.2]octenones under various conditions except with 2,3-dimethylbutadiene.

In conclusion, our studies throw light on the nature of masked *o*-benzoquinones and have resulted in the development of a simple method for the synthesis of highly functionalized *cis*-decalins. More detailed studies on the nature of masked *o*-benzoquinones and the transformation of decalin **19f** into (±)-vernolepin are in progress in our laboratory.

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Footnotes and References

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† *General procedure* for the Diels–Alder reaction: In a preheated oil bath was placed a flask containing phenol (2 mmol) and diene (20 mmol) in MeOH (8 ml) was immersed. DAIB (2.4 mmol) in MeOH (6 ml) was added over the period given in the Table 1. The reaction was stirred for 10 min, and then MeOH and excess diene were removed and the residue was dissolved in CH_2Cl_2 (20 ml). The solution was washed with saturated aq. $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent followed by column chromatography yielded compounds **18** and **19**. The ratio of **18** and **19** was determined by ^1H NMR analysis of the crude reaction mixture.

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