Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2965–2969

TETRAHEDRON: *ASYMMETRY*

Enantioselective Diels–Alder reactions of chiral racemic acyclic dienes with (S*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone

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Received 10 July 1998; accepted 10 August 1998

Abstract

Enantiopure sulfinylnaphthoquinone (+)-**1** reacted with racemic acyclic dienes **2a**–**f** bearing a stereogenic allylic center, through a tandem cycloaddition/pyrolytic sulfenic acid elimination, to afford enantio-enriched compounds **4a**–**f** and **5a**–**f** with good like:unlike selectivities (ca. 75:25) and good enantiomeric excesses (68–82%), arising from the partial kinetic resolution of the racemic dienes. © 1998 Elsevier Science Ltd. All rights reserved.

Among the stereochemical features of Diels–Alder reactions, π-facial diastereoselectivity has been the subject of increasing attention in order to understand the factors responsible for the excellent results observed and further develop stereocontrolled routes for the synthesis of natural products. Both theoretical and experimental studies have focused on chiral dienophiles and/or chiral dienes[1–4] bearing a single stereogenic center at the allylic position. Distinct works, concerned with three sets of experimental results for cyclic,[1a,2] semicyclic[2b,3] and acyclic[1a,2b,4] dienes, showed that good to excellent π-facial diastereoselectivities could be achieved by the proper choice of allylic substituent and by the introduction of an adequate *cis*-substituent at C-2 on the diene framework.[4g] In spite of such good results, enantioselective synthetic applications of these kind of dienes are limited due to the difficulties encountered in obtaining homochiral derivatives.[4f]

In connection with our work devoted to the use of enantiopure sulfoxides in asymmetric synthesis,[5] we have shown the ability of the sulfinyl group situated on a quinonic framework to promote a double induction in a Diels–Alder cycloaddition, leading to the efficient resolution of some chiral racemic semicyclic dienes containing a stereogenic allylic carbon.[6] The tandem Diels–Alder reaction/pyrolytic sulfenic acid elimination, in addition to the resolution of semicyclic dienes occurring with optically pure sulfinyl quinones, is now established as a general one-pot strategy to enantiomerically enriched polycyclic hydroquinones.

In order to extend these excellent results, we decided to investigate if such a double asymmetric induction process could also take place with acyclic dienes bearing a stereogenic allylic substituent. In

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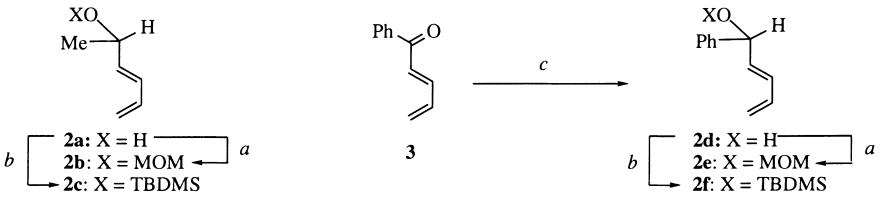
PII: S0957-4166(98)00323-1

this paper we report the study of Diels–Alder reactions of enantiomerically pure (S*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **1**[7] with several chiral racemic open-chain dienes **2a**–**f**, showing a carbinol and a different type of substitution at the allylic position.

Hexadiene derivatives **2b**[8] and **2c**[4a] were prepared from known dienol **2a**[9] following conventional procedures in 63% and 71% yields, respectively (Scheme 1). The synthesis of 5-phenyl substituted pentadienes **2d**–**f** was carried out starting from phenylketone **3**.[10] Luche reduction with $NaBH_4/CeCl_3$[11] allowed the carbinol **2d**[12] to be obtained, whose treatment with MOMCl–DIPEA and TBDMSCl–imidazole afforded dienes **2e**[8] and **2f**[8] in 66% and 67% yields, respectively (Scheme 1).



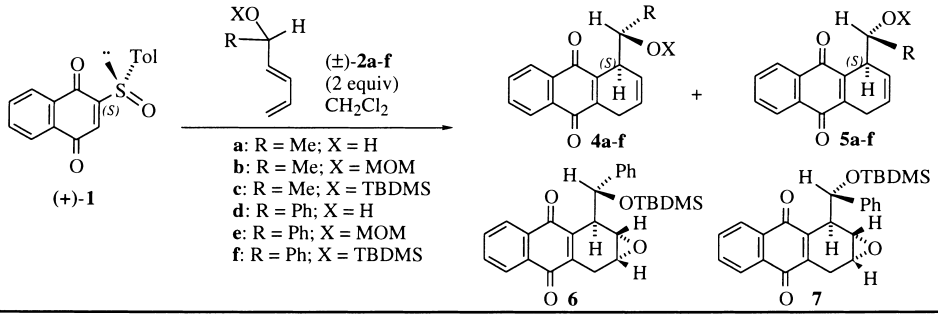
[a]MOMCl, DIPEA, CH_2Cl_2, rt, 24h. [b]TBDMSCl, imidazole, DMF, rt, 24h. [c]$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 1h, 91%.

Scheme 1.

Diels–Alder cycloadditions of (+)-**1** and **2** were carried out in CH_2Cl_2 and the results are collected in Table 1. As can be seen, methylsubstituted dienes **2a**–**c** and phenylcarbinol **2d** reacted at rt (48–72 h) whereas phenyl-substituted dienes **2e**,**f** only proceeded under reflux of the solvent. In all cases, after pyrolytic elimination of the sulfinyl group in the initially formed cycloadducts, we obtained a diastereoisomeric mixture of compounds **4** and **5**.

Cycloaddition between (+)-**1** and dienol **2a** afforded a non separable 70:30 mixture of **4a**[8,13] and **5a**[8,13] in enantio-enriched 31% yield. The ee of both adducts was determined after transformation into the separable mixture of OMOM ethers **4b** and **5b** [$CH_2(OMe)_2$, P_2O_5, $CHCl_3$, rt, 1 h, 22%],[14] by using Pr(hfc)$_3$ (70% for **4a**) and Eu(hfc)$_3$ (74% for **5a**) as chiral lanthanide shift reagents.[15] These enantio-purities were the result of the partial kinetic resolution of the racemic diene partner. In the

Table 1
Diels–Alder reactions of enantiopure sulfinylquinone (+)-**1** and chiral racemic dienes **2a**–**f**



Entry	Diene	T (°C)	t (h)	Products Ratio	Yield (%)	Enantiomeric Ratios
1	**2a**	20	48	**4a** (70) + **5a** (30)	31	**4a** (85:15) + **5a** (87:13)
2	**2b**	20	72	**4b** (75) + **5b** (25)	36	**4b** (91: 9) + **5b** (90:10)
3	**2c**	20	72	**4c** (75) + **5c** (25)	45	**4c** (84:16) + **5c** (86:14)
4	**2d**	20	48	**4d** (75) + **5d** (25)	83	**4d** (87:13) + **5d** (84:16)
5	**2e**	40	24	**4e** (75) + **5e** (25)	37	**4e** (84:16) + **5e** (84:16)
6	**2f**	40	24	**4f** (76) + **5f** (24)	51	**4f** (84:16) + **5f** (86:14)

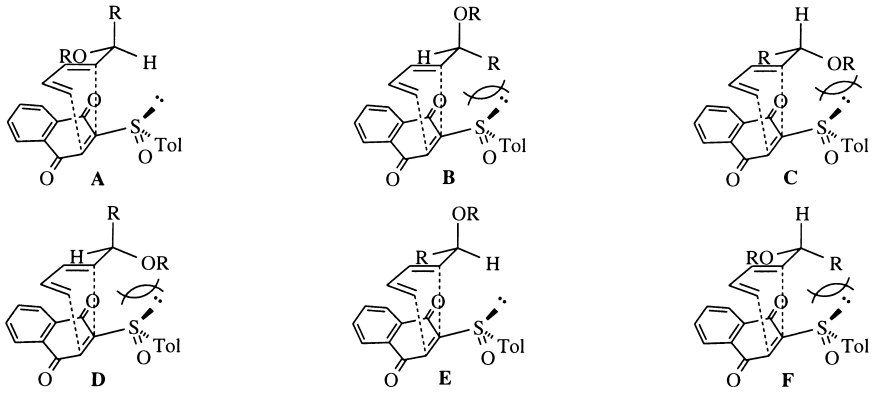


Fig. 1.

same way, reaction of (+)-**1** and diene **2b** yielded a 75:25 mixture of compounds (+)-**4b**[8,13] (ee=82%) and (+)-**5b**[8,13] (ee=80%). In this case, we could recover unreacted diene (+)-**2b** in optically active form {$[\alpha]_D^{20}$=+19.3 (*c* 2.4, $CHCl_3$)}. Finally, cycloaddition of (+)-**1** with diene **2c**, gave a non separable 75:25 mixture of compounds **4c**[8,13] and **5c**[8,13] in 45% yield. The enantio-purity of these derivatives could not be determined at this stage and thus, we transformed the mixture of **4c** and **5c** into the corresponding mixture of OMOM derivatives **4b** and **5b** (i. HF, CH_3CN, rt, 1 h; ii. $CH_2(OMe)_2$, P_2O_5, $CHCl_3$, rt, 1 h, 24%). After chromatographic separation, we could establish a 68% of ee for **4c** and 72% for **5c**.

Diels–Alder reactions of (+)-**1** with phenyl-substituted dienes **2d–f** followed a similar pattern. Cycloaddition with dienol **2d** afforded a 75:25 mixture of **4d**[8,13] and **5d**[8,13] that could be separated by flash chromatography. The ee of both adducts was determined after transformation into the OMOM ethers **4e** and **5e** by using $Pr(hfc)_3$ (74% for **4d**) and $Eu(hfc)_3$ (66% for **5d**) as chiral lanthanide shift reagents. Reaction of (+)-**1** and diene **2e** yielded a nonseparable 75:25 mixture of compounds **4e**[8,13] (ee=68%) and **5e**[8,13] (ee=68%). Finally, cycloaddition of (+)-**1** with diene **2f**, gave a 76:24 mixture of compounds **4f**[8,13] and **5f**[8,13] in 51%. The enantio-purity of these derivatives could only be determined after transformation of the mixture of **4f** and **5f** into the epoxides **6**[8,13] and **7**[8,13] (*m*-CPBA, CH_2Cl_2, 68%). We could determine an ee of 68% for **4f** and 72% for **5f** by using $Pr(hfc)_3$ as a chiral lanthanide shift reagent.

In accordance with our previous results from other cycloadditions with similar dienophiles,[5,6] the major evolution of sulfinylnaphthoquinone **1** through the less hindered upper face of the *S-cis* conformation represented in Fig. 1, accounts for the (*S*) configuration at C-1 of the resulting 1,4-dihydroanthraquinones **4** and **5** (Table 1), assuming a complete *endo* addition.

Compounds **4**, resulting from the unlike[16] (R=Me) and like[16] approaches (R=Ph), are the major products in all cycloadditions. To account for this preferred evolution, we must consider the conformational arguments already invoked for this kind of reaction,[4a,h] as well as the interactions emerging in the transition states: cycloadditions must take place through conformers which are staggered with respect to forming bonds.[17] As represented in Fig. 1, three transition states **A**, **B** and **C**, giving rise to diastereoisomers **4**, result from an unlike approach (R=Me).[18] The most favored situation corresponds to **A** where the largest R group of the allylic center of the diene is oriented *anti*, being the smallest H on the same face of the attacking sulfinyl dienophile. In approaches **B** and **C**, the R and OR groups are situated at the same side of the approaching dienophile giving rise to unfavourable steric and/or electrostatic interactions. Thus, approach **A** would explain the favored reaction of the (*R*) enantiomer of the diene (R=Me) through the matched pair and the observed resolution to give the major isomer **4**.[19]

A similar analysis for like approaches (R=Me) **D–F** yielding derivatives **5**, reveals that **D** and **F** show similar destabilizing interactions, (OR in **D** and R in **F** are situated on the same side of the approaching

dienophile). For **E** approach, where the smallest H is on the bottom side of the diene, the bulky R group is in a *gauche* disposition with respect to the C_2–C_3 double bond and also in the face of the approaching dienophile. This could be the origin of the formation of minor compounds **5**. The matched pair in this like approach arose from the evolution of (*S*)-**2a**–**c** or (*R*)-**2d**–**f** dienes. According to previous results, π-facial diastereoselectivity of cycloadditions with sulfinylquinones strongly increases with low temperatures. Thus, the moderate reactivity of dienes **2**, which reacted at rt or 40°C could justify the formation of a minor amount (9–16%) of the corresponding enantiomers of **4** and **5** (see Table 1).

In summary, the enantioselective reaction of acyclic dienes bearing an allylic stereogenic center with (*S*)-2-*p*-tolylsulfinyl-1,4-naphthoquinone is reported as a useful synthetic approach to chiral 1,4-dihydro-9,10-anthraquinone derivatives which takes advantage of the kinetic resolution of racemic dienes observed in these processes. The extension of this methodology to the synthesis of other quinones of interest is under way.

Acknowledgements

We thank Dirección General de Investigación Científica y Técnica (Grant PB95-0174) for financial support. CDV thanks FAPESP-Fundação de Amparo à Pesquisa do Estado de São Paulo for a post-doctoral fellowship.

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18. The discussion is focused on methyl substituted dienes **2a**–**c**. Although the stereochemical descriptor changes from R=Me to R=Ph, the relative stability of the transition states is similar in both cases.
19. For phenyl substituted dienes **2d**–**f**, the (*S*) enantiomer reacts faster.