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Highly Diastereoselective Diels–Alder Reactions with Enantiopure Sulfinyl-Substituted 1-Hydroxymethyldienes

Roberto Fernández de la Pradilla,* Carlos Montero, Mariola Tortosa, and Alma Viso[a]

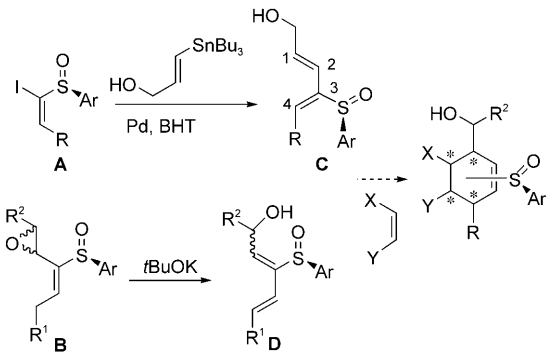
Abstract: Enantiopure hydroxy-2- and -3-sulfinyldienes undergo highly selective Diels–Alder cycloadditions with various dienophiles controlled by the chiral sulfur atom. The related hydroxy-2-sulfonyldienes display complementary π-facial selectivity.

Keywords: asymmetric synthesis · cycloaddition · Diels–Alder · sulfones · sulfoxides

Introduction

The asymmetric Diels–Alder reaction is a fundamental process in modern synthetic chemistry, since up to four enantio- and diastereomerically pure stereogenic centers are created in a single step.[1] Within this field the use of chiral dienophiles has been extensively studied and more recently the use of chiral Lewis acids as catalysts has achieved good levels of asymmetric induction.[2] In contrast, the use of enantiopure dienes has received far less attention, perhaps, due to the difficulty often associated with the preparation of these substrates.[3] Simple 2-sulfinyldienes[4,5] are especially appealing, since, after a highly selective Diels–Alder cycloaddition, a vinyl sulfoxide is generated allowing for subsequent chirality-transfer operations.[6]

In recent years, we have been involved in the development of different strategies for the synthesis of the enantiopure hydroxy-3- and -2-sulfinyldienes **C** and **D** (Scheme 1).[7,8] Since these routes gave access to substrates with different substitution patterns, we thought it would be interesting to carry out a general study of their Diels–Alder reactivity.[9] Moreover, the synthesis of enantiopure dienes **D** would provide a unique opportunity to assess the relative π-facial stereodirecting abilities of two powerful elements of stereocontrol in a Diels–Alder process.[5,10,11] In addition, in some cases we have explored the influence of the nature of the sulfinyl Ar group in the cycloaddition process. Herein we describe in detail our efforts in this field.



Scheme 1. Diastereoselective Diels–Alder cycloadditions with sulfinyl-substituted 1-hydroxymethyldienes.

Results

Preparation of starting materials: To begin our study we synthesized several enantiopure dienols (Shown here). Hydroxy-3-sulfinyldienes **1** and **2** were prepared by Stille coupling from the corresponding iodo vinyl sulfoxides.[8] Dienols **1a–c** were selected to evaluate the effect of representative R groups and different Ar substituents on sulfur. Compound **2** was selected to test the influence of the *E*/*Z* geometry of the dienol.

Hydroxy-2-sulfinyldienes **3** and **5** were synthesized from enantiopure epoxy vinyl sulfoxides following our own methodology.[7] We selected (*Z*,*E*)-dienes **3a–c** and (*E*,*E*)-dienes **5a–c** with different R^2 and Ar groups to modulate 1,3-allylic strain[13] and substrates **3d** and **5d** to explore the behavior

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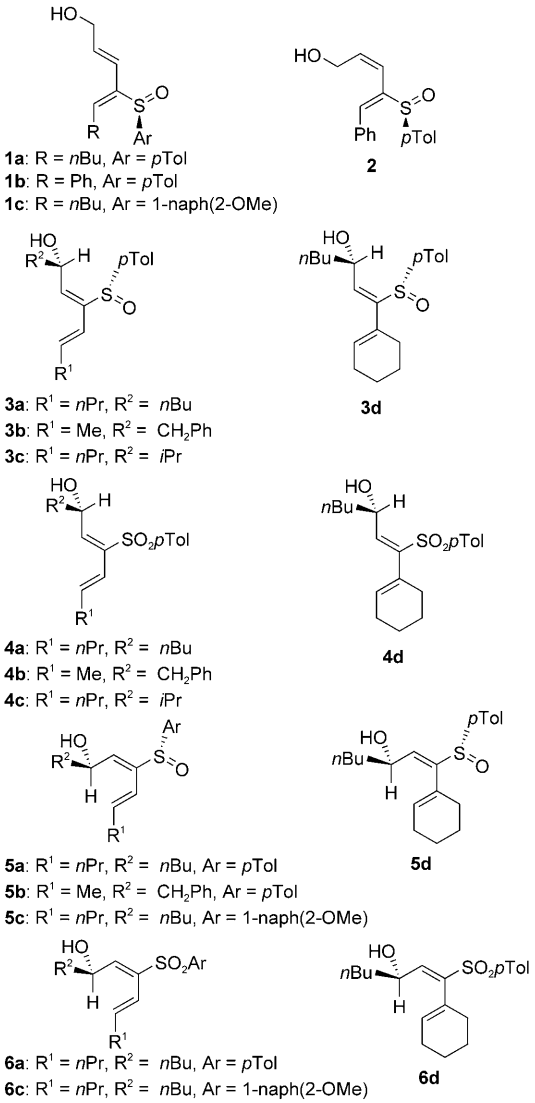
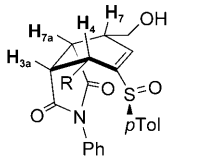


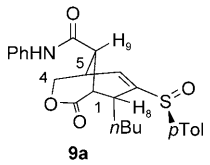
of a tetrasubstituted diene. Moreover, we prepared sulfonyldienols **4a–d** and **6a**,**c**,**d**, by oxidation of the corresponding sulfoxides, to clarify the role of the sulfinyl moiety on the Diels–Alder process.

Diels–Alder cycloadditions with hydroxy-3-sulfinyldienes: For our initial studies, we selected enantiopure dienes **1a–c** and the dienophile *N*-phenylmaleimide (NPM) (Table 1). Treatment of **1a** with NPM at room temperature afforded cycloadduct **7a** as a single isomer (Table 1, entry 1). The process was also compatible with the presence of a conjugated phenyl group (Table 1, entry 2), affording cycloadduct **7b** in good yield and with high selectivity. The influence of the Ar substituent on sulfur was then addressed by using the readily available 2-MeO-1-naphthyl moiety;[13] we found a striking enhancement of the rate with respect to the *p*-tolyl analogue. Diene **1c** underwent smooth Diels–Alder cycloaddition affording **7c** in just 2 h at 0 °C with excellent yield and selectivity (Table 1, entry 3).

Treatment of a solution of these cycloadducts with silica gel resulted in regioselective lactonization affording mixtures of lactones **8** and **9**. The structure of these compounds was derived from their ^{1}H and ^{13}C NMR spectra as well as differential NOE data (Figure 1). At this stage, the structure



NOE	H_{3a}	H_4	H_{7a}
H_{3a}	—	9.4%	7.2%
H_4	6.7%	—	—
H_7	—	8.0%	9.7%
H_{7a}	6.7%	8.0%	—



$J_{5\text{-}9} \leq 2$ Hz
NOE H_1-H_8: 11.4%

Figure 1. Spectral data for imide **7a** and amide **9a**.

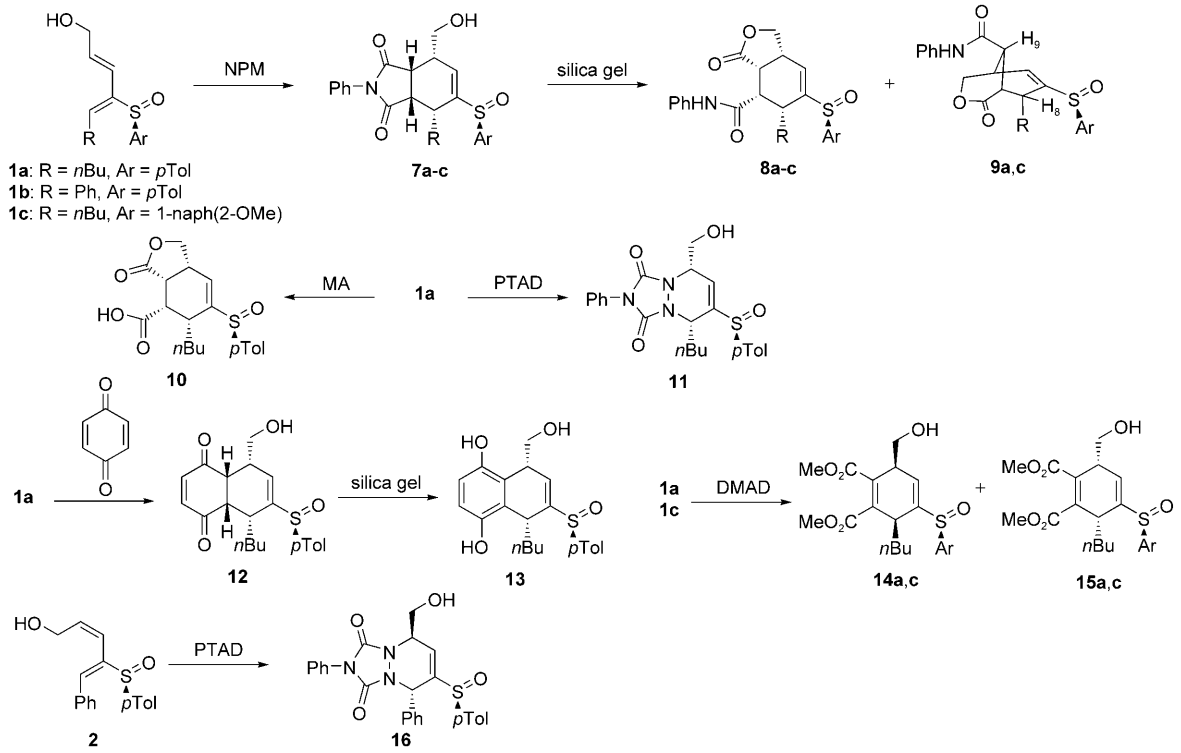
assigned for minor isomer **9** made us readdress our previous results on Diels–Alder cycloadditions with hydroxy-2-sulfinyldienes and led us to revise our initial assignment (see below).[9]

We then set out to explore the reactivity of diene **1a**, as a model substrate, with different dienophiles. The use of maleic anhydride (MA) afforded lactone **10** practically as a single isomer (Table 1, entry 4). Additionally, the reaction with phenyltriazolinedione (PTAD) and *p*-benzoquinone (Table 1, entries 5 and 6) took place with complete π-facial selectivity to produce adducts **11** and **12** respectively. Compound **12** was isolated by recrystallization from the crude mixture, as purification by chromatography on silica gel led to the formation of the aromatic derivative **13**.

In contrast, the use of dimethyl acetylenedicarboxylate (DMAD, Table 1, entry 7) required heating at 50 °C for seven days, and produced a nonselective mixture of the diastereoisomers **14a** and **15a**. Encouraged by the remarkable rate enhancement observed for **1c** with NPM, we explored the reactivity of this diene with DMAD (Table 1, entry 8). To our delight, the introduction of a 2-MeO-1-naphthylsulfinyl substituent resulted in higher reactivity and π-facial selectivity affording an 80:20 mixture of adducts **14c** and **15c**. Finally, to investigate the influence of the geometry of the diene in the Diels–Alder process, the behavior of dienol **2** with NPM was examined with disappointing results. Treatment of **2** with NPM in CH_2Cl_2 for two days afforded cycloadduct **7b** and isomeric diene **1b**. We believe dienol **2** isomerized to diene **1b**, which reacted with NPM as described above. In contrast, the more reactive PTAD gave a smooth reaction with dienol **2** and cycloadduct **16** was obtained in good yield and with high selectivity (Table 1, entry 9).

Diels–Alder cycloadditions of hydroxy-2-sulfinyldienes: Initially, we selected dienes **3a–c** and NPM for our studies

Table 1. Diels–Alder cycloadditions of hydroxy-3-sulfinyldienes.



Entry	Substrate	Conditions[a]	Products[b]	Yield [%][c]	Conditions[d]	Products[b]	Yield [%][c]
1	**1a**	NPM, 2 d	**7a**	85	2 d	**7a** (8), **8a** (78), **9a** (14)	71
2	**1b**	NPM, 3 d	**7b**	100	20 d	**7b** (3), **8b** (97)	89
3	**1c**	NPM, 0 °C, 2 h	**7c**	93	20 d	**7c** (6), **8c** (72), **9c** (22)	75
4	**1a**	MA, 1 d	**10**	94			
5	**1a**	PTAD, CH_2Cl_2, −78 °C to RT, 2 h	**11**	86			
6	**1a**	*p*-benzoquinone, 1 d	**12**	83		**13**	70[e]
7	**1a**	3.0 equiv, DMAD, 10 d; then 50 °C, 7 d	**14a** (50), **15a** (50)	40			
8	**1c**	3.0 equiv DMAD, 11 d	**14c** (80), **15c** (20)	50			
9	**2**	PTAD, CH_2Cl_2, −78 to 0 °C, 1 h	**16**	82			

[a] Unless otherwise noted, the reactions were carried out with 1.5 equiv of dienophile in toluene at RT. [b] Diastereomeric ratios are shown in parentheses. [c] Combined yields of pure products after column chromatography. [d] Unless otherwise noted, the reactions were carried out with silica gel in CH_2Cl_2 at RT. [e] Obtained after silica gel chromatography of **12**.

(Table 2). Diene **3a** afforded cycloadduct **18a** as a single isomer (shown by 300 MHz ^{1}H NMR spectroscopic analysis of the crude reaction mixture), which was isolated in good yield by recrystallization (Table 2, entry 1). To assess the influence of intramolecular hydrogen bonding on the stereochemical outcome of this process, the cycloaddition between diene **3a** and NPM was carried out in MeOH and adduct **18a** was easily obtained (Table 2, entry 2). However, treatment of a solution of **18a** with silica gel resulted in spontaneous lactonization and produced a 25:75 mixture of amides **19a** and **20a**. The structure of these compounds was also established from their ^{1}H and ^{13}C NMR spectroscopic data. Moreover, amides **19a** and **20a** displayed significant NOE enhancements between H_a and H_b (11.5% and 10.4% respectively). Considering the behavior observed for the lactonization of related compounds,[14] we initially assigned amide **20a** as lactone **E**, derived from **19a** by epimerization of the carboxamide bearing center (Figure 2). However, a detailed ^{1}H NMR spectroscopic study, the NOE enhancements observed, and the assignment made for amides **9** revealed that the correct structure of **20a** was a regioisomeric lactone.

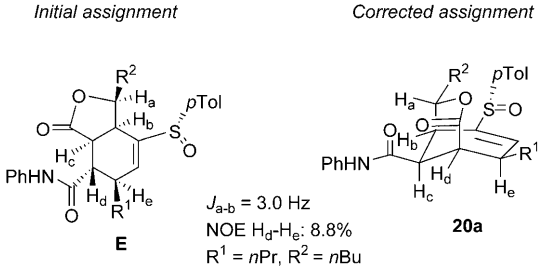
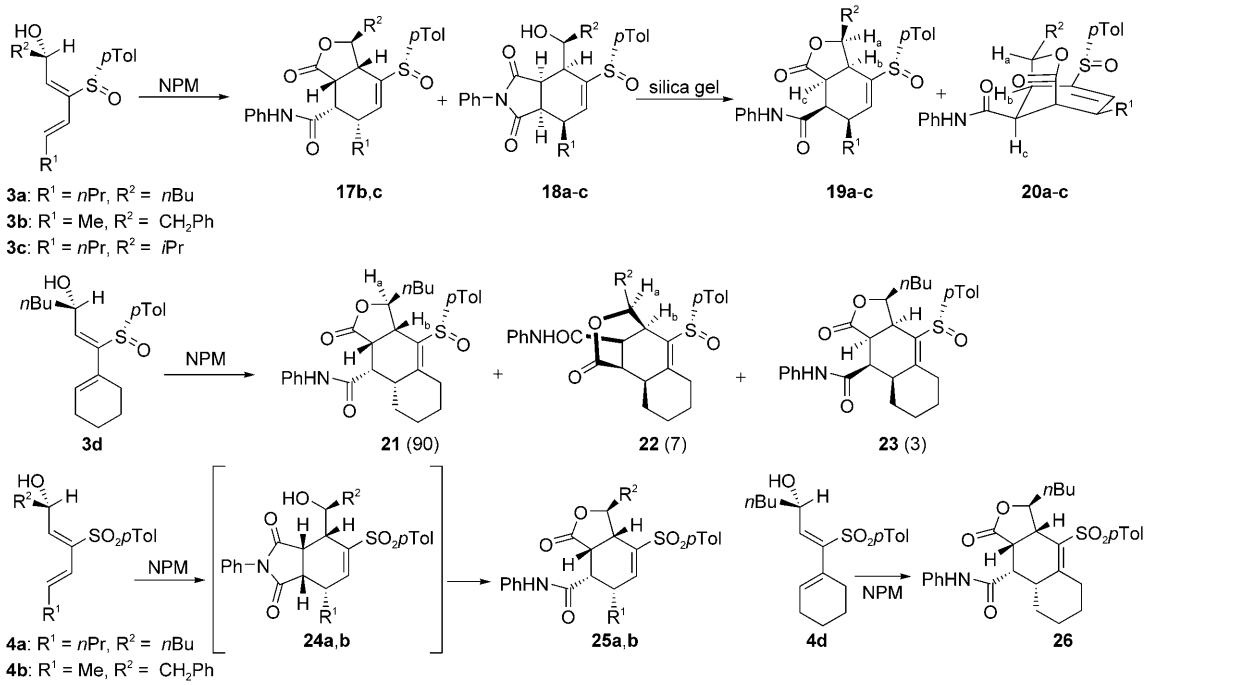


Figure 2. Structural assignment for amide **20a**.

Table 2. Diels–Alder cycloadditions of hydroxy-2-sulfinyl- and -sulfonyldienes with NPM.



Entry	Substrate	Conditions[a]	Products[b]	Yield [%][c]	Conditions[e]	Products[b]	Yield [%][d]
1	**3a**	5 d	**18a**	71	5 d	**19a** (25), **20a** (75)	81
2	**3a**	MeOH, 5 d	**18a**				
3	**3b**	1.1 equiv NPM, 3 d	**17b** (5), **18b** (95)	74	1 d	**20b**	100
4	**3c**[f]	1.0 equiv NPM, 18 d	**17c** (8), **18c** (92)		1 d	**20c**	65 (2 steps)
5	**3d**	100 °C, 3 d	**21** (90), **22** (7), **23** (3)	50			
6	**4a**	5 d	**24a**			**25a**	66
7	**4b**	2.3 equiv NPM, 3 d	**25b**				81
8	**4d**	100 °C, 3 d	**26**				50

[a] Unless otherwise noted, the reactions were carried out with 1.5 equiv of NPM in toluene at RT. [b] Diastereomeric ratios are shown in parentheses. [c] Combined yield after recrystallization. [d] Combined yields of pure products after column chromatography. [e] Unless otherwise noted, the reactions were carried out with silica gel in CH_2Cl_2 at RT. [f] 90% conversion.

Diene **3b** ($R^2 = CH_2Ph$) afforded a 95:5 mixture of cycloadduct **18b** and amide **17b**, respectively, as shown by the ^1H NMR spectrum of the crude reaction mixture (Table 2, entry 3). Treatment of **18b**, isolated by recrystallization, with silica gel resulted in a smooth cyclization affording amide **20b** and trace amounts of **19b**. Diene **3c** ($R^2 = iPr$) produced a 92:8 mixture of **18c** and **17c** after a longer reaction time of 18 days (Table 2, entry 4). Treatment of cycloadduct **18c** with silica gel produced lactone **20c** exclusively.

We then studied the cycloaddition of the tetrasubstituted diene **3d** with NPM (Table 2, entry 5), which required heating at 100 °C for three days to afford a 90:7:3 mixture of **21**, **22**, and **23**. The coupling constants and NOE enhancements observed for H_b-H_c ($J_{Hc\text{-}Hb} = 8.8$ Hz, NOE (H_b-H_c) = 11.8%, NOE (H_c-H_b) = 10.4%) and H_a-H_b ($J_{Ha\text{-}Hb} < 1$ Hz, NOE (H_a-H_b) = 2.8%) revealed that the major isomer **21** was derived from opposite diastereofacial selectivity relative to the examples above.

To extend the scope of our methodology and seeking additional support for the stereochemical assignments, we synthesized enantiopure hydroxysulfonyldienes **4** from sulfoxides **3** by oxidation with MMPP (MMPP = magnesium bis(monoperoxyphthalate) hexahydrate).[15] Dienes **4a** (Table 2, entry 6) and **4b** (Table 2, entry 7), with different steric requirements, underwent cycloaddition with NPM affording the very unstable cycloadduct **24**, which lactonized spontaneously in the reaction media to give **25**. Tetrasubstituted diene **4d** (Table 2, entry 8) was also an appropriate substrate although it was found to be less reactive. These results show that the allylic hydroxyl group is a powerful element of stereocontrol in these compounds.

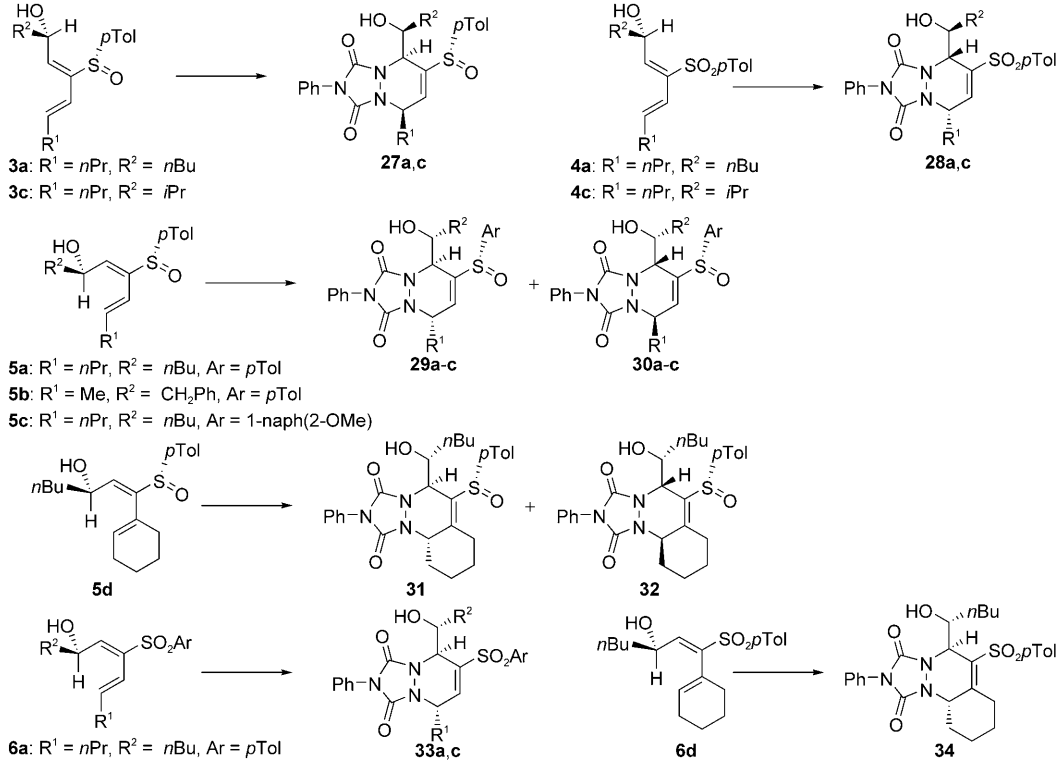
We believe that after treatment with silica gel, cycloadducts **18** afford amides **20** as major isomers as a consequence of the location of the R^2 group in the sterically demanding concave region of the molecule in lactones **19**, while for amides **21** and **25**, R^2 is placed on the convex face. This fact would also explain the higher regioselectivity found upon the lactonization of **18b** and **18c**.

Our results for the cycloaddition between hydroxy-2-sulfinyl and -2-sulfonyldienes and PTAD are presented in

Table 3. The cycloaddition of (*Z*,*E*)-dienes **3** (Table 3, entries 1 and 2) and **4** (Table 3, entries 3 and 4) took place with complete π-facial selectivity, essentially controlled by the oxidation state at sulfur, and in high yield to produce adducts **27** and **28**, respectively.

Next, we explored the reactivity of (*E*,*E*)-hydroxy-2-sulfinyldienes. Treatment of diene **5a** with NPM, under a variety of conditions, resulted in the recovery of the starting material. In contrast, the use of PTAD afforded cycloadducts **29a** and **30a** in high yield and with moderate π-facial selectivity (Table 3, entry 5). We tried to diminish the extent of allylic control by changing the polarity of the solvent; however, this only led to a modest increase in the amount of **30a** produced (Table 3, entries 6–9).[11] To our surprise, the diene with the bulkier R^2 substituent, **5b**, produced a practically nonselective mixture (Table 3, entry 10). To increase control by the sulfinyl group we carried out the reaction of **5c** with a 2-MeO-1-naphthyl moiety in CH_3CN affording, surprisingly, **29c** as a single isomer in very good yield (Table 3, entry 11). These somewhat unexpected results suggest that for these dienes there is a reinforcing relationship[16] between the two elements of stereocontrol involving a conformational change (see below). Diene **5d**, with a tetrasubstitution pattern afforded practically a single isomer with PTAD (Table 3, entry 12).

Table 3. Diels–Alder cycloadditions of hydroxy-2-sulfinyl- and -sulfonyldienes with PTAD.

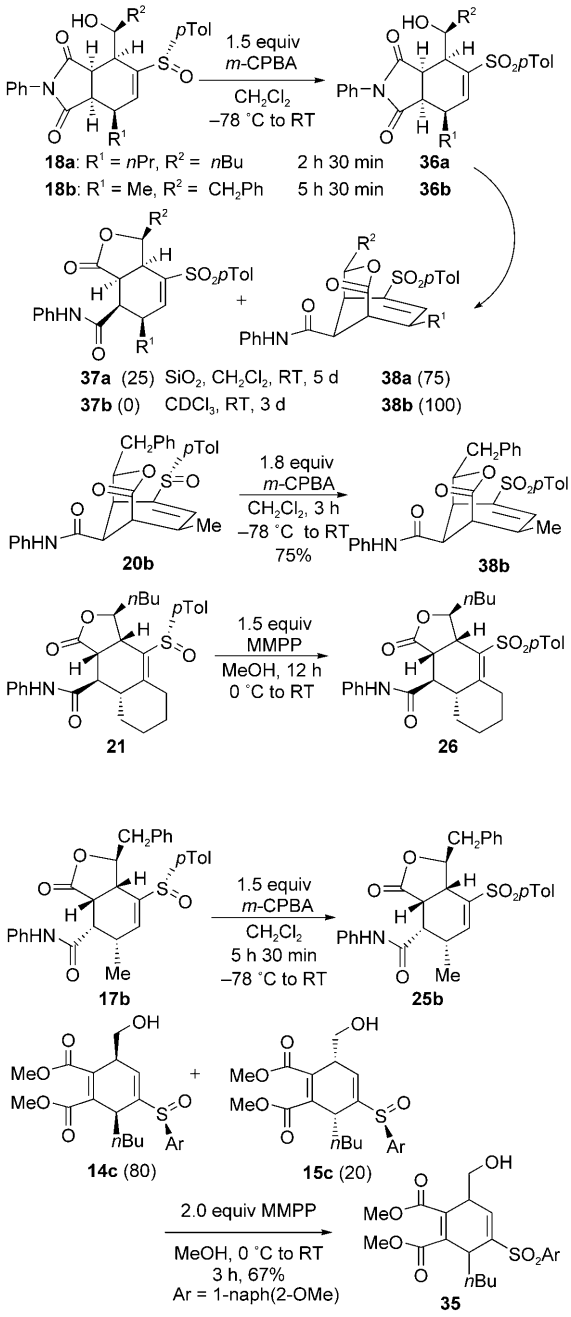


Entry	Substrate	Conditions[a]	Products[b]	Yield [%][c]
1	**3a**	−78 to 0 °C, 1 h 15 min	**27a**	87
2	**3c**	2.0 equiv PTAD, −78 °C to RT, 15 h	**27c**	90
3	**4a**	−78 to 0 °C, 1 h 15 min	**28a**	78
4	**4c**	2.0 equiv PTAD, −78 °C to RT, 15 h	**28c**	90
5	**5a**	−78 to 0 °C, 1 h 30 min	**29a** (83), **30a** (17)	83
6	**5a**	1% THF/CH_2Cl_2, −78 to 0 °C, 1 h 30 min	**29a** (76), **30a** (14)	–
7	**5a**	CH_3CN, −78 to 0 °C, 1 h 30 min	**29a** (58), **30a** (42)	–
8	**5a**	acetone, −78 to 0 °C, 1 h 30 min	**29a** (48), **30a** (52)	–
9	**5a**	DMF, −78 to 0 °C, 1 h 30 min	**29a** (48), **30a** (52)	–
10	**5b**	2.0 equiv PTAD, −78 to 0 °C, 1 h 30 min	**29b** (60), **30b** (40)	90
11	**5c**	CH_3CN, −40 to 0 °C, 1 h	**29c**	92
12	**5d**	toluene, −78 °C to RT, 4 h	**31d** (99), **32d** (1)	82
13	**6a**	−78 to 0 °C, 1 h 30 min	**33a**	74
14	**6c**	−78 to 0 °C, 1 h	**33c**	63
15	**6d**	−78 °C to RT, 12 h	**34d**	100

[a] Unless otherwise noted, the reactions were carried out with 1.5 equiv of PTAD in CH_2Cl_2. [b] Diastereomeric ratios are shown in parentheses. [c] Combined yields of pure products after column chromatography.

Finally, sulfonyldienes **6a**,**c**,**d** produced cycloadducts **33a**,**c** and **34**, respectively, as single products (Table 3, entries 13, 14, and 15) in good yield and with high selectivity, demonstrating once again the powerful stereocontrol of the allylic stereocenter.

Chemical characterizations: To support the stereochemical assignments discussed previously, we carried out several sulfoxide oxidations using either MMPP or *m*-CPBA (*meta*-chloroperbenzoic acid) (Schemes 2 and 3). Scheme 2 shows both the oxidations of the cycloadducts obtained from the



Scheme 2. Chemical characterizations by oxidation and lactonization.

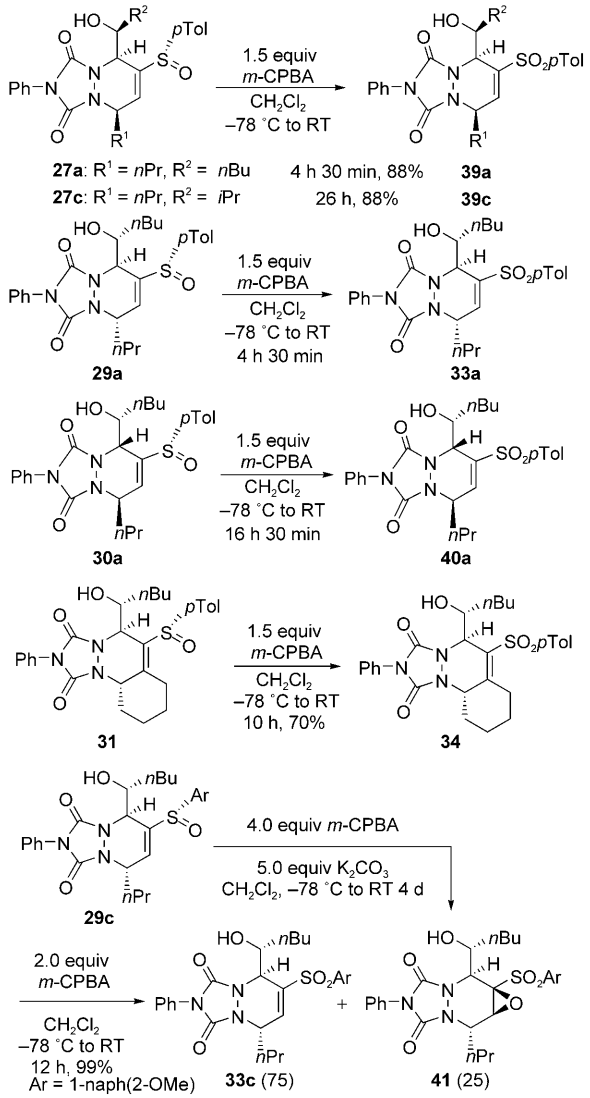
(*Z*,*E*)-hydroxy-2-sulfinyldienes and from the mixture of **14c**/**15c** derived from the 3-sulfinyldienol. Thus, imide **18a** was oxidized to sulfone **36a**, which upon treatment with silica gel afforded a 25:75 mixture of amides **37a** and **38a**. Additionally, the oxidation of **18b**, which contained the bulkier R^2 group, produced the unstable sulfone **36b**. This compound cyclized spontaneously to afford sulfone **38b**, which was also obtained by oxidation of lactone **20b**. The diastereomeric relationship found between amides **25** and **37**/**38**, along with the NOE enhancement observed between H_a-H_b in amides **19** and **20**, establishes that the π-facial selectivity of the cycloaddition between dienes **3a**–**c** and NPM is exclusively controlled by the chiral sulfur atom. However, the oxidation of **21** afforded tricyclic sulfonyl amide **26**, identical to the product obtained from the cycloaddition of the sulfonyl dienol **4d** with NPM.

For further verification of the stereochemical assignments, the minor isomer **17b** was oxidized with *m*-CPBA affording amide **25b**, which was also previously prepared from sulfonyl diene **4b**. This result confirmed that **17b** was derived from the approach of the dienophile to the chiral sulfinyldiene with opposite diastereofacial selectivity. Finally, the oxidation of a mixture of **14c** and **15c** resulted in the observation of just a single sulfone in the ^{1}H NMR spectrum of the crude product, corroborating their diastereomeric relationship.

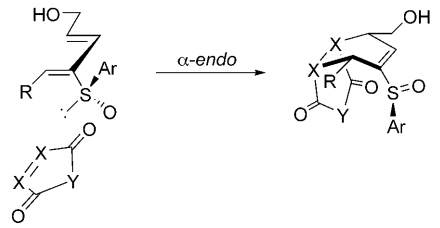
Scheme 3 shows the results found for cycloadducts synthesized from hydroxy-2-sulfinyldienes and PTAD. Standard oxidation of **27a**,**c** afforded **39a**,**c**, the spectral features of which indicated a diastereomeric relationship to **28a**,**c**. In analogy with the Diels–Alder reaction with NPM, these observations established a sulfur-directed π-facial selectivity for hydroxy sulfoxides **3** with PTAD and an allylic control for hydroxydienyl sulfones **4**. The stereochemical assignment for **29a** and **30a** was made by oxidation of these compounds and comparison of their spectral features to those of cycloadduct **33a**, previously prepared from sulfonyl diene **6a**. Finally, oxidation of **31** and **29c** revealed a similar stereochemical outcome for the reaction of sulfoxides **5c,d** and their corresponding sulfones **6c,d** with PTAD. Surprisingly, in the oxidation of **29c** with *m*-CPBA epoxy sulfone **41** was detected.[17] This compound was obtained as a single product by using an excess of the oxidizing agent and longer reaction time.

Discussion

We believe that this process is primarily controlled by stereoelectronic effects. An early transition state is proposed in each case with the most stable conformation also being the most reactive. The stereochemical outcome of the Diels–Alder cycloaddition for hydroxy-3-sulfinyl dienes may be rationalized by an exclusive *endo* approach of the dienophile from the least hindered, highest electron density face of the diene (α-face), for which an *S-cis* C=C/S−: arrangement is proposed (Scheme 4).[18]

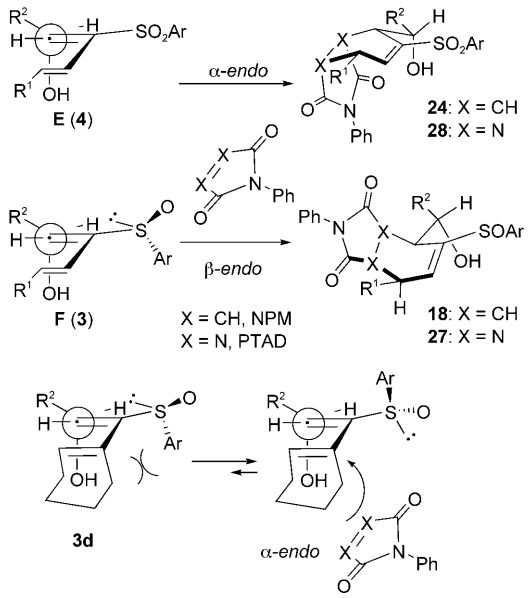


Scheme 3. Chemical characterizations of PTAD-derived cycloadducts by oxidation.



Scheme 4. Stereochemical rationalization for 3-sulfinyldienes.

The preferred conformation for hydroxy-2-sulfonyl- and -sulfinyldienes is likely to be dictated by 1,3-allylic strain between the hydroxyl-bearing stereocenter and the *cis* substituent. For (*Z*,*E*)-dienes the coupling constant between allylic and vinylic protons ($J = 8$–9 Hz) defined a dihedral angle of 180°, which is in agreement with the proposed conformations **E** and **F** (Scheme 5).[19] For (*Z*,*E*)-sulfonyldienes



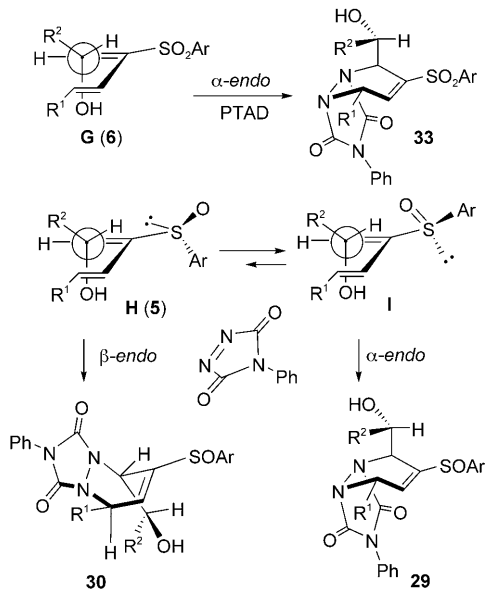
Scheme 5. Stereochemical rationalization for (*Z*,*E*)-sulfinyl- and -sulfonyldienes.

the allylic stereocenter directs the approach of the dienophile from the α-face, *anti* to R^2, presumably with the aid of attractive interactions between the hydroxyl group and the dienophile.[11] However, for (*Z*,*E*)-sulfinyldienes the two elements of stereocontrol are in a nonreinforcing relationship and the dienophile approaches the diene from the β-face, *anti* to the Ar group on sulfur. The opposite π-facial selectivity observed for diene **3d** may be rationalized by assuming that the conformation around the C–S bond changes in order to minimize steric interactions between the cyclohexenyl group and the Ar substituent (Scheme 5). Now the allylic stereocenter and the sulfinyl group are in a reinforcing relationship. This rationalization is in agreement with the results observed by Aversa et al. for related 2-sulfinyldienes substituted at C3.[4b]

In the case of hydroxy (*E*,*E*)-2-sulfonyldienes (Scheme 6) an α-approach of the dienophile, *anti* to R^2, is observed. Finally, the results found for (*E*,*E*)-2-sulfinyldienols (Scheme 6) are likely to be a reflection of the conformational equilibrium about the carbon–sulfur bond. Nevertheless, for this dienophile both nonconcerted and stepwise mechanisms have been proposed that could explain the low selectivity found.[20] For diene **5d** we also assumed that a conformational change around the C–S bond similar to that proposed for **3d** was occurring. This meant that the C–S bond was more constrained due to C3 substitution, which justified the selectivity enhancement observed with respect to **5a**.

Conclusion

Hydroxy-2- and -3-sulfinyldienes display highly π-face selective Diels–Alder cycloadditions with various dienophiles generating densely functionalized cycloadducts. Additional-



Scheme 6. Stereochemical rationalization for (*Z*,*E*)-sulfinyl and -sulfonyldienes.

ly, for 2-sulfinyldienes a reversal of π-facial selectivity is found, relative to related sulfonyldienes, demonstrating that the sulfinyl group is an extremely powerful element of stereocontrol for intermolecular Diels–Alder cycloadditions. We are currently addressing the application of these densely functionalized cycloadducts in synthesis, particularly focusing on subsequent regio- or stereocontrolled sulfur-directed transformations,[6,21] and taking advantage of the remarkable control of the π-facial selectivity of the cycloaddition by the oxidation state at sulfur.

Experimental Section

General: Reagents and solvents were handled by using standard syringe techniques. All reactions were carried out under an argon atmosphere. Hexane, toluene, and CH_2Cl_2 were distilled from CaH_2; THF and Et_2O from sodium. Crude products were purified by flash chromatography on 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on silica gel plates with detection by UV light, iodine, acidic vanillin solution, and/or 10% phosphomolybdic acid solution in ethanol. All reagents were commercial products. Throughout this section, the volume of solvents is reported in mL mmol^{-1} of starting material. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, 400, or 500 MHz (^{1}H) in $CDCl_3$ and with the residual solvent signal as an internal reference ($CDCl_3$, $\delta = 7.24$ and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Melting points are uncorrected. Optical rotations were measured at 20 °C using a sodium lamp and in $CHCl_3$. Low-resolution mass spectra were recorded using the electronic impact technique (EI) with an ionization energy of 70 eV or using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes.

General procedure for the cycloadditions between hydroxy sulfinyl/sulfonyldienes and dienophiles excluding *N*-phenyltriazolinedione (PTAD): The dienophile (1–2.3 equiv) was added to a solution of hydroxydiene (1.0 equiv) in toluene (10–15 mL mmol^{-1}) at RT. Subsequently, the mixture was stirred at RT until all of the starting material had disappeared (determined by TLC analysis or ^{1}H NMR spectroscopic analysis); the solvent was then removed under reduced pressure and the crude product was purified by recrystallization or by column chromatography on silica gel by using the appropriate mixture of solvents.

General procedure for the cycloadditions between hydroxy sulfinyl/sulfonyldienes and *N*-phenyltriazolinedione (PTAD): A pre-cooled solution of *N*-phenyltriazolinedione (PTAD) (1.5–2.2 equiv) in CH_2Cl_2 (10 mL mmol^{-1} of PTAD) was added by syringe to a solution of hydroxy diene (1.0 equiv) in CH_2Cl_2 (10 mL mmol^{-1}) at −78 °C. The mixture was then rapidly warmed to 0 °C whilst stirring. Once all of the starting material had disappeared from the reaction mixture (determined by TLC analysis) the solvent was removed under reduced pressure and the crude product was purified by recrystallization or by column chromatography on silica gel using the appropriate mixture of solvents.

(+)-(5*S*,8*S*,*S*$_S$)-5-Butyl-8-hydroxymethyl-2-phenyl-6-(*p*-tolylsulfinyl)-2*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(5*H*,8*H*)-dione (11): Following the general procedure cycloadduct **11** was obtained after 2 h from diene **1a**[8] (10 mg, 0.036 mmol, 1.0 equiv) and PTAD (10 mg, 0.054 mmol, 1.5 equiv) in CH_2Cl_2 (0.4 mL). Purification by chromatography (30–80% EtOAc/hexane) afforded **11** (14 mg, 0.031 mmol, 86%) as a white solid that was recrystallized from EtOAc/hexane. $R_f = 0.31$ (80% EtOAc/hexane); m.p. 90–92 °C; $[\alpha]_D^{20} = +104.3$ ($c = 0.54$ in acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.1$ Hz, 3H), 1.17–1.38 (m, 4H), 1.71 (m, 1H), 1.95 (m, 1H), 2.41 (s, 3H), 3.97 (ddd, $J = 12.0$, 6.3, 2.7 Hz, 1H), 4.14 (ddd, $J = 12.0$, 10.0, 2.7 Hz, 1H), 4.24 (dd, $J = 10.0$, 2.6 Hz, 1H), 4.26 (td, $J = 5.1$, 1.9 Hz, 1H), 4.65 (m, 1H), 6.73 (dd, $J = 2.8$, 0.8 Hz, 1H), 7.32–7.48 (m, 7H), 7.53 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.7$, 21.6, 22.4, 27.0, 32.8, 52.0, 60.9, 64.8, 122.9, 125.4 (2C), 125.9 (2C), 128.6, 129.2 (2C), 130.6, 130.8 (2C), 137.9, 143.7, 145.2, 149.7, 154.1 ppm; IR (KBr): $\tilde{\nu} = 3421$, 3043, 2957, 2927, 2862, 1769, 1711, 1503, 1421, 1298, 1136, 1052, 811, 766 cm^{-1}; MS (ES): *m/z* (%): 929 [2*M*+Na]$^+$, 907 [2*M*+H]$^+$, 476 [*M*+Na]$^+$, 454 [*M*+H]$^+$ (100); elemental analysis calcd (%) for $C_{24}H_{27}N_3O_4S$ (453.5): C 63.56, H 6.00, N 9.26, S 7.07; found: C 63.62, H 6.14, N 9.18, S 7.16.

(−)-(3a*R*,4*S*,7*S*,7a*R*,*S*$_S$)-4-[(1*S*)-Hydroxypentyl]-7-propyl-2-phenyl-5-(*p*-tolylsulfinyl)-1,3,3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione (18a): Following the general procedure cycloadduct **18a** was obtained after five days from diene **3a**[7] (38 mg, 0.12 mmol, 1.0 equiv) and NPM (63 mg, 0.36 mmol, 1.5 equiv) in toluene (1.5 mL). The product was obtained as a white solid (42 mg, 0.085 mmol, 71%) after recrystallization (EtOAc/hexane). In a related experiment cycloadduct **18a** was obtained as a single isomer from diene **3a** (10 mg, 0.031 mmol) and NPM (8 mg, 0.046 mmol, 1.5 equiv) in MeOH (1 mL). The yield was not determined. $R_f = 0.20$ (30% EtOAc/hexane); m.p. 180–182 °C; $[\alpha]_D^{20} = -92.0$ ($c = 0.65$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.2$ Hz, 3H), 1.02 (t, $J = 7.0$ Hz, 3H), 1.21–1.61 (m, 7H), 1.73 (m, 1H), 1.91 (m, 1H), 2.07 (m, 1H), 2.13 (s, 3H), 2.53 (m, 1H), 2.77 (m, 1H), 3.28 (dd, $J = 9.0$, 7.6 Hz, 1H), 3.43 (dd, $J = 9.1$, 5.2 Hz, 1H), 4.38 (m, 1H), 5.25 (dd, $J = 3.3$, 1.3 Hz, 1H), 6.75 (d, $J = 7.9$ Hz, 2H), 6.87 (dd, $J = 3.7$, 2.4 Hz, 1H), 7.21 (m, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.38 (m, 1H), 7.45 ppm (t, $J = 7.3$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.9$, 14.1, 21.2, 21.4, 22.7, 27.2, 32.7, 34.1, 38.3, 42.9, 43.3, 49.4, 67.1, 124.5 (2C), 125.8 (2C), 128.1, 128.7 (2C), 130.0 (2C), 138.0, 141.4, 143.6 (2C), 147.6, 174.4, 175.0 ppm; IR (KBr): $\tilde{\nu} = 3480$, 3320, 2960, 2940, 2860, 1710, 1600, 1500, 1455, 1370, 1330, 1180, 1140, 1120, 1080, 1030, 1015, 960, 940, 810, 750, 690, 625 cm^{-1}; MS (EI): *m/z* (%): 494 [*M*+H]$^+$, 476, 392, 348, 268, 217, 174, 139, 123, 91 (100), 77, 55, 41; elemental analysis calcd (%) for $C_{29}H_{35}NO_4S$ (493.7): C 70.56, H 7.15, N 2.84, S 6.50; found: C 70.65, H 7.06, N 2.93, S 6.58.

(−)-(1*S*,3a*R*,4*R*,5*S*,7a*S*,*S*$_S$)-1-Butyl-3-oxo-5-propyl-7-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-*N*-phenylcarboxamide (19a) and (−)-(1*S*,4*S*,5*S*,8*S*,9*R*,*S*$_S$)-4-butyl-3-oxa-8-propyl-6-(*p*-tolylsulfinyl)bicyclo-[3.3.1]non-6-en-2-one-9-*N*-phenylcarboxamide (20a): Following the general procedure regioisomeric lactones **19a** and **20a** were obtained after five days from diene **3a**[7] (38 mg, 0.12 mmol, 1.0 equiv) and NPM (63 mg, 0.36 mmol, 1.5 equiv) in toluene (1.5 mL). Purification was achieved by slow chromatography (5–50% EtOAc/hexane) and recrystallization (MeOH) producing a 37:63 mixture of the regioisomeric lactones **19a** (18 mg, 0.036 mmol) and **20a** (30 mg, 0.061 mmol) as white solids

(81% combined yield). In a related experiment, lactone **19a** (10 mg, 0.020 mmol) was dissolved in CH_2Cl_2 (2 mL, 100 mL mmol^{-1}), and silica gel (430 mg, 2 g mmol^{-1}) was added. The reaction mixture was stirred at RT and monitored by TLC (5 days). After this time, the silica gel was removed by filtration with EtOAc to yield a 25:75 mixture (determined by ^{1}H NMR spectroscopic analysis) of **19a** and **20a** (90%). A similar mixture of lactones was obtained from the treatment of cycloadduct **18a** with silica gel.

Data for 19a: R_f=0.25 (50% EtOAc/hexane); m.p. 182–183 °C; $[\alpha]_D^{20}$=−12.0 (c=0.52 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, J=7.1 Hz, 3H), 0.91 (t, J=7.0 Hz, 3H), 1.31–1.72 (m, 9H), 1.87 (m, 1H), 2.40 (s, 3H), 2.80 (m, 1H), 2.85 (t, J=4.9 Hz, 1H), 2.95 (m, 1H), 3.40 (dd, J=8.9, 4.5 Hz, 1H), 4.44 (m, 1H), 7.09 (t, J=7.4 Hz, 1H), 7.28–7.33 (m, 4H), 7.36 (d, J=5.1 Hz, 1H), 7.45 (d, J=8.2 Hz, 2H), 7.55 (d, J=7.5 Hz, 2H), 10.15 ppm (brs, 1H); NOE between H-1/H-7a: 11.5%, between H-3a/H-7a: 11.0%, between H-3a/H-4: 11.0%; ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.8, 14.0, 21.3, 21.5, 22.3, 29.0, 33.4, 33.5, 38.4, 40.6, 42.0, 47.6, 82.5, 120.1 (2C), 124.5, 126.1 (2C), 128.9 (2C), 130.6 (2C), 136.4, 138.0, 139.4, 139.7, 143.3, 168.9, 178.9 ppm; IR (CCl_4): $\tilde{\nu}$= 3300, 3150, 2970, 2940, 2880, 1750, 1680, 1600, 1550, 1500, 1490, 1450, 1200, 1080, 1050, 1020 cm^{-1}; MS (EI): m/z (%): 493 $[M]^+$, 476, 444, 391, 354, 285, 243, 217, 174, 139, 123, 93, 91 (100), 77, 41; elemental analysis calcd (%) for $C_{29}H_{35}NO_4S$ (493.7): C 70.56, H 7.15, N 2.84, S 6.50; found: C 70.49, H 7.07, N 2.95, S 6.40.

Data for 20a: R_f=0.17 (50% EtOAc/hexane); m.p. 183–185 °C; $[\alpha]_D^{20}$=−66.8 (c=1.84 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85 (t, J=6.9 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H), 1.20–1.69 (m, 10H), 2.33 (brs, 1H), 2.44 (s, 3H), 2.56 (brs, 1H), 2.68 (m, 1H), 3.12 (d, J=6.0 Hz, 1H), 4.37 (tt, J=8.5, 3.1 Hz, 1H), 6.89 (d, J=2.5 Hz, 1H), 7.10 (t, J=7.3 Hz, 1H), 7.16 (brs, 1H), 7.28–7.39 (m, 6H), 7.55 ppm (d, J=8.1 Hz, 2H); NOE between H-1/H-9: 4.4%, between H-1/H-8: 8.9%, between H-4/H-5: 10.4%, between H-5/H-9: 3.0%, between H-5/H-4: 13.7%; ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 20.4, 21.6, 22.4, 27.9, 29.7, 34.0, 34.1, 35.0, 41.2, 41.4, 47.9, 79.0, 119.8 (2C), 125.1, 126.4 (2C), 129.1 (2C), 130.4 (2C), 133.9, 136.9, 139.3, 140.7, 143.1, 168.8 ppm (2C); IR (CCl_4): $\tilde{\nu}$= 3340, 3320, 2960, 2940, 2880, 1740, 1680, 1610, 1550, 1500, 1450, 1385, 1320, 1260, 1210, 1180, 1080, 1040, 810, 760, 690 cm^{-1}; MS (EI): m/z (%): 494 $[M+H]^+$, 477, 476 (100), 392, 348, 268, 217, 174, 123, 93, 91, 77, 65, 57, 41; elemental analysis calcd (%) for $C_{29}H_{35}NO_4S$ (493.7): C 70.56, H 7.15, N 2.84, S 6.50; found: C 70.45, H 7.05, N 2.75, S 6.59.

(+)-(1*S*,3a*S*,4*S*,5*R*,7a*R*)-1-Butyl-3-oxo-5-propyl-7-(*p*-tolylsulfonyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-*N*-phenylcarboxamide (25a): Following the general procedure amide **25a** was obtained after five days from diene **4a**[7] (12 mg, 0.035 mmol, 1.0 equiv) and NPM (9 mg, 0.053 mmol, 1.5 equiv) in toluene (0.5 mL). Recrystallization of the crude (EtOAc) produced amide **25a** as a white solid (12 mg, 0.023 mmol, 66%). This product was subjected to chromatography on silica gel (5–50% EtOAc/hexane) uneventfully. In a separate experiment the reaction described above was monitored by ^{1}H NMR spectroscopy, and after 24 h was found to show a 60:40 mixture of **24a** and **25a** with 47% conversion.

Partial data for 24a (from the crude reaction mixture after 24 h): ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.41 (s, 3H), 3.31 (dd, J=9.0, 6.8 Hz, 1H), 3.64 (d, J=4.1 Hz, 1H), 3.80 (dd, J=8.9, 6.0 Hz, 1H), 4.54 (m, 1H), 6.96 (dd, J=4.7, 2.1 Hz, 1H).

Data for 25a: R_f=0.38 (50% EtOAc/hexane); m.p. 190–192 °C; $[\alpha]_D^{20}$=101.5 (c=0.98 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, J=6.9 Hz, 6H), 1.19–1.78 (m, 9H), 1.80 (m, 1H), 2.44 (s, 3H), 2.87–2.88 (m, 2H), 3.10 (brd, J=9.3 Hz, 1H), 3.44 (dd, J=9.3, 4.7 Hz, 1H), 4.86 (m, 1H), 7.10 (t, J=7.3 Hz, 1H), 7.27–7.36 (m, 5H), 7.52 (d, J=8.3 Hz, 2H), 7.77 (d, J=8.3 Hz, 2H), 9.97 ppm (brs, 1H); NOE between H-1/H-7a: 1.5%, between H-3a/H-7a: 7.4%, between H-3a/H-4: 6.6%; ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 21.1, 21.6, 22.2, 27.3, 33.3, 35.4 (2C), 38.2, 39.6, 40.9, 46.5, 83.5, 120.3 (2C), 124.7, 127.7 (2C), 129.0 (2C), 130.1 (2C), 136.1, 136.6, 137.8, 144.9, 145.7, 168.7, 178.5 ppm; IR (KBr): $\tilde{\nu}$= 3440, 3380, 2960, 2860, 1760, 1680, 1600, 1530, 1500, 1440, 1310, 1260, 1140, 1090, 1030, 800, 760, 690, 670 cm^{-1}; MS (EI): m/z (%): 510 $[M+1]^+$, 354, 233, 155, 139, 117, 91 (100), 93, 77, 55, 41; elemental analysis calcd (%) for $C_{29}H_{35}NO_5S$ (509.7): C 68.34, H 6.92, N 2.75, S 6.29; found: C 68.48, H 6.84, N 2.67, S 6.17.

General procedure for oxidation with *m*-CPBA: *m*-CPBA (55 or 70% by weight, 1.5–1.8 equiv) was added to a solution of sulfoxide (1.0 equiv) in CH_2Cl_2 (15 mL mmol^{-1}) at −78 °C. The reaction mixture was stirred and gradually warmed to RT. Once the starting material had disappeared (determined by TLC analysis) the mixture was quenched with a saturated solution of $Na_2S_2O_4$ (4 mL mmol^{-1}) and diluted with EtOAc, and the layers were separated. The organic phase was washed three times with $NaHCO_3$ solution (5%, 50 mL mmol^{-1}), once with a saturated solution of NaCl (10 mL mmol^{-1}), dried over anhydrous $MgSO_4$, and concentrated to give the crude product, which was then purified by column chromatography or by recrystallization.

(−)-(3a*R*,4*S*,7*S*,7a*R*)-4-[(1*S*)-Hydroxypentyl]-5-(*p*-tolylsulfonyl)-7-propyl-2-phenyl-1,3,3a,4,7,7a-tetrahydro-*2H*-isoindole-1,3-dione (36a): Following the general procedure sulfonyl cycloadduct **36a** was obtained after 2 h 30 min from cycloadduct **18a** (27 mg, 0.054 mmol, 1.0 equiv) and *m*-CPBA (25 mg, 0.081 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). Recrystallization (EtOAc) produced the sulfonyl cycloadduct **36a** as a white solid (18 mg, 0.035 mmol, 65%). This compound was unstable in $CDCl_3$ and evolved into a 50:50 mixture of the corresponding lactones after three days. R_f=0.18 (30% EtOAc/hexane); m.p. 152–160 °C; $[\alpha]_D^{20}$=−65.6 (c=0.67 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (t, J=7.3 Hz, 3H), 0.97 (t, J=7.2 Hz, 3H), 1.21–1.60 (m, 6H), 1.78–1.89 (m, 1H), 1.96–2.06 (m, 3H), 2.23 (s, 3H), 2.45 (m, 1H), 2.73 (m, 1H), 3.28 (dd, J=8.9, 7.3 Hz, 1H), 3.49 (dd, J=9.0, 5.0 Hz, 1H), 4.37 (brs, 1H), 4.55 (m, 1H), 6.90 (dd, J=4.4, 2.2 Hz, 1H), 6.96 (d, J=7.9 Hz, 2H), 7.14 (dt, J=7.0, 1.6 Hz, 2H), 7.44–7.46 (m, 3H), 7.57 ppm (d, J=8.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 14.1, 21.3, 21.6, 22.7, 27.3, 32.5, 34.3, 35.3, 38.1, 43.1, 48.0, 67.4, 125.9 (2C), 128.2 (2C), 128.3, 128.8 (2C), 129.9, 130.2, 131.6, 144.5, 144.9, 146.3, 161.2 ppm (2C); MS (ES): m/z (%): 1041 $[2M+Na]^+$, 1019 $[2M+H]$, 532 $[M+Na]^+$, 510 $[M+H]^+$ (100).

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