First Diels–Alder Reactions of Enantiomerically Pure 1-*p*-Tolylsulfinyl Dienes: Straightforward Access to Cyclohexenols through Tandem Cycloaddition/[2,3]-Sigmatropic Rearrangement

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The asymmetric Diels–Alder reactions of (*R*)-1-(*p*-tolylsulfinyl)-1,3-butadienes **3a–c** with *N*-methylmaleimide (NMM) have been explored. The cycloadditions are stereospecific: only one *endo* adduct is formed, the π-facial diastereoselectivity being controlled by the sulfoxide both in thermal and catalytic conditions. The *in situ* cycloaddition/sulfoxide sulfenate [2,3]-sigmatropic rearrangement starting from chiral **3a–c** in the presence of an excess of NMM, which acts as thiophilic agent, provides a convenient one-step access to enantiomerically pure and *all-cis* functionalized cyclohexenols (−)-**5a–c**.

The utility of Diels–Alder reactions in asymmetric synthesis is increasingly important. The enantioselective version of these cycloadditions has been achieved by using optically active dienophiles,[1] dienes,[1d,2] and Lewis acid catalysts.[1d,3] Comparatively, reactions of dienes have been much less extensively studied. The use of enantiomerically pure dienes has been limited to systems containing ester[4] or amide groups[5] and a carbohydrate moiety[6] as substituents on the C_1 position. The enantioselectivities reported for these systems are not very high. With respect to C_2-substituted dienes, low diastereoselectivities have been also reported[7] except when 2-amino-1,3-butadienes[8] derived from (*S*)-2-(methoxymethyl)pyrrolidine were used. During the preparation of this manuscript, a paper related to the cycloaddition of an enantiomerically pure 2-substituted sulfinyl diene has appeared.[9] The results published therein indicated that it was possible to achieve high diastereoselection with these dienes under some experimental conditions.

In connection with our studies directed to the determination of the role of the sulfinyl group in the control of the π-facial diastereoselectivity of [4 + 2] cycloadditions, mainly focused on sulfinyl quinones[10] and sulfinyl maleates,[11] we thought to study the behavior of enantiomerically pure 1-sulfinyl substituted dienes. The few examples so far reported dealt with racemic systems, but the high *endo*[12–15] and face diastereoselectivities[14–16] achieved in their cycloadditions made them attractive candidates for the enantioselective Diels–Alder reactions.[17]

With the aim of extending these good stereochemical results to the enantiopure sulfinyl diene family, we undertook a study of Diels–Alder reactions with (*R*)-1-(*p*-tolylsulfinyl)-4-substituted-1,3-butadienes **3a–c**[18] (Scheme 1). These were available in two steps starting from commercially available α,β-unsaturated aldehydes through a method previously described.[19] We report herein the results of this study which corroborate the usefulness of the sulfoxide in attaining highly diastereoselective Diels–Alder cycloadditions. Furthermore, the adducts were transformed to enantiomerically pure functionalized cyclohexenols.

Compounds **3a,b** (Scheme 1) were synthesized starting from the corresponding α,β-unsaturated aldehydes **1a,b**.[19a] The synthesis of (*R*)-1-ethoxy-2-methyl-4-(*p*-tolylsulfinyl)-1,3-butadiene (**3c**) was achieved from 3-ethoxy-2-methyl-

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(16) Naperstkow, A. M.; Macaulay, J. B.; Newlands, M. J.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 5077. In order to facilitate the reading, 2,5-dimethyl thiophene *S*-oxide studied in this reference has been considered as a 1,4-dialkyl substituted 1-sulfinyl diene.

(17) To our knowledge, only two examples concerning the use of enantiomerically pure sulfinyl dienic systems have been published to date. One of them corresponds to ref 9 and the other is related to use of α'-sulfinyl α,β-unsaturated ketone as a chiral heterodiene: Hiroi, K.; Umemura, H.; Fujisawa, A. *Tetrahedron Lett.* **1992**, *33*, 7161.

(18) In order to facilitate the reading of the paper we consider dienes **3** as 1-sulfinyl-4-subtituted although in the case of **3c** the IUPAC name is (*R*)-1-ethoxy-2-methyl-4-(*p*-tolylsulfinyl)-1,3-butadiene.

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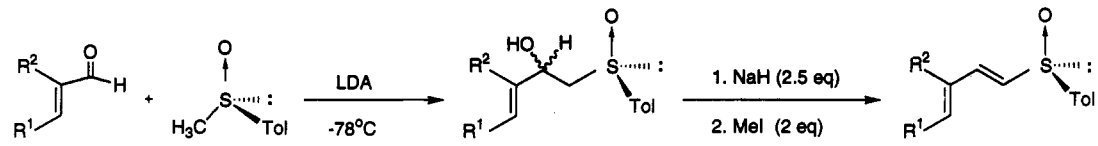
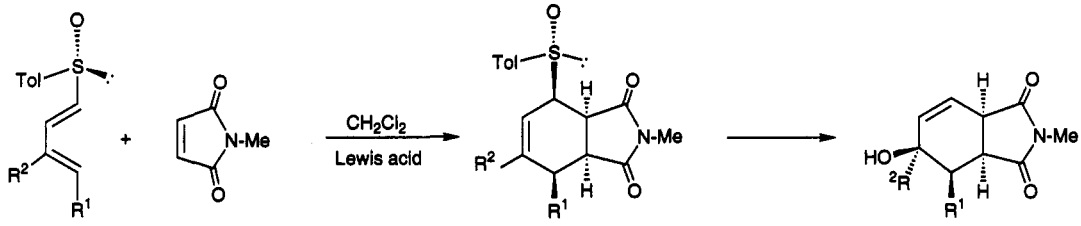
Scheme 1



1 2 3

Aldehyde	R^1	R^2	Diene	Overall yield (%)
1a	CH_3	H	3a	64
1b	Ph	H	3b	67
1c	OEt	CH_3	3c	64

Scheme 2



3a-c 4 5

a: R^1=CH_3 ; R^2=H
b: R^1=Ph ; R^2=H
c: R^1=OEt ; R^2=CH_3

2-propenal (1c) with a 64% overall yield. Thus, addition of the anion obtained from treatment of (*R*)-methyl *p*-tolyl sulfoxide[20] with LDA to aldehyde 1c afforded a mixture of diastereomeric carbinols 2c. Subsequent elimination in the presence of NaH/MeI produced the (*E,E*)-diene 3c.

The reactivity of 1-sulfinyl substituted dienes was known to be highly dependent on the substitution pattern. Thus, whereas 3-sulfinyl substituted 2-pyrone underwent mild inverse electron demand Diels–Alder reaction with 1,1-dimethoxyethylene,[21] 1-(phenylsulfinyl)-1,3-butadiene[12] was shown to be only moderately electron-deficient, reacting with an enamine. The presence of electron-donating substituents in the form of a 4-acylamine,[13] 2-alkyl(or alkoxy),[14] 4-alkyl(or aryl)-2-alkyl(or alkoxy),[14,15] or 1,4-dialkyl group[16] activated the 1-sulfinyl dienic systems to cycloaddition with some electron-deficient dienophiles. These results showed that the behavior of the sulfinyl dienes seemed to be mainly ruled by the electronics of substituents other than the sulfoxide.

In order to explore the reactivity profile of the 1-(*p*-tolylsulfinyl)-1,3-butadiene system with only one additional substituent on C_4, we carried out the reactions of dienes 3a and 3b with both electron-rich and electron-poor dienophiles. The electron-rich dienophiles ethyl vinyl ether and 3,4-dihydro-2*H*-pyran yielded no cycloadducts either thermally or under Lewis acid (BF_3·OEt_2, $ZnBr_2$, $SnCl_4$, Eu(fod)$_3$, Et_2ClAl) catalyzed conditions. However as expected from the aforementioned reactivity pattern, dienes 3a–c did react with the electron-deficient dienophile *N*-methylmaleimide (NMM).[22] The results of reactions of dienes 3a–c with this dienophile are collected in Scheme 2 and Table 1.

As can be deduced from the reaction times, the reactivity of the sulfinyl diene increased in the presence of Lewis acids. The best results for dienes 3a and 3b were achieved with $SnCl_4$ (entries 5 and 9, Table 1). Diene 3c with a 4-alkoxy substituent[18] decomposed in the presence of either $ZnBr_2$ or $SnCl_4$. Cycloadduct could be obtained under thermal conditions (entries 10 and 11) or by using Eu(fod)$_3$ as catalyst (entry 12). The instability of 4c makes difficult its isolation, and consequently it is only possible to obtain 4c in a 28% yield by preparative layer chromatography (PLC). Although the reactivity of diene 3c with an electron-donating OEt substituent on C_4 is higher than that of 3a and 3b under thermal conditions (compare reaction times, entries 1, 6, and 10), we would expect a much higher difference.[23] In the case of 3c the electron-

Table 1. Diels–Alder Reactions of 1-Sulfinyl Substituted Dienes with *N*-Methylmaleimide

entry	diene	NMM (equiv)	Lewis acid (equiv)	*T* (°C)	time (d)	yield (%)	4:5
1	3a	4		30	34	66	56:44
2	3a	10		30	20	*a*	60:40
3	3a	10		30	50[b]	96	32:68
4	3a	3	$ZnBr_2$ (3)	rt	6	68	100:0
5	3a	3	$SnCl_4$ (6)	rt	6	84	100:0
6	3b	4		30	48	65	0:100
7	3b	10		30	40	72	0:100
8	3b	3	$ZnBr_2$ (3)	rt	18	65	100:0
9	3b	3	$SnCl_4$ (6)	rt	12	65	100:0
10	3c	4		rt	20	*a,c*	60:40
11	3c	5		rt	27[b]	66	0:100
12	3c	3	Eu(fod)$_3$ (1)	rt	7	*c*	50:50

[a] Reaction carried out in the NMR sample tube. [b] Diels–Alder cycloaddition was completed after 20 days but longer times were required to complete the adduct's transformation. [c] Yield could not be determined due to decomposition of 4c. See Experimental Section.

(20) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.
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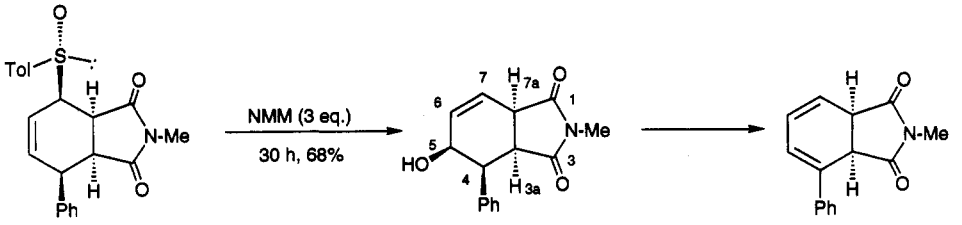
(22) With the diene 3a, neither reaction with methyl propiolate nor ethyl methacrylate was observed. When *p*-benzoquinone was used as dienophile, a very slow reaction took place, but only some traces of aromatized Diels–Alder adduct could be detected in the ^1H NMR spectrum of the crude reaction mixture after 1 month.

Scheme 3



4b **5b** **6**

donating substituent seemed not to exert the expected strong activating effect on the diene. This reactivity pattern was not without precedent. A net deactivating effect of an alkoxy substituent on a sulfinyl diene was already observed by Overman et al.[15] when the alkoxy group is on C_2 and was explained by assuming that the extended conjugation between the sulfoxide and the OR group in the diene is lost in the adduct, thus slowing down the cycloaddition. This could also be the reason for the relatively low reactivity of **3c**.

As represented in Scheme 2 *endo* adduct **4** was formed in a highly π-diastereofacial selective manner. According to previously reported results on related dienes,[13,15] this high stereoselectivity seems to be dependent on both the nature of diene and dienophile.[24] Depending on reaction conditions, the initially formed adducts **4** evolved into enantiomerically pure highly functionalized cyclohexenol derivatives **5** through the stereospecific sulfoxide–sulfenate [2,3]-sigmatropic rearrangement. These products are not accessible by direct cycloaddition. The ratio of compounds **4** and **5** was determined from the crude reaction mixtures by integration of the signals corresponding to the vinylic protons which were well separated.

When (*R*)-1-(*p*-tolylsulfinyl)-1,3-pentadiene (**3a**) was used, cyclohexenol **5a** resulting from the [2,3]-sigmatropic rearrangement of the initially formed allylic sulfoxide[12,25] **4a** was detected as a single diastereomer in the crude reaction mixture (entry 1). The ratio **4a:5a** was dependent on the amount of dienophile and on the reaction time. The higher the excess of NMM and the reaction time, the higher the ratio of cyclohexenol **5a** (entries 1–3). These results suggested that the NMM was acting as a thiophilic agent,[26] trapping the intermediate sulfenate ester resulting from the allylic sulfoxide **4a** in the [2,3]-sigmatropic rearrangement. The sulfenate ester was not stable enough to be isolated. We further demonstrate that the consecutive cycloaddition and [2,3]-sigmatropic rearrangement could be achieved in one step by carrying out the cycloaddition with an excess of NMM and extending the reaction time to allow for the further rearrangement of the initially formed adduct. Thus, in the cases of reaction with dienes **3b** and **3c** (entries 7 and 11), carbinols **5b** and **5c** could be isolated as pure compounds in 72% and 66% yields, respectively. Diene **3b** evolved into **5b** when 4 equiv of NMM was used (entry 6), but the yield was slightly lower and the reaction time longer than when 10 equiv of NMM was present. In the presence of this high excess of NMM (10 equiv), diene **3a** (entry 3) gave a 32:68 mixture of **4a** and **5a** from which **5a** was isolated after flash chromatography in 66% yield. The complementarity of cycloaddition and [2,3]-sigmatropic rearrangement has previously been pointed out by Evans.[12] Our results show that it is possible to obtain good yields of the cyclohexenol derivatives **5** in one step from dienes **3** without isolation of the intermediate Diels–Alder adducts **4**.

The transformation of adduct **4b** was independently achieved when a dichloromethane solution with 3 equiv of NMM was heated under reflux (Scheme 3). Under these conditions, only some traces of the corresponding carbinol **5b** could be detected by NMR in the crude reaction mixture and compound **6**, resulting from the elimination of H_2O on **5b**, was the only product isolated (68% yield). Presumably, the formation of **6** was favored by the heating. When treated with thiophilic agents such as $Na_2S{\cdot}9H_2O$,[12] $P(MeO)_3$,[25a] or piperidine,[25a] compounds **4a** and **4b** were recovered unaltered or evolved into a complex reaction mixture.

These results allowed us to choose the reaction conditions in order to select the reaction products. Long reaction times and an excess of NMM favored the formation of alcohols **5**, whereas the presence of Lewis acids allowed the clean isolation of Diels–Alder adducts **4**.

The evidence that Diels–Alder adducts **4** resulted from *endo*-cycloaddition followed from their ^1H NMR parameters (Table 2), mainly chemical shifts and multiplicity of H_7 (δ 3.44–3.50, m) and H_{7a} (δ 3.77–3.96, dd, 8.0–9.0 Hz and 5.0–5.4 Hz), which are quite similar to those of the racemic compounds already described.[14,15] Furthermore, the large coupling constant observed between the bridgehead hydrogens ($J_{3a-7a} \approx$ 8.0–9.0 Hz) suggested the "extended" boat conformation[14,27] for the cyclohexene ring represented in the Figure 1. The low δ values shown by H_6 (5.50, 5.62, and 5.13) when compared with the corresponding absorptions in other similar cyclohexene systems (δ 6.2–5.9)[27] may be due to the rigid disposition of the sulfinyl group in the Diels–Alder adducts shown in Figure 1, where the aromatic tolyl ring exerts a net shielding effect. Moreover H_{7a} is always deshielded (δ 3.77–3.96) with respect to H_{3a} (δ 3.18–3.45). This effect, already reported in the literature,[28] suggests that the sulfinyl oxygen adopts the stereochemistry shown (1,3-parallel

(23) In the work described in ref 9, the reaction of a 1-methoxy-3-(alkylsulfinyl)-1,3-butadiene with methyl acrylate in similar conditions took place in 16 h.

(24) Reactions between 5-alkenyl-1,3-oxathiole 3-oxides, 3-vinyl-4,5-dihydrothiophene *S*-oxide,[14,15] or 2,5-dimethylthiophene *S*-oxide[16] and *N*-phenylmaleimide afforded only an *endo* adduct, whereas the cycloaddition between 1-(acylamino)-4-sulfinyl-1,3-dienes and methyl vinyl ketone[13] gave mixtures of all the possibles *endo* and *exo* diastereomers.

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(28) (a) Foster, A. B.; Inch, T. D.; Weber, J. M. *J. Chem. Soc., Chem. Commum.* **1968**, 1086. (b) Carreño M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.

Table 2. ^{1}H NMR Data for Compounds 4a–c and 5a–c

	δ (ppm), multiplicity, J (in Hz)					
proton	4a	4b	4c	5a	5b	5c
H_{3a}	3.18, t, 8.2	3.43, m	3.45, m	3.1, dd, 8.4, 6.7	3.6, dd, 9.1, 7.5	3.27, bs
H_4	2.36, m	3.55, m	3.98, bd, 7.5	2.35, m	3.7, t, 6.2	3.78, m
R^2	5.70, ddd, 9.3, 3.1, 3.1	6.14, ddd, 10.0, 3.6, 2.5	1.73, s	4.3, m	4.7, m	1.25, s
H_6	5.50, ddd, 9.3, 3.3, 3.3	5.62, ddd, 10.0, 3.5, 2.7	5.13, m	6.0, m	6.2, m	6.0, d, 10.0
H_7	3.44, m	3.5, m	3.50, m	6.0, m	6.2, m	5.76, d, 10.0
H_{7a}	3.94, dd, 8.7, 5.3	3.96, dd, 8.0, 5.4	3.77, dd, 9.0, 5.0	3.4, bd, 8.3	3.47, m	3.27, bs
R^1	1.38, d, 7.5	7.02, dd, 2H, 7.3, 1.6, 7.24, m, 3H	3.54–3.41, m, 2H 1.22, t, 3H, 6.8	1.12, d, 7.5	7.37–7.25, m	3.65 and 3.55, m, 2H 1.1, t, 7.0
CH_3N	3.00, s	2.8, s	3.00, s	2.98, s	2.58, s	3.0, s
CH_3–Ar	2.40, s	2.36, s	2.40, s			
AA'BB'	7.71 and 7.30	7.69 and 7.28	7.63 and 7.32			

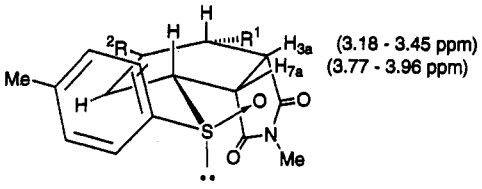

Figure 1. General stereostructure of Diels–Alder adducts 4.

disposition of the S–O and C–H_{7a} bonds). This disposition must be the most stable due to the rigid structure of the *all-cis*-substituted system.

The (*S*) absolute configuration at the hydroxylic center of **5a** (and presumably of all **5** derivatives) as well as its optical purity (>98% ee) was established by ^{1}H NMR from the MTPA esters. Both (*R*)-MTPA and (*S*)-MTPA esters were prepared from pure **5a**, giving the *SR* and *SS* pairs in 72% and 80% yields, respectively. The differences observed in the chemical shifts of carbinol substituents in both diastereomers allowed the configurational correlation according to the model developed by Mosher and Dale.[29]

This high optical purity is consistent with the highly efficient 1,3-chirality transfer which follows from the [2,3]-sigmatropic shift of allylic sulfoxides **4** in a suprafacial manner,[12,25,30] which in its turn had to be diasteromerically pure. According to the (*S*)-carbinol configuration of **5** and the *endo* structure of the precursors **4**, we can assign the 3a*S*,4*R*,5*S*,7a*R* absolute configuration to compounds **5**. Taking into account the (*R*) configuration at the sulfinyl sulfur of the diene, which remains unaltered during the cycloadditions, the absolute configuration of adducts **4** must be 3a*S*,4*S*,7*R*,7a*S*,(S)*R*, as indicated in Scheme 2.

The stereochemical course of these cycloadditions may be explained by considering the relative stabilities of the transition states resulting from the *endo* approach of the dienophile to the different conformations of the diene around the C–S bond. When the diene adopts the s-*trans* disposition of the S=O and C=C bonds represented in Figure 2, the bottom face is sterically hindering the approach of the dienophile. Thus, minimum steric and electrostatic repulsions between the carbonyl oxygen of NMM and the sulfinyl oxygen[14] result in the approach indicated, yielding adducts **4** in a high diastereoselective manner. In the presence of Lewis acids, a chelation-controlled model already proposed in the literature,[9] involving coordination between the sulfinyl oxygen and one of the maleimide carbonyls, could explain the observed stereochemical results.

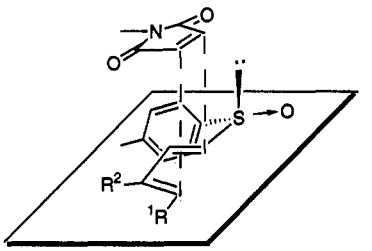

Figure 2. Favored approach of *N*-methylmaleimide in Diels–Alder reactions of (*R*)-1-(*p*-tolylsulfinyl)-1,3-butadienes **3**.

Conclusion

Enantiomerically pure 1-sulfinyl substituted dienes, easily available from α,β-unsaturated aldehydes, have been shown to exhibit high *endo* and π-facial diastereoselectivities in their reactions with *N*-methylmaleimide, making it possible to isolate the Diels–Alder adducts in reactions carried out in catalytic conditions. An enantioselective synthesis of *all-cis* highly functionalized cyclohexene derivatives has been achieved in one pot by a tandem Diels–Alder cycloaddition and [2,3]-sigmatropic rearrangement starting from (*R*)-1-(*p*-tolylsulfinyl)butadienes **3**. These products are not accessible by direct cycloaddition. A model transition state based on minimum steric and electrostatic interactions has been proposed to explain the good stereochemical results.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200.1 and 50.3 MHz in $CDCl_3$. ^{1}H NMR data of compounds **4** and **5** are collected in Table 2. Mass spectra (MS and HRMS) were recorded in the electron impact mode at 70 eV. All solvents were dried before use. Tetrahydrofuran and Et_2O were distilled from sodium–benzophenone under argon. CH_2Cl_2 was dried over P_2O_5. Diisopropylamine was distilled from sodium hydroxide. $ZnBr_2$ was dried at 160 °C for 12 h with P_2O_5 under vacuo. $SnCl_4$, Eu(fod)$_3$, $TiCl_4$, DMAP, iodomethane, 3-ethoxymethacrolein, and NMM were purchased from Aldrich and used without further purification. MTPA-Cl was purchased from Jeanneret, Pousad, Soerensen Chimie and used without further purification. Flash chromatography was performed using silica gel (MN-Kieselgel 60, 230–400 mesh). The apparatus for inert atmosphere experiments was dried by flaming in a steam of dry argon. Yields of Diels–Alder reactions are recorded in Table 1.

[(S)*R*]-4-Ethoxy-3-methyl-1-(*p*-tolylsulfinyl)-3-buten-2-ol (2c). To a solution of diisopropylamine (210 μL, 1.49 mmol) in dry THF (2 mL) at −78 °C was added a solution of BuLi in hexane (2.2 M, 700 μL, 1.56 mmol) under argon. The mixture was stirred at −78 °C for 30 min. Then a solution of (+)-(*R*)-methyl *p*-tolyl sulfoxide (200 mg, 1.3 mmol) in THF (4 mL) cooled to −78 °C was added slowly, and the resulting mixture was stirred at the same temperature for 20 min. The mixture was allowed

(29) See: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 125. (c) Chan, T. H.; Nwe, K. T. *J. Org. Chem.* **1992**, *57*, 6107.

(30) Aggarwal, V. K.; Warren, S. *Tetrahedron Lett.* **1986**, *27*, 101.

to reach 0 °C and then 3-ethoxymethacrolein (309.2 μL, 2.6 mmol) was added. The resulting solution was stirred for 2 h, allowed to reach room temperature, hydrolyzed by addition of a saturated aqueous NH_4Cl solution (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), and dried with Na_2SO_4, and the solvent was evaporated. Compound **2c** was isolated as a 60:40 mixture of diastereomers at C_2 after flash chromatography (ethyl acetate–hexane 1:1) (279 mg, 80% yield): ^1H NMR δ (the signals of both diastereomers were well differentiated) major diastereoisomer: δ 7.47 and 7.25 (AA'BB' syst, 4H), 6.18 (bs, 1H), 4.28 (dd, J = 5.4 Hz and J = 7.6 Hz, 1H), 3.70 (q, J = 7 Hz, 2H), 3.10 (dd, J = 7.6 Hz and J = 12.6 Hz, 1H), 2.70 (dd, J = 5.4 Hz and J = 12.6 Hz, 1H), 2.32 (s, 3H), 1.55 (s, 3H), and 1.15 (t, J = 7 Hz, 3H); ^1H NMR minor diastereoisomer: δ 7.47 and 7.25 (AA'BB' syst, 4H), 6.10 (bs, 1H), 4.50 (dd, J = 1.6 Hz and J = 10 Hz, 1H), 3.68 (q, J = 7 Hz, 2H), 3.0 (dd, J = 10 Hz and J = 12 Hz, 1H), 2.68 (dd, J = 1.6 Hz and J = 12 Hz, 1H), 2.32 (s, 3H), 1.50 (s, 3H), and 1.15 (t, J = 7 Hz, 3H); ^{13}C NMR major diastereomer: δ 142.9, 140.5, 139.6, 129.7 (2C), 123.2 (2C), 111.8, 68.4, 67.0, 61.9, 20.6, 14.5, and 7.5; ^{13}C NMR minor diastereoisomer: δ 143.5, 141.2, 139.9, 129.7 (2C), 123.7 (2C), 113.1, 67.6, 67.4, 62.6, 21.1, 15.0, and 8.4. Anal. Calcd for $C_{14}H_{15}SO_2$: C, 68.01; H, 6.07. Found: C, 68.31; H, 6.29.

(+)-[(S)*R*]-1-Ethoxy-2-methyl-4-(*p*-tolylsulfinyl)-1,3-butadiene (3c). A solution of the diastereomeric mixture of β-hydroxy sulfoxides **2c** (200 mg, 0.93 mmol) in dry THF (5 mL) was slowly added to a cold (0 °C) slurry of NaH (56 mg, 2.3 mmol) in THF (7.5 mL). After 20 min of stirring, MeI (143 μL, 2.3 mmol) was added via a syringe, and the resulting mixture was kept for 30 min at 0 °C and was allowed to reach room temperature. Stirring was continued for 20 h until total conversion of the starting material (TLC, hexane–acetate 7:3). After dilution with Et_2O and filtration through Celite, the resulting solution was washed twice with a saturated solution of $NaHCO_3$ (2 × 20 mL) and dried with Na_2SO_4, and the solvents were evaporated. Diene **3c** was purified by flash chromatography (hexane–acetate 8:2) (186 mg, 80% yield): $[\alpha]^{20}_D$ = +19.0 (c = 1.3, $CHCl_3$); IR ($CHCl_3$) 3000, 1635, 1570, 1230, 1200, and 1040 cm^{-1}; ^1H NMR δ 7.51 and 7.28 (AA'BB' syst, 4H), 6.94 (d, J = 15 Hz, 1H), 6.54 (bs, 1H), 6.05 (d, J = 15 Hz, 1H), 3.96 (q, J = 7 Hz, 2H), 2.38 (s, 3H), 1.66 (s, 3H), and 1.29 (t, J = 7 Hz, 3H); ^{13}C NMR δ 153.2, 141.6, 140.3, 139.7, 129.3 (2C), 126.1, 123.9 (2C), 111.5, 68.6, 20.8, 14.7, and 8.8; MS m/z (relative intensity) 250 (18, M^+), 192 (59), 177 (100), 160 (31), 145 (88), 123 (50), 101 (12), 91 (37), 77 (19), and 65 (24); HRMS calcd for $C_{14}H_{18}SO_2$ 250.1027, found 250.1030.

General Procedures for Diels–Alder Reactions. Method A. To a solution of NMM (1.2–3.0 mmol, see Table 1) in 1 mL of CH_2Cl_2 at room temperature was added a solution of the diene **3** (0.30 mmol) in the minimum amount of CH_2Cl_2. The mixture was kept at the temperature indicated in Table 1 and monitored by TLC (ethyl acetate–hexane 7:3). After completion of the reaction (see Table 1 for reaction times), the solvent was evaporated in vacuo and the resulting mixture was separated by flash chromatography [in the cases of compounds **5a** and **5b** with a gradient of CH_2Cl_2–acetone 9:1 (250 mL) to 5:1; for compound **5c** a gradient of ethyl acetate–hexane 3:7 (250 mL) to 1:1 was used].

Method B. A solution of NMM (93.3 mg, 0.84 mmol) in CH_2Cl_2 was added to $ZnBr_2$ (189 mg, 0.84 mmol) or $Eu(fod)_3$ (290 mg, 0.28 mmol) under argon at 0 °C. In the case of the $SnCl_4$, a 1 M solution in CH_2Cl_2 (1.68 mL, 1.68 mmol) was added dropwise to the solution of NMM in CH_2Cl_2 under argon at 0 °C. The mixture was stirred for 30 min and then the diene **3** (0.28 mmol) was added disolved in the minimum amount of CH_2Cl_2. The reaction mixture was kept at room temperature and monitored by TLC (ethyl acetate–hexane 7:3). After completion (see Table 1 for reaction times), water was added (in the case of the reaction with the diene **3c**, some drops of 10% HCl were added at 0 °C to eliminate the $Eu(fod)_3$). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. After drying with Na_2SO_4, the solvent was evaporated in vacuo. The crude product was purified by chromatography [flash column for compounds **4a** and **4b** (CH_2Cl_2–acetone 5:1) and PLC for compound **4c** (CH_2Cl_2–acetone 5:1)].

(+)-[3a*S*,4*S*,7*R*,7a*S*,(S)*R*]-2,4-Dimethyl-7-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (4a). Compound **4a** was obtained from diene **3a** following method A (Table 1, entries 1 and 3, 42% and 30% isolated yields, respectively) and method B (Table 1, entries 4 and 5): mp 128–130 °C; $[\alpha]^{20}_D$ = +195.0 (c = 1.1, $CHCl_3$); IR ($CHCl_3$) 3010, 1700, 1690, 1610, 1275, 1200, and 1010 cm^{-1}; ^{13}C NMR δ 176.3, 176.2, 142.8, 140.3, 137.1, 130.2 (2C), 125.3 (2C), 122.5, 63.4, 44.2, 41.3, 31.3, 29.6, 21.5, and 16.3; MS m/z (relative intensity) 177 (32.3), 144 (31.6), 139 (35), 124 (29), 120 (60), 119 (30), 105 (70), 91 (100), and 77 (53); HRMS calcd for $C_{10}H_{11}NO_2$ (M^+ – HSOTol) 177.0789, found 177.0783.

(+)-[3a*S*,4*S*,7*R*,7a*S*,(S)*R*]-2-Methyl-4-phenyl-7-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (4b). Compound **4b** was obtained from diene **3b** following method B as a yellow oil (Table 1, entries 8 and 9): $[\alpha]^{20}_D$ = +57.7 (c = 1, $CHCl_3$); IR ($CHCl_3$) 3080, 3000, 1800, 1725, 1640, 1315, 1160, 1110, 1060, and 840 cm^{-1}; ^{13}C NMR δ 175.9, 175.1, 142.9, 140.1, 137.8, 133.7, 130.3 (2C), 128.6 (2C), 128.4 (2C), 127.4, 125.5 (2C), 63.2, 46.1, 41.9, 40.6, 24.7, and 21.5; MS m/z (relative intensity) 379 (0.14, M^+), 240 (52.7), 239 (53.8), 182 (32), 155 (68), 154 (100), 140 (38.7), and 139 (31.6); HRMS calcd for $C_{22}H_{21}NSO_3$ 379.1263, found 379.1242.

[3a*R*,4*S*,7*R*,7a*S*,(S)*R*]-4-Ethoxy-2,5-dimethyl-7-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (4c). Compound **4c** was obtained from diene **3c** following method B (Table 1, entry 12, 28% isolated yield). The low yield obtained is a consequence of the low stability of **4c** which could be only isolated by PLC.

(–)-(3a*S*,4*R*,5*S*,7a*R*)-5-Hydroxy-2,4-dimethyl-3a,4,5,7a-tetrahydroisoindole-1,3-dione (5a). Compound **5a** was obtained from **3a** following method A (Table 1, entries 1 and 3, 24% and 66% isolated yields, respectively): mp 113 °C (ethyl ether); $[\alpha]^{20}_D$ = –7.0 (c = 0.84, $CHCl_3$); IR ($CHCl_3$) 3445, 2935, 1700, 1285, 1100, 1010, and 810 cm^{-1}; ^{13}C NMR δ 178.1, 176.5, 132.3, 122.8, 67.0, 41.3, 41.0, 34.2, 24.6, and 11.0; MS m/z (relative intensity) 195 (100, M^+), 177 (89), 166 (17.5), 152 (14), 140 (65), and 110 (91); HRMS calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0899.

(–)-(3a*S*,4*S*,5*S*,7a*R*)-5-Hydroxy-2-methyl-4-phenyl-3a,4,5,7a-tetrahydroisoindole-1,3-dione (5b). Compound **5b** was obtained from compound **4b** as a brown oil following method A (Table 1, entry 6 and 7): $[\alpha]^{20}_D$ = –11.0 (c = 1.1, $CHCl_3$); IR ($CHCl_3$) 3460, 3030, 2925, 1770, 1695, 1680, 1130, 1070, and 995 cm^{-1}; ^{13}C NMR δ 176.4, 175.9, 134.5, 133.5, 130.1 (2C), 128.5 (2C), 127.8, 122.9, 67.4, 45.1, 42.4, 40.5, and 24.3; MS m/z (relative intensity) 257 (18.8, M^+), 239 (20), 229 (17), 213 (19.3), 182 (9.3), 154 (34.7), and 131 (100); HRMS calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1053.

(–)-(3a*R*,4*R*,5*S*,7a*R*)-4-Ethoxy-5-hydroxy-2,5-dimethyl-3a,4,5,7a-tetrahydroisoindole-1,3-dione (5c). Compound **5c** was obtained from diene **3c** following method A (Table 1, entry 11) and method B following the conditions indicated on entry 12, waiting 20 days after hydrolysis of the reaction mixture to allow the total transformation of **4c** to **5c**: yield 71%; mp 188–190 °C (ethyl ether); $[\alpha]^{20}_D$ = –4.0 (c = 0.63, $CHCl_3$); IR ($CHCl_3$) 3490, 2970, 1765, 1700, 1385, 1345, 1285, 1245, and 1145 cm^{-1}; ^{13}C NMR δ 176.7, 176.1, 135.5, 119.8, 80.3, 70.8, 69.6, 43.1, 39.1, 24.7, 24.6, and 15.6; MS m/z (relative intensity) 239 (1.4, M^+), 196 (12), 151 (20), 128 (57), 99 (100), and 71 (29); HRMS calcd for $C_{12}H_{17}NO_4$ 239.1157, found 239.1167.

(+)-(3a*R*,7a*R*)-2-Methyl-4-phenyl-3a,7a-dihydroisoindole-1,3-dione (6). To a solution of NMM (40 mg, 0.33 mmol) in 1 mL of CH_2Cl_2 was added a solution of **4b** (42 mg, 0.11 mmol) in 1 mL of CH_2Cl_2. The mixture was heated under reflux for 2 days. Then, the solvent was evaporated in vacuo and the crude product was purified by flash chromatography (gradient of hexane–CH_2Cl_2 1:1 (200 mL) to 1:5): yield 18 mg, 68%; mp 155 °C; $[\alpha]^{20}_D$ = +407.0 (c = 0.31, $CHCl_3$); IR ($CHCl_3$) 3000, 1750, 1700, 1100, 990, 790, and 700 cm^{-1}; ^1H NMR δ 7.25–7.12 (m, 5H), 7.03 (dd, J = 2.9 Hz and J = 5 Hz, 1H), 6.50 (dd, J = 4.8 Hz and J = 9.7 Hz, 1H), 6.31 (dd, J = 9.7 Hz and J = 5.7 Hz, 1H), 4.14 (dd, J = 5.7 Hz and J = 9.7 Hz, 1H), 3.92 (dd, J = 2.9 Hz and J = 9.7 Hz, 1H), and 2.88 (s, 3H); ^{13}C NMR δ 174 (2C), 136.2, 134, 128.9, 128.6, 128.4, 127.8, 126.5, 124.9, 44.1, 38.4, and 24.4; MS m/z (relative intensity) 239 (63.2, M^+), 21.0 (11.8), 182 (97.3), and 154 (100); HRMS calcd for $C_{15}H_{13}NO_2$ 239.0946, found 239.0939.

General Procedure for Preparation of MTPA Esters.[26c] To a solution of **5a** (9 mg, 0.05 mmol) and DMAP (12.4 mg, 0.10

mmol) in 3 mL of CH_2Cl_2 was added the corresponding MTPA-Cl [(*R*) or (*S*)] (15 μL, 0.083 mmol). The mixture was stirred overnight at 30 °C and then the reaction was quenched as follows: 1 mL of water and 3 mL of Et_2O were added and the reaction mixture was stirred for 15 min. The solution was washed successively with 4 mL of 1 N HCl, 4 mL of 1 N NaOH, and brine and dried over $MgSO_4$. After evaporation of the solvents, the corresponding MTPA ester was obtained and characterized without further purification. Yield: 72% (13.5 mg, 0.033 mmol) and 80% (15 mg, 0.036 mmol), respectively.

^{1}H NMR (*SS*)-MTPA ester δ 7.40 (bs, 5H), 6.17 (m, 2H), 5.40 (bs, 1H), 3.56 (bs, 3H), 3.45 (bd, J = 10 Hz, 1H), 3.05 (t, J = 7 Hz, 1H), 2.65 (s, 3H), 2.45 (m, 1H), and 1.29 (d, J = 7.5 Hz, 3H); (*SR*)-MTPA ester δ 7.42 (bs, 5H), 6.22 (m, 1H), 5.45 (bs, 1H), 3.55(m, 1H), 3.45 (bs, 3H), 3.08 (t, J = 6.8 Hz, 1H), 2.81 (s, 3H), 2.49 (m, 1H), and 1.10 (d, J = 7.5 Hz, 3H).

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Supplementary Material Available: ^{1}H NMR spectra of compounds **3c**, **4a–c**, **5a–c**, **6**, and (*SS*)- and (*SR*)-MTPA esters (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.