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Divergent enantioselective synthesis of (*P*)- and (*M*)-dihydro[5]helicenequinones from a common tetrahydroaromatic precursor

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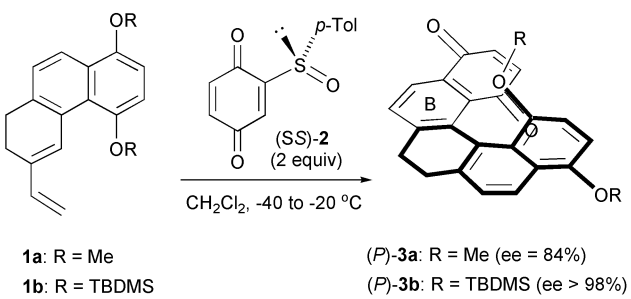
The domino asymmetric Diels–Alder reaction/spontaneous sulfoxide elimination process between a vinyl dihydrophenanthrene as diene and enantiopure (*SS*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone gave access to a tetrahydroaromatic pentacyclic derivative possessing central chirality which led, in a divergent way, to helically chiral (*P*) or (*M*) enantiomers of dihydro[5]helicenequinones in good to excellent chemical and optical yields simply by selecting the appropriate oxidant reagent which makes the final aromatization.

The potential use of the fascinating helicenes,[1] possessing excellent self-assembling,[2] and chiroptical and photochromic properties,[3] as new nonlinear optical materials[4] and in asymmetric molecular recognition[5] and catalysis[6] depends on the facility of obtaining them in enantiomerically pure form.

The most efficient syntheses of non-racemic helicenes reported to date are mainly based on chromatographic,[7] chemical[8] or enzymatic[9] resolutions. Several enantio- or diastereoselective approaches have been described,[10] but, in general, with moderate asymmetric inductions. Thus, versatile enantioselective methods that proceed with high optical yields will allow to extend the range of applications of such derivatives.

During recent years we have studied the dienophilic behavior of enantiomerically pure sulfinyl quinones and have established the domino Diels–Alder reaction/pyrolytic sulfoxide elimination as a general one-pot strategy to enantiomerically enriched polycyclic quinones.[11] This process has been applied to the asymmetric synthesis of the (*M*) and (*P*) enantiomers of [5]helicenebisquinones by using vinyl phenanthrenes as dienes, albeit in moderate chemical and optical yields due to the low reactivity of the aromatic dienes.[12] Later, the methodology was significantly improved by simply modifying the diene partner structure to the much more reactive dihydroarylethenes.[13,14] So, as outlined in Scheme 1, the cycloaddition of vinyl dihydrophenanthenes **1a** and **1b** with enantiopure (*SS*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**2**) could be performed under very mild conditions to afford enantioenriched dihydro[5]-helicenequinones **3a** and **3b** in good chemical yields and good to excellent enantiomeric purities. The reaction sequence involves the elimination of the sulfoxide in the initially formed cycloadduct and *in situ* aromatization of the corresponding tetrahydroaromatic derivative in the presence of an excess of the chiral sulfinylquinone. Under these conditions, only enantiomers with (*P*) helicity could be obtained.[14]



Scheme 1 Enantioselective synthesis of (*P*)-dihydro[5]helicenequinones.

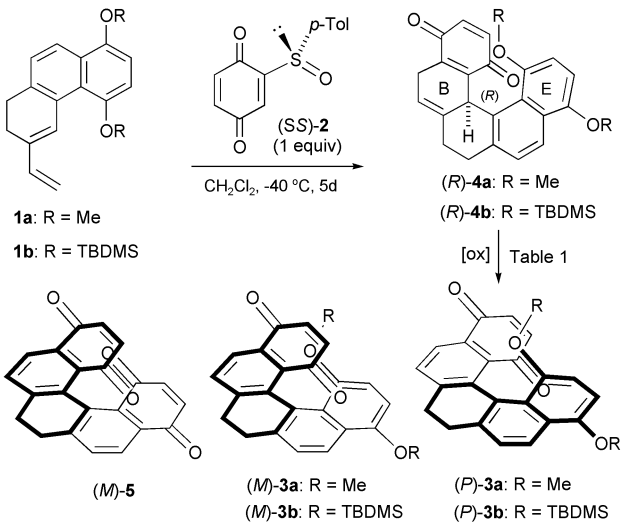
In this communication, we report the synthesis of pentacyclic tetrahydroaromatic derivatives (*R*)-**4a**,**b** from the Diels–Alder reactions of vinyl dihydrophenanthrenes **1a** and **1b** and a stoichiometric amount of enantiopure (*SS*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**2**),[15] as well as the transformation of such centrally chiral compounds, after partial aromatization using common oxidants, into both (*P*) and (*M*) enantiomers of the helically chiral dihydro[5]helicenequinones **3** and **5** in excellent optical yields, by choosing the appropriate aromatizing reagent.

In one of the experiments, the one-pot synthesis of helicene **3a** from **1a** with an excess of (*SS*)-**2**,[14] had not been completed (Scheme 2). Then, we decided to accelerate the final aromatization of the B ring of **4a** to yield **3a** by adding a powerful oxidant agent such as DDQ. After flash chromatography, we isolated helical derivative **3a** almost in racemic form. Initially, we reasoned that the achiral nature of DDQ compared with the chiral sulfinylquinone **2** acting as oxidant, could be the origin of the different behaviour observed.

Intrigued by this result, we decided to repeat the reaction of aromatization with DDQ after the previous isolation of the tetrahydroaromatic derivative **4a** (Scheme 2). The cycloaddition between diene **1a** and one equivalent of enantiopure (*SS*)-**2** in CH_2Cl_2 at −40 °C afforded, after flash chromatography, (*R*)-**4a** showing a stereogenic center {$[\alpha]_D^{20}$ = −736 (*c* 0.012, $CHCl_3$)}, in 61% yield. The aromatization of the B ring of (*R*)-**4a** with DDQ in CH_2Cl_2 (Table 1, entry 2) gave rise to optically active helicenequinone **3a** {$[\alpha]_D^{20}$ = −1530 (*c* 0.003, $CHCl_3$)} in 44% ee†, but surprisingly, showing the opposite (*M*) helicity to that obtained in the presence of an excess of (*SS*)-**2**.

With this new result in hand, we decided to investigate more deeply this aromatization process by using different oxidant reagents. The results obtained are summarized in Table 1.

Firstly, we wanted to know if the enantiomeric purity of (*SS*)-**2** as oxidant could have an essential role in defining the absolute



Scheme 2 Divergent enantioselective synthesis of (*P*) and (*M*) enantiomers of dihydro[5]helicenequinones.

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Table 1 Aromatization with different oxidants of tetrahydroaromatic derivatives **4a**,**b** to dihydro[5]helicenequinones **3a**, **3b** and **5**

Entry	Comp.	Oxid.	*T*/°C	Helicene	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Ee (%)	Yield (%)
1[a]	—	(+)-**2**	−20	(*P*)-**3a**	+2800 (0.003)	84	72
2	(*R*)-**4a**	DDQ	0	(*M*)-**3a**	−1530 (0.003)	44	95
3	(*R*)-**4a**	(±)-**2**	−20	(*P*)-**3a**	+2760 (0.003)	**80**	85
4	(*R*)-**4a**	DBU	−20	(*P*)-**3a**	+1500 (0.005)	42	70
5	(*R*)-**4a**	CAN	rt	(*M*)-**3a**	−3030 (0.003)	**90**	67
6[a]	—	(+)-**2**	−20	(*P*)-**3b**	+2690 (0.003)	> 98	75
7	(*R*)-**4b**	DDQ	rt	(*P*)-**3b**	+2670 (0.003)	**96**	88
8	(*R*)-**4b**	CAN	rt	(*M*)-**5**	−3600 (0.015)	**92**	60

[a] Without isolation of **4a**-**b** (see Scheme 1).

configuration of the final helicene **3a**. We thus performed the aromatization of (*R*)-**4a** in the presence of racemic sulfinylquinone **2**[15] (Table 1, entry 3). In this case, the (*P*) helimer of **3a** was obtained in 80% ee {$[\alpha]_D^{20}$ = +2760 (*c* 0.003, $CHCl_3$)}, indicating that the optical purity of the oxidant seemed to have no influence on the helicity of **3a** and suggesting that the final result could depend on the structure or mechanism of action of the corresponding oxidant. We then used another oxidant such as DBU acting with a different mechanism of reaction (entry 4). The treatment of (*R*)-**4a** with DBU in CH_2Cl_2 at −20 °C afforded again helicene (*P*)-**3a** showing a lower 42% ee {$[\alpha]_D^{20}$ = +1500 (*c* 0.005, $CHCl_3$)}. When the aromatization of (*R*)-**4a** was carried out with cerium ammoniun nitrate (CAN) in CH_3CN–H_2O (Table 1, entry 5), compound (*M*)-**3a** {$[\alpha]_D^{20}$ = −3030 (*c* 0.003, $CHCl_3$)} was obtained with an excellent 90% ee, showing that it was possible to gain access to both enantiomers of helicene **3a** with very good optical purities.

The oxidation procedures were then extended to the synthesis of helicenequinone **3b**, which showed the TBDMS protecting groups on the diphenolic ring. The (*P*) enantiomer of this helicene had been obtained in enantiomerically pure form (entry 6) from diene **1b** and an excess of (*SS*)-**2** (Scheme 1).[14]

The cycloaddition between **1b** and one equivalent of (*SS*)-**2** in CH_2Cl_2 at −40 °C, allowed isolation of tetrahydroaromatic derivative (*R*)-**4b** {$[\alpha]_D^{20}$ = −240 (*c* 0.02, $CHCl_3$)} in 51% yield (Scheme 2). The aromatization of the B ring of compound (*R*)-**4b** by using DDQ as the oxidant agent (Table 1, entry 7) afforded the (*P*) enantiomer of helicene **3b** {$[\alpha]_D^{20}$ = +2670 (*c* 0.003, $CHCl_3$)} with an excellent 96% ee.‡ This stereochemical result, which was the same as that obtained in the cycloaddition with an excess of (*SS*)-**2** (Scheme 1), showed that the chirality of the oxidant is not essential to obtain an excellent optical purity of the final helicene. Under the same conditions (entry 2) derivative (*R*)-**4a** had given rise to the corresponding (*M*) enantiomer indicating that the different substitution on the E ring could have an important role in defining the final helicity.

Finally, the treatment of (*R*)-**4b** with CAN in CH_3CN–H_2O (Table 1, entry 8) did not yield the expected helicenequinone **3b** (Scheme 2) but allowed us to obtain the helicenebisquinone **5** {$[\alpha]_D^{20}$ = −3600 (*c* 0.015, $CHCl_3$)}, with the opposite (*M*) absolute configuration, showing again an excellent 92% ee.§

Although these results are not easy to rationalize, an inspection of molecular models for **4** suggest that conformers resulting from the boat inversion of the B ring[16] must have different stabilities depending on the E ring substitution due to spatial interactions between the OR substituents and the quinone ring. The evolution of each conformer, which would yield a different enantiomer of the helicene, must depend not only on its stability but also on the oxidation mechanism and the nature of the reagent used in the aromatization step.

In summary, we have described experimental conditions for the synthesis of centrally chiral tetrahydroaromatic derivatives (*R*)-**4a**,**b** and to gain access to (*P*) and (*M*) enantiomers of helically chiral dihydro[5]helicenequinones in good to excellent chemical and optical yields simply by variying the common oxidant reagent which makes the final aromatization. We are currently investigating the origin of this interesting behaviour.

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Notes and references

† The ee was evaluated by ^{1}H-NMR analysis using $Pr(hfc)_3$ as chiral lanthanide shift reagent.

‡ The ee was determined by HPLC (Chiralcel OD, hexane–isopropyl alcohol 99:1, 0.2 mL min^{-1}, R_t = 35.9 min (*P*) and 38.9 min (*M*).

§ The ee was evaluated by ^{1}H-NMR analysis using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral solvating agent.[17]

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