Short and efficient route to substituted linear triquinanes from 2-methoxyphenols

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Highly oxygenated and substituted *cis,anti,cis* fused linear triquinanes are prepared from commercially available 2-methoxyphenols and cyclopentadiene.

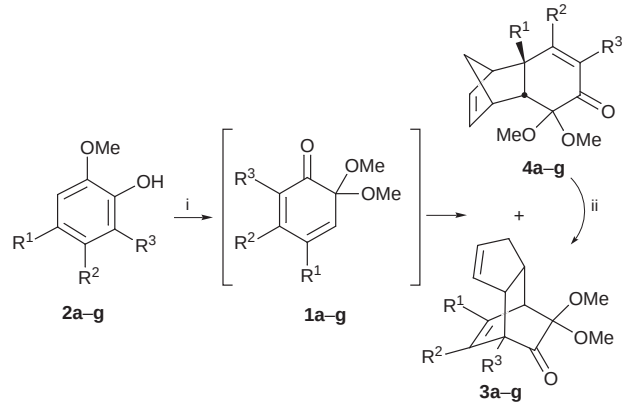
Extensive efforts by synthetic organic chemists during the last two decades towards the synthesis of polyquinane natural products have resulted in the development of several elegant approaches.[1] However, except for a few, most of these approaches are either target oriented or require fairly long sequences of reactions to arrive at the desired carbon framework. Consequently, the search for new methodologies that provide efficient and rapid access to desired quinane skeletons continues.

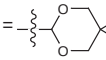
Masked *o*-benzoquinones **1** bearing an array of functional groups can be easily generated *in situ* by the oxidation of commercially available 2-methoxyphenols with hypervalent iodine reagents such as (diacetoxy)iodobenzene (DAIB) and [bis(trifluoroacetoxy)]iodobenzene (BTIB) in MeOH.[2] Masked *o*-benzoquinones **1**, being the most easily accessible cyclohexa-2,4-dienones, readily undergo Diels–Alder reactions in various modes, *i.e*. they act as dienes and dienophiles in both inter- and intra-molecular reactions.[2–6] We have already made use of these reactions in the synthesis of highly functionalized bicyclo-[2.2.2]octenones,[2] *cis*-decalins,[3,4] linear and angular triquinanes[5] and in the synthesis of several natural products.[6] We herein report the development of a new and simple approach to facilitate stereoselective synthesis of highly substituted linear triquinanes using Diels–Alder reactions of cyclopentadiene with *in situ* generated masked *o*-benzoquinones and oxa-di-π-methane (ODPM) photorearrangement as the key steps.

Accordingly, we have carried out the Diels–Alder reactions of cyclopentadiene with masked *o*-benzoquinones **1**, generated *in situ* by adding a solution of a 2-methoxyphenol **2** (2 mmol) in MeOH (8 ml) to a mixture of DAIB (3 mmol) and cyclopentadiene (50 mmol) in MeOH (6 ml) at reflux during 1 h. It was observed that products **3** were produced exclusively except in the cases of **1d** and **1f** (Scheme 1, Table 1). Masked *o*-benzoquinones **1d** and **1f** produced both the possible adducts, *i.e.* **3d** and **4d** and **3f** and **4f**, respectively. Compound **4d** was isolated in pure form while the thermally unstable compound **4f** was found to rearrange to **3f** rapidly. Then the adduct **4d** was subjected to rearrangement in mesitylene at 160 °C for 10 min. As expected compound **3d** was produced in almost quantitative yield. To simplify the preparation of compounds **3d** and **3f**, the concentrated reaction mixtures obtained individually from the reactions of **1d** and **1f** with cyclopentadiene were heated, without purification, in mesitylene at 160 °C for 10 min to furnish compounds **3d** and **3f** in 86 and 76% yield, respectively. It was also observed that by extending the Diels–Alder reaction time to 6 h for **1d** and 18 h for **1f** the desired products could also be obtained exclusively (Table 1).

The observation of products **4d** and **4f** and their isomerization to **3d** and **3f** respectively suggests that a tandem process involving a Diels–Alder reaction followed by Cope rearrangement is in operation in the formation of the latter compounds which are secondary products at least in part if not all. However, controlled experiments carried out at 0 °C made it clear that there are two competetive Diels–Alder reactions taking place. Importantly, in both the modes these cycloadditions are regio- and stereo-selective. In such cycloaddition reactions of cyclopentadiene,[7] this is the first time that a stable and thoroughly characterized norbornene-type adduct, **4d**, has been isolated.

For the conversion of compounds **3a–g** into triquinanes, they were irradiated in acetone using light of wavelength centered at 300 nm in a Rayonet reactor. While **3a** provided the desired ODPM rearrangement product **5a** in 68%, **3b** furnished the expected triquinane **6b** in 45% yield. In other cases a complex reaction mixture was a regular feature. These results are not unexpected since only in the cases of **3a** and **3b** does the biradical intermediate enjoy resonance stabilization by the methoxycarbonyl group. Treatment of **5a** with Ac_2O and BF_3•OEt_2[8] resulted in the highly oxygenated linear triquinane **6a** (Scheme 2). The overall yield of compound **6a** from **2a** is *ca*. 42%. The stereochemical assignments of the triquinane **6a** were based on NOE studies.



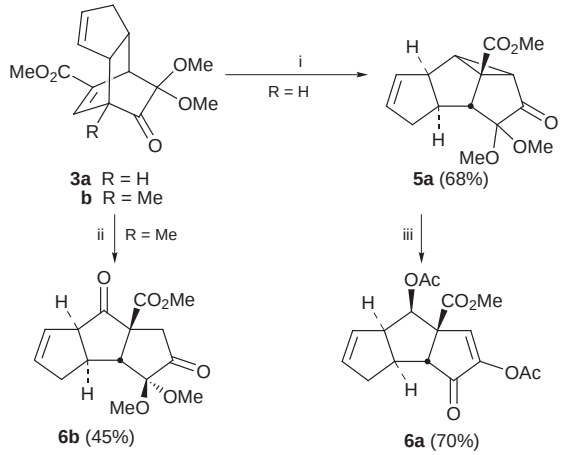
a $R^1 = CO_2Me$, $R^2 = R^3 = H$
b $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OMe$
c $R^1 = H$, $R^2 = CO_2Me$, $R^3 = H$
d $R^1 = R^2 = R^3 = H$
e $R^1 = Me$, $R^2 = R^3 = H$
f $R^1 = R^3 = H$, $R^2 = Me$
g R^1 =  , $R^2 = R^3 = H$

Scheme 1 *Reagents and conditions*: i, cyclopentadiene, DAIB, MeOH, reflux, 1 h; ii, reflux

Table 1 Diels–Alder reactions of masked *o*-benzoquinones (MOBs) with cyclopentadiene

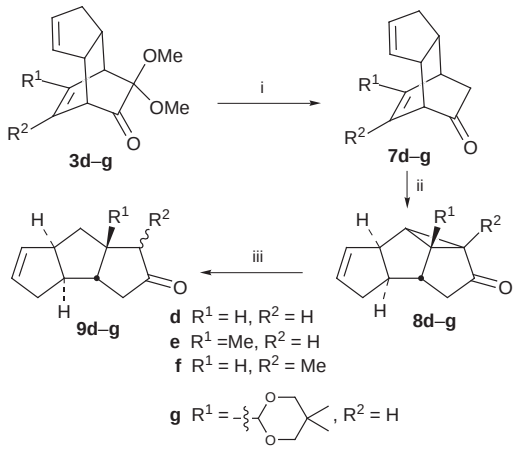
Phenol	MOB	*t*/h	Products	Yield[a] (%)
2a	**1a**	1	**3a**	87
2b	**1b**	1	**3b**	83
2c	**1c**	1	**3c**	80
2d	**1d**	1	**3d** + **4d**	55 + 27
2d	**1d**	6	**3d**	82
2e	**1e**	1	**3e**	91
2f	**1f**	1	**3f** (+**4f**)[b]	
2f	**1f**	18	**3f**	78
2g	**1g**	1	**3g**	85

[a] Yields are of isolated products and are unoptimized. [b] Observed in the ^1H NMR spectrum of the crude reaction mixture.



Scheme 2 *Reagents and conditions*: i, *hν* (1% in acetone), 18 h; ii, *hν* (1% in acetone), 10 h; iii, Ac_2O, BF_3•OEt_2, CH_2Cl_2, 60 °C, 3 h

It was anticipated that reductive removal of the ketal group in compounds **3c–f**, which is known to stabilize free radicals, would minimize the undesired photodecarbonylation. Accordingly, the demethoxylation of **3d–g** was achieved by reduction with SmI_2 to produce compounds **7d–g** in excellent yields.[9] Irradiation of compounds **7d–g** in acetone gave the desired products **8d–g** in agreement with our prognostications. Attempted cleavage of the cyclopropane ring of compound **8d** under the conditions previously employed for the transformation of compound **5a** into **6a** proceeded in an undesired fashion. Consequently, the procedure recently developed by Enholm and Jia for the cleavage of analogous compounds was adopted.[10] Thus treatment of compounds **8d–g** with Bu_3SnH and AIBN in refluxing benzene provided the desired linear triquinanes **9d–g** in good yields (Scheme 3, Table 2). A single stereoisomer was obtained in all cases with one exception. Compound **9f** was produced as a 1:10 mixture of epimers.

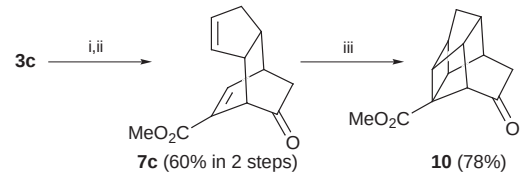


Scheme 3 *Reagents and conditions*: i, SmI_2 (4 equiv.), THF–MeOH, room temp., 10 min; ii, *hν* (1% in acetone), 24 h; iii, Bu_3SnH, AIBN, benzene, reflux

Table 2 Stereoselective synthesis of linear triquinanes (**3**→**7**→**8**→**9**)

Substrate	Product[a]	Yield (%)	Product[b]	Yield (%)	Product[c]	Yield (%)
3d	**7d**	91	**8d**	65	**9e**	70
3e	**7e**	93	**8e**	50	**9f**	81
3f	**7f**	79	**8f**	48	**9g**	83
3g	**7g**	95	**8g**	58	**9h**	93

[a] See ref. 9 for experimental procedure. [b] A 1% solution in acetone was irradiated for 24 h. [c] See ref. 10 for experimental procedure.



Scheme 4 *Reagents and conditions*: i, $HS(CH_2)_3SH$, BF_3•OEt_2, CH_2Cl_2, room temp.; ii, Raney Ni, EtOH; iv, *hν*, acetone

For the removal of the ketal group in compound **3c**, which cannot be affected by SmI_2, it was subjected to transketalization followed by reduction with partially deactivated Raney nickel,[11] to obtain **7c**. Irradiation of compound **7c** in acetone, however, gave [2+2] photocyclization product **10** instead of the desired ODPM rearrangement product (Scheme 4). This is an undesired result and is probably due to the localization of the triplet excited state energy in the α,β-unsaturated ester moiety to give the [2+2] adduct, rather than localization of the triplet excited state energy in the keto group, which is necessary for ODPM rearrangement to proceed.

The stuctures of all the new compounds **3**, **4d** and **5**–**10** were thoroughly established by IR, ^1H and ^{13}C NMR and mass spectral analysis. In the cases of compounds **3a**,**c–f**, H–H COSY spectra assisted in fixing the position of the double bond in the five-membered ring. The stucture of compound **10** was also unambiguously established with the help of a H–H COSY spectrum.

In conclusion the above methodology provides appropriately oxygenated and variously substituted linear triquinane skeletons with naturally occurring *cis*,*anti*,*cis* stereochemistry making use of inexpensive readily available aromatic compounds as starting materials. The present methodology is complementary to the existing related ones such as Wender's approach based on arene-alkene *meta* photoaddition and Singh's methodology based on ODPM rearrangement.[12,13] Application of this methodology to the total synthesis of *Lycopodium* alkaloids of the magellanane group,[14] using compound **9g** as the key intermediate, is in progress in our laboratory.

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Notes and References

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