Novel methodology for stereocontrolled synthesis of *cis*-decalins

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Highly functionalized *cis*-decalins are stereoselectively prepared from commercially available catechol derivatives.

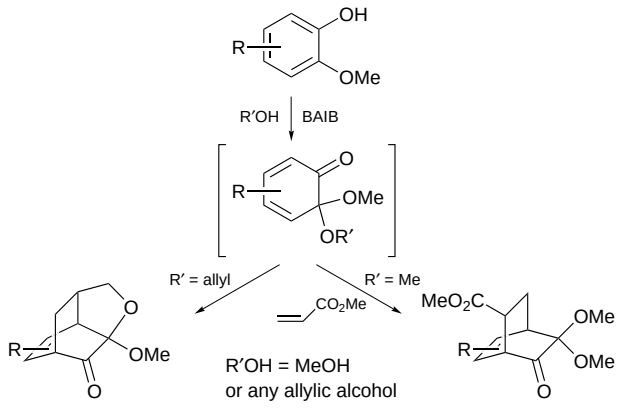
A large variety of natural products of biological importance contain the decalin skeleton as an integral part of their structures.[1–3] Owing to the importance of this structural type in nature, a large number of methodologies have been developed. The Robinson annulation has been the most popular among these strategies. The requirements of modern day stereocontrolled synthesis have been the root cause of the sustained interest in this area, as reflected by the flurry of recent reports by various groups including ours.[4–11]

In our laboratory, a research programme towards the development of a general strategy for the synthesis of clerodane and labdane diterpenoids[2] is underway. The basic skeleton of these terpenoids is a decalin moiety with a considerable number of chiral centres. Towards this end we have recently developed a four-step methodology for the stereocontrolled synthesis of *cis*-decalins starting from commercially available catechol derivatives (Scheme 1).[11] We have already made use of this methodology in the synthesis of an alleged *cis*-clerodane diterpenoic acid.[12] We now report a more simple and efficient methodology starting from commercially available catechol derivatives and 2,4-dienols.

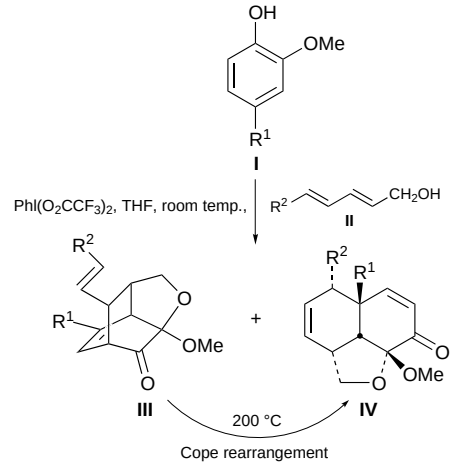
We have been quite successful in using masked *o*-benzoquinones, generated *in situ* from 2-methoxyphenols *via* oxidation by bis(acetoxy)iodobenzene (BAIB) or bis(trifluoroacetoxy)iodobenzene (BTIB), as dienes in inter- and intra-molecular Diels–Alder reactions.[13] The use of this type of cyclohexadienone as a dienophile has not been investigated much.[14] Since the cyclohexadienone moiety can act either as a diene or dienophile, it occurred to us that, if the allylic alcohol is replaced with a 2,4-dienol, it might give rise to *cis*-decalins **IV** and/or tricyclic compounds of the type **III** (Scheme 2).

Accordingly, we first carried out the reaction of *trans*-penta-2,4-dienol and methyl vanillate, which gave both the expected products **IIIe** and **IVe** in 1 : 1 ratio. The tricyclic compound **IIIe**, when heated to 200 °C in mesitylene, underwent Cope rearrangement smoothly. The total yield of decalin is about 60% (procedure A†). Then we extended this methodology to a variety of catechol derivatives and dienols. The ratio of **III** to **IV** depends on the substituents. The reaction conditions and results are shown in Table 1. To make the whole transformation simple, the crude Diels–Alder reaction mixtures were concentrated using a kugelrohr apparatus after the usual work-up and the residues were dissolved in mesitylene and heated to 200 °C to obtain decalins as the sole products in good yields (Table 1, procedure B‡).

As shown in Scheme 3, the intramolecular Diels–Alder reaction can afford three products. However, we could isolate only two products **III** and **IV**. Therefore, in both modes, the cycloaddition seems to be *endo*-selective.

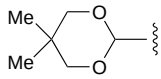


Scheme 1



Scheme 2

Table 1 Preparation of *cis*-decalins

		Yield (%)		Ratio	Yield of **IV** (%)		
R^1	R^2	**III**	**IV**	**III : IV**	From **III**	Procedure A	Procedure B
Me	Me	46	16	3 : 1	95	60	72
	H	40	20	2 : 1	93	57	62
CO_2Me	Me	16	46	1 : 3	93	61	55
	H	31	31	1 : 1	92	60	50
	Me	60	10	6 : 1	93	66	73
	H	57	19	3 : 1	100	76	60

When *cis*-penta-2,4-dienol **V** was employed as a dienol, only tricyclic compounds **VI** were obtained (Table 2). This may be due to the fact that the *o*-benzoquinone moiety acts more efficiently as a diene than a dienophile (Table 1). In addition to this, the equilibrium between s-*trans* and s-*cis* forms of the acyclic diene moiety should favour the s-*trans* form as a consequence of steric requirements. Predictably, these compounds did not undergo Cope rearrangement.

All the new compounds were characterized by IR, ^{1}H and ^{13}C NMR and mass spectral analysis. The stereochemistry of **IVa** was established by NOE studies, and those of other compounds **IV** were assigned by analogy with **IVa**.

In conclusion, our methodology should be among the simplest for the preparation of such highly functionalized decalins with total stereocontrol. The utilization of this methodology in the synthesis of decalin-based natural products is under active investigation in our laboratory.

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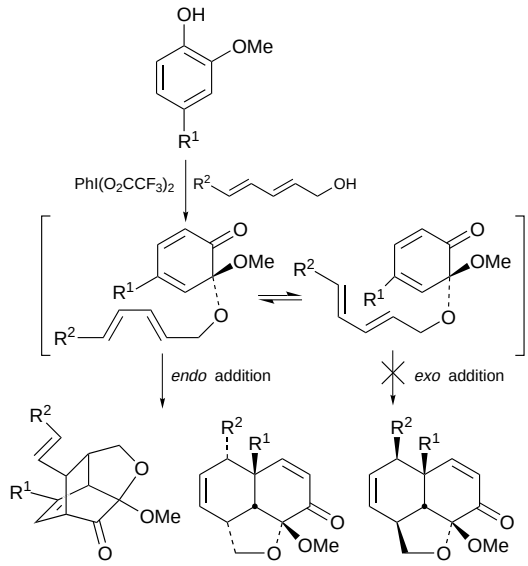
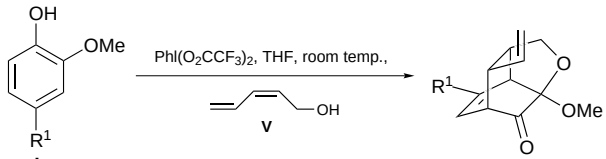
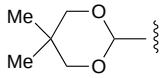


Scheme 3

Table 2 Diels–Alder reaction of *cis*-penta-2,4-dienol



R^1	Yield (%)
Me	52
CO_2Me	47
	36

Footnotes

† *Procedure A: Diels–Alder reaction:* To a stirred mixture of catechol derivative (10 mmol) and dienol (100 mmol) in dry THF (25 ml), a solution of bis(trifluoroacetoxy)iodobenzene (BTIB) (15 mmol) in dry THF (25 ml) was added dropwise during 10 min using a syringe pump at room temperature under nitrogen atmosphere. After 6 h stirring, solid $NaHCO_3$ (30 mmol) was added. After 10 min stirring, water (25 ml) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 25 ml). The combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure on a rotavapor, followed by removal of the excess dienol using a kugelrohr apparatus. The two products **III** and **IV** were separated by column chromatography on silica gel using 15% ethyl acetate in hexane as eluent.

Cope rearrangement: To a solution of compound **III** (5 mmol) in mesitylene was added trimethyl orthoformate (5 mmol) and the resulting mixture was degassed with argon for 30 min. The reaction mixture was then heated for 8 h at 200 °C, cooled and the mesitylene was removed using a kugelrohr apparatus under reduced pressure to give pure product **IV** in excellent yield.

‡ *Procedure B:* The Diels–Alder reaction mixture after work-up (see Procedure A) was concentrated using a kugelrohr apparatus and the crude product mixture thus obtained was dissolved in mesitylene. To this was added 1 equiv. of trimethyl orthoformate and the resulting mixture was degassed and subjected to heating at 200 °C for 8 h. Then mesitylene was removed using a kugelrohr apparatus and the residue thus obtained was purified by column chromatography on silica gel using 15% ethyl acetate in hexane as eluent to give compound **IV** as the sole product.

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