Enantiopure Dihydro-[5]-helicenequinones via Diels−Alder Reactions of Vinyl Dihydrophenanthrenes and (*SS*)-2-(*p*-Tolylsulfinyl)-1,4-benzoquinone

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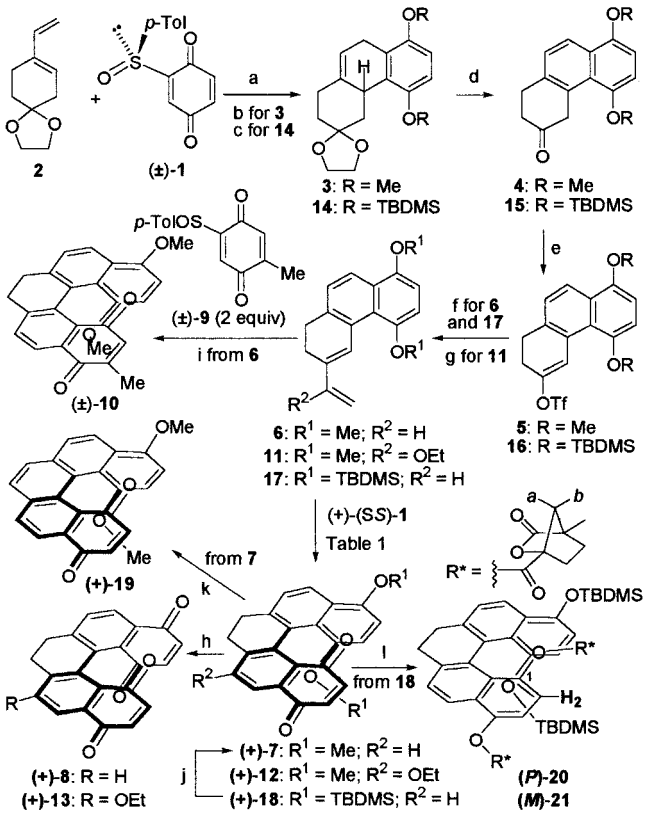
The unique structure of helicenes[1] makes them excellent candidates as new materials and chiral auxiliaries in asymmetric synthesis.[2] The potential use of such species depends on the facility of obtaining them in enantiomerically pure form. Therefore, several new methodologies have emerged during the past decade[3] to provide useful alternatives to the classical synthesis of helicenes based on the UV light-mediated electrocyclization of stilbene-type precursors.[4] The most efficient syntheses of nonracemic helicenes reported up to date are based on resolutions of racemic derivatives.[2b,3a,b,g,5] Although several enantio- or diastereoselective approaches have been described, they suffer from moderate asymmetric inductions.[3c,e,f,h,6] Thus, versatile enantioselective methods that proceed with high optical yields will allow the extension of the range of application of functionalized derivatives. Mild conditions are also required since racemization barriers of helicenes are low[7] and their configurational integrity is essential not only to achieve efficient enantioselective syntheses but also for further applications.

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[8] we have recently developed the first asymmetric approach to [5]-helicenebisquinones[9] based on the domino cycloaddition/sulfoxide elimination/oxidation process between enantiopure (+)-(S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone and vinyl benzenes and naphthalenes. This method allowed us to obtain both (*M*) and (*P*) enantiomers of fully aromatic helical structures. Nevertheless, due to the low reactivity of the vinyl arenes as dienes, cycloadditions took place only at reflux of high boiling solvents or under high pressure conditions being both the chemical and optical yields only moderate. In this communication, we report that the use of more reactive vinyl dihydrophenanthrenes allows the cycloaddition with enantiopure (+)-(S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**1**) to proceed under very mild conditions leading to new helical dihydroquinones with good chemical yields and excellent enantiomeric purities. The presence of a central hydroaromatic ring in the resulting helicenes increases the racemization barrier in comparison with that of the fully aromatic derivatives.[10] The synthetic sequence outlined in Scheme 1 shows the additional advantage of introducing the chirality in the last steps, thus avoiding possible racemization processes.

The cycloaddition between racemic quinone **1**[11] and diene **2**[12] afforded, after spontaneous elimination of the sulfoxide in the

Scheme 1[a]



[a] Conditions: (a) CH_2Cl_2, room temperature, 6 h, 73%; (b) i. $Na_2S_2O_4$, ii. Me_2SO_4, K_2CO_3/acetone, reflux, 5 h, 84%; (c) i. $Na_2S_2O_4$, ii. TBDMSCl, imidazole, DMF, room temperature, overnight, 81%; (d) i. DDQ, CH_2Cl_2, room temperature, 30 min, ii. $CeCl_3 \cdot 7H_2O$, NaI, CH_3CN, reflux, 3 h, 85% for **4** and 95% for **15**; (e) Tf_2NPh, KHMDS, THF, −78 °C, 30 min, 95% for **5** and 72% for **16**; (f) $CH_2{=}CHSnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux, 1−5 h, 82% for **6** and 74% for **17**; (g) $CH_2{=}C(OEt)$-$SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux, 2 h, 67%; (h) CAN, $CH_2Cl_2/CH_3CN/H_2O$, room temperature, 2 h, 82% from **7**, 90% from **12**, 71% from **18**; (i) i. CH_2Cl_2, −20 °C, 7 d, ii. DDQ, room temperature, 30 min, 67%; (j) CsF, MeI, DMF, room temperature, 24 h, 70%; (k) DDQ, benzene, reflux, 4 d, 71%; (l) Zn, (−)-camphanoyl chloride, DMAP, Et_3N, CH_2Cl_2, reflux, 1 h, 48% for (*P*)-**20** and 45% for (*M*)-**21** from (±)-**18**, 92% for (*P*)-**20** from (+)-(*P*)-**18**.

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Table 1. Diels−Alder Reactions between 2 Equiv of (+)-**1** and Dienes **6**, **11**, and **17** in CH_2Cl_2

entry	diene	*T* (°C)	*t* (d)	product	yield (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	ee (%)
1	**6**	20	0.75	**7**	72	+2260 (0.002)	72
2	**6**	−20	2	**7**	53	+2480 (0.004)	76
3	**6**	−40	12	**7**	72	+2800 (0.003)	84
4	**11**	−60	6	**12**	62	+2980 (0.003)	92
5	**17**	20	1	**18**	50	+2330 (0.004)	88
6	**17**	−40	17	**18**	75	+2690 (0.003)	>98

initially formed cycloadduct, the corresponding hexahydrophenantrenequinone, which was reduced and methylated to yield derivative **3** (Scheme 1). Aromatization of the central ring of **3** with DDQ followed by acetal deprotection with $CeCl_3$/NaI/CH_3-CN[13] gave ketone **4**. Treatment of **4** with Tf_2NPh/KHMDS afforded enol triflate **5** which was submitted to Stille coupling with tributylvinylstannane to yield compound **6**.

The cycloaddition of diene **6** and 2 equiv[14] of enantiopure quinone (+)-**1**[11] at room temperature (Table 1, entry 1) gave optically active helical quinone (+)-**7**, which showed 72% ee.[15] This optical purity could be enhanced to 76% and 84% ee working at −20 (entry 2) and −40 °C (entry 3), respectively.[16] CAN oxidation of the dimethoxy-substituted aromatic ring of (+)-**7** allowed the synthesis of helical bisquinone (+)-**8** {$[\alpha]_D^{20}$ +2670 (*c* 0.011, $CHCl_3$), 72% ee}. With the aim of knowing the regiochemistry of the initial cycloaddition, we performed the reaction between diene **6** and racemic 5-methyl-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**9**)[17] at −20 °C. The initially formed cycloaddition/sulfoxide elimination product was further aromatizated with DDQ yielding 3-methyl-substituted helical quinone **10** as the only regioisomer, showing that the cycloaddition had occurred with complete ortho regioselectivity. The correct structure of **10** was established by X-ray diffraction.

The optical purity of the final helical quinone could be improved by using the more reactive diene **11**, bearing an oxygenated substituent at the vinylic moiety, which was prepared from enol triflate **5** by Stille coupling with 1-ethoxyvinyltrybutylstannane (Scheme 1). The cycloaddition of **11** with (+)-**1** took place at −60 °C (Table 1, entry 4) giving helical quinone (+)-**12** with an excellent 92% ee.[15] CAN oxidation of (+)-**12** allowed the synthesis of helical bisquinone (+)-**13** {$[\alpha]_D^{20}$ +3370 (*c* 0.0065, $CHCl_3$), 92% ee}.

In accord with the model already proposed to explain the stereoselectivity of cycloadditions between vinyl arenes and (+)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone,[9] we reasoned that the incorporation of a bulkier substituent such as TBDMS into the diphenolic system of the diene partner could also improve the enantioselectivity of the process. Thus, we prepared diene **17** (Scheme 1) from compound **2** through the corresponding intermediates **14**−**16**, following a synthetic pathway similar to that used for diene **6**. Indeed, the reaction of **17** and (+)-**1** at room temperature (Table 1, entry 5) afforded helical quinone (+)-**18** with 88% ee,[18] indicating a significant increase in the selectivity of the cycloaddition if compared with the reaction of diene **6** under

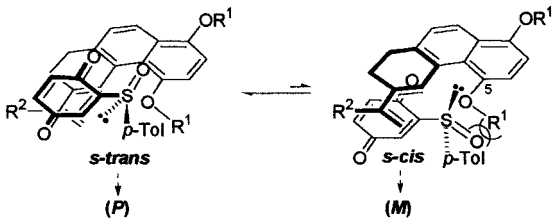

Figure 1. Endo approaches of vinyl dihydrophenanthrenes on the s-trans and s-cis conformations of sulfinylquinone (+)−(*SS*)-**1**.

the same conditions (entry 1, 72% ee). Helicene (+)-**18** could be obtained in enantiomerically pure form[18] through the cycloaddition of **17** and (+)-**1** at −40 °C (entry 6). CAN oxidation of (+)-**18** allowed the synthesis of helical bisquinone (+)-**8** {$[\alpha]_D^{20}$ +3700 (*c* 0.015, $CHCl_3$), ee >98%}. Finally, transformation of enantiopure helicene (+)-**18** into (+)-**7** {$[\alpha]_D^{20}$ +3200 (*c* 0.004, $CHCl_3$), >98% ee} with CsF and MeI, followed by oxidation with DDQ, afforded fully aromatized helicene quinone (+)-**19** {$[\alpha]_D^{20}$ +1430 (*c* 0.009, $CHCl_3$), ee >98%}[15] in 50% yield for the two steps.

The (*P*) absolute configuration of all helical quinones was initially assigned considering the preferred formation of the Diels−Alder adduct resulting from the endo approach of dienes **6**, **11**, and **17** to the lower face of sulfinylquinone (+)-**1** adopting the s-trans conformation (Figure 1). This should be the most favored situation from the steric point of view since, when the dienophile reacts through the s-cis rotamer, usually the most stable in vinyl sulfoxides,[19] the approach of the diene from the less encumbered upper face gives rise to a transition state where a severe unfavorable interaction between the OR^1 group at C-5 of dienes and the sulfinylic oxygen of (+)-**1** appears.

This configurational assignment was confirmed by applying the methodology described by Katz[5d] based on the different O=C−C−O conformations of (*M*)- and (*P*)-helicenol camphanates which bring about a different polarity and NMR behavior of each diastereoisomer. Thus, we prepared di-(−)-camphanates (*P*)-**20** and (*M*)-**21** from racemic **18** and diastereoisomer (*P*)-**20** from enantiopure (+)-**18** (Scheme 1). The lower R_f (0.42) shown by diastereoisomer (*P*)-**20** on silica gel (eluent hexane/EtOAc 2:1) with respect to that of (*M*)-**21** (R_f = 0.49), as well as the differentiated NOESY enhancements between H_2 and methyl groups *a* and *b* of the inside camphanates (OR* at C-1, Scheme 1) in (*M*) and (*P*) isomers, is consistent with the data reported[5d] for determining the absolute configuration of these derivatives.

In summary, the one-pot domino cycloaddition/sulfoxide elimination/oxidation process starting from enantiopure (*SS*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone and vinyl dihydrophenanthrenes is a short and versatile strategy for the enantioselective synthesis of new dihydro-[5]-helicenequinones under very mild conditions. We are now extending this methodology to the enantioselective preparation of higher and smaller analogues of [5]-helicenes.

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Supporting Information Available: Experimental, spectral, and crystallographic information (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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