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Enantiopure 2-sulfinylbuta-1,3-dienes in Diels–Alder cycloadditions: a stereoselective approach to an azasteroidal skeleton

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Abstract—The synthesis of enantiopure 4-[1-(alkylsulfinyl)vinyl]-1,2-dihydronaphthalenes and their Diels–Alder reactions are described. Cycloadditions with *N*-phenylmaleimide occur under thermal conditions, very slowly but with notable stereoselection, giving in each case just one of the two *endo* adducts in high yield. The obtained 16-azasteroid derivatives undergo chiral auxiliary removal in the presence of TMSI. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Steroids and heterosteroids are regarded by synthetic chemists as attractive target molecules because of their important bioactivities and the effect that even minor structural modifications of their skeleton can play on their biological role. For instance, the incorporation of a nitrogen atom in the steroidal system helps the formation of stable substrate–enzyme complexes which are the foundations of antibacterial, antifungal and many other kind of activities shown by azasteroids, including the inhibition of steroid biosynthesis.[1]

In the development of our research, directed towards the synthesis of enantiopure sulfinyldienes[2–4] and their use in stereoselective homo and hetero Diels–Alder (DA) reactions, we have planned the synthesis of enantiopure sulfinyldienes **1**–**4** (Scheme 1), whose DA reactions with the appropriate dienophiles would give a straightforward approach to estrone-like compounds.

Dienes **1**–**4** resemble 1,2-dihydro-7-methoxy-4-vinylnaphthalene (Dane's diene) which was often been used for the preparation of steroid derivatives via DA reactions. Dane's diene has been reacted with several achiral dienophiles,[5] some enantiopure sulfinyldienophiles,[6,7] and in the presence of chiral Lewis acids,[5] but, to the best of our knowledge, this is the first report of enantiomerically pure dienes involved in a direct and asymmetric DA approach to steroidal skeletons. The stereogenic sulfoxide group, linked in position 2 of the conjugate diene systems of dihydro(vinyl)naphthalenes **1**–**4**, represents an efficient differentiating element[2–4] for the stereoselective synthesis of cycloadducts which can be subsequently transformed into enantiopure compounds with steroidal and azasteroidal skeletons.

2. Results and discussion

Dienes **1**–**4** have been obtained following a well-assessed synthetic strategy[2–4] whose crucial step is the addition of an enantiopure sulfenic acid (Scheme 1) to the triple bond of an opportune enyne. The sulfenic acid precursors **5**[2] and **6**[3] were thermolyzed in boiling mixed xylenes or toluene, respectively, in the presence of the trapping enyne **7a** or **7b**. The syntheses of 1,2-dihydro-4-ethynylnaphthalene **7a**[8] and 1,2-dihydro-4-ethynyl-7-methoxynaphthalene **7b**[9] have already been reported in the literature.

The addition of sulfenic acid/enyne was completely regioselective in each case, giving two sulfinyldienes,

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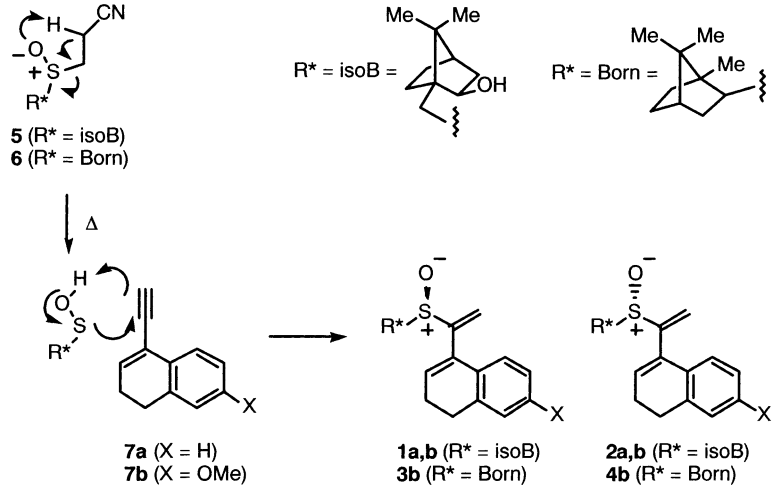
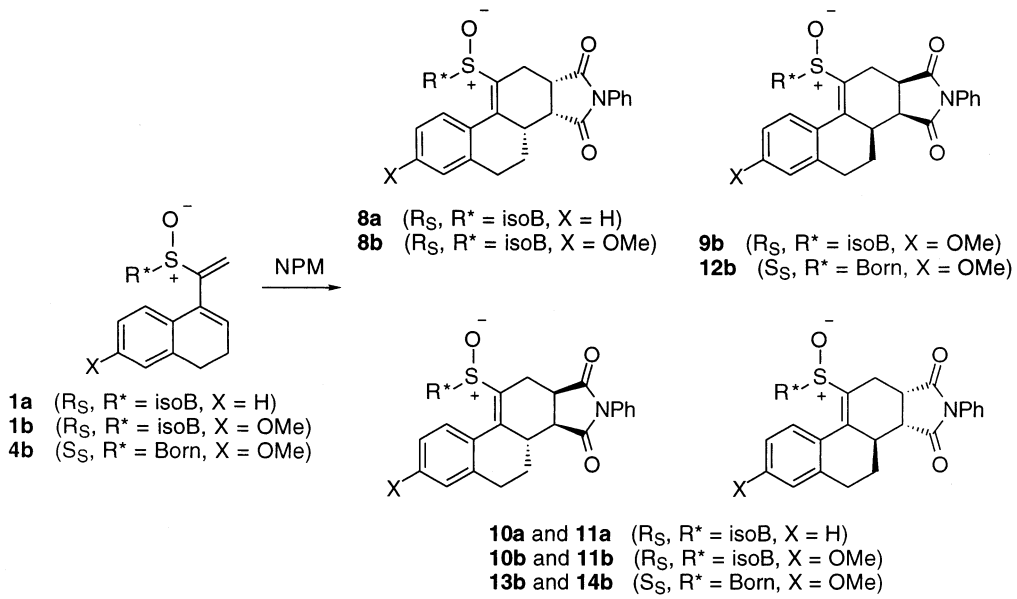


Scheme 1.

epimeric at the sulfur atom, in good total yield and in different amounts. Dienes **1a** and **2a**, **1b** and **2b** were obtained in a 3:1 ratio from the thermolysis of sulfoxides **5** in the presence of enynes **7a** and **7b**, respectively, whereas thermolysis of sulfoxides **6** in the presence of **7b** led to the formation of dienes **3b** and **4b** in a 1:2 ratio. All the epimeric mixtures of sulfinyldienes can be easily separated by column chromatography. Dienes **1**–**4** are stable compounds. Their absolute configurations at sulfur were assigned on the basis of the previously observed stereochemical outcomes of sulfenic acid/enyne addition reactions.[2,3]

The major products of our synthetic procedure, dienes **1a**, **1b** and **4b** have been submitted to DA cycloaddition (Scheme 2) with *N*-phenylmaleimide (NPM) which is a good, very reactive and *endo*-directing dienophile; it also gave very good results in terms of facial diastereoselectivity in cycloadditions with other sulfinyldienes.[4,10] Moreover, the stereoselective cycloaddition of dienes **1**–**4** with NPM would lead to enantiopure cycloadducts showing the 16-azasteroid skeleton. On the basis of present knowledge 16-azasteroids do not exist in nature, but they have been synthesized previously in racemic form and biologically tested.[11]

The conditions and results of the performed DA reactions are reported in Table 1. Diastereomeric cycloadducts were obtained in very good total yields and are easily separable by column chromatography. Very long reaction times show the low DA reactivity of sulfinyldienes **1**–**4**, even if the presence of the methoxy substituent appears to significantly increase the reaction rate. Almost all cycloadducts were isolated in solid form and the crystallization of adduct **12b** from ethyl acetate afforded very good crystals, suitable for X-ray analysis. The diffractometry results (Fig. 1) show the (3a*S*,3b*R*,11a*R*) configuration of the new-generated stereogenic centers and confirm the (*S*) configuration previously assigned to the sulfoxide function. The struc-



Scheme 2.

Table 1. Cycloadditions of dienes **1a**, **1b**, **4b** to NPM in refluxing CH_2Cl_2

Entry	Diene	Time (days)	Total yield (%)	Adducts		
				endo	*exo*	[Ratio]
1	**1a**	40	95	**8a**:	**10a** and **11a**	[42:29:29]
2	**1b**	18	93	**8b**:**9b**:	**10b** and **11b**	[52:5:23 (less mobile):20 (more mobile)]
3	**4b**	26	95	**12b**:	**13b** and **14b**	[67:19 (less mobile):14 (more mobile)]

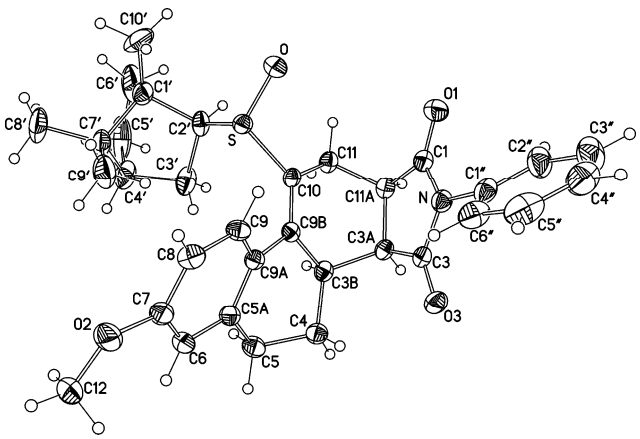


Figure 1. ORTEP view of adduct **12b**.

tures of the adducts shown in Scheme 2 were assigned moving from these X-ray data and taking advantage of several NMR parameters which allow discrimination of the *endo*- and *exo*-adducts. Particularly meaningful are the ^{1}H NMR resonances in the range 4–3 ppm, where H_A-11 resonates as a doublet of doublets, H-11a is seen as a double doublet of doublets, and H-3a appears as a doublet of doublets in the *endo* adducts and a *pseudo*-triplet in the *exo* adducts (see Table 2).

Some comments have to be devoted to the stereochemical outcome of the DA reactions under study. It is evident (Table 1) that *endo*/*exo* diastereoselectivity was low in all cases, and for diene **1a** quite in favor of the usually unfavored *exo*-isomers. Very good diastereofacial selectivity was observed for the *endo* approach, while both *exo*-isomers were obtained in almost equal amounts. A tentative rationalization of these results is based on the high steric requirements of both diene and dienophile, such that the less sterically congested *exo* approaches occur in high percentage but without significant facial discrimination, while the *endo* approach, which is much more sterically demanding, requires almost complete facial selection. This last aspect is potentially very useful from a synthetic point of view. We suggest that the formation of the *endo* adduct **12b** comes from the NPM approach to the *Si* face of (S_S)-diene **4b** in its **B** conformation (Fig. 2). Concordantly (R_S)-dienes **1a** and **1b** undergo *endo* cycloaddition mainly from their *Re* face in conformation **A**. Previously we had observed preferential *endo* approach to the opposite face of analogous sulfinyldienes {the 1*Re*,2*Re*,3*Si* face for (R_S,*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-methoxybuta-1,3-diene[2] and the 1*Si*,2*Si*,3*Re* face for (S_S,*E*)-3-[(1*S*-*exo*)-2-bornylsulfinyl]-1-methoxybuta-1,3-diene[3]}, but the conformational preferences proposed for these cases (the same as **C** and **D**) can be overcome here by electrostatic repulsion between the sulfinyl oxygen and the π-system of the fused benzene ring.

With the aim of getting experimental support for the considerations reported above, we oxidized diene **4b** to 4-{1-[(1*S*-*exo*)-2-bornylsulfonyl]vinyl}-1,2-dihydro-7-methoxynaphthalene following our usual procedure with *m*-CPBA,[2] and submitted this sulfone, without isolation,[†] to DA cycloaddition with NPM. We followed the DA procedure reported in the experimental part (Section 4.3) for 8 days, and then the reaction mixture, dissolved in 1,2-dichloroethane, was maintained at reflux for a further 8 days, but unreacted diene and dienophile were recovered. This failure of the sulfone cycloaddition can be ascribed to its concurrent steric and electronic requirements which prevent fruitful DA approaches with NPM in the adopted reaction conditions.

Cycloadduct **8b,** which is the major *endo* product of NPM cycloaddition to diene **1b**, was submitted to treatment with iodotrimethylsilane (TMSI) in order to remove the chiral auxiliary.[12] The reaction, followed by ^{1}H NMR experiments, required a 2.5:1 molar ratio of TMSI/substrate to be completed and afforded compound **15** as a useful intermediate in the synthesis

Table 2. Selected ^{1}H NMR parameters of compounds **8**–**14** [chemical shifts in δ (ppm) and coupling constants J in Hz]

Cycloadducts	δ H-3a	δ H_A-11	δ H-11a	$J_{3a,3b}$	$J_{3a,11a}$	$J_{11A,11a}$	$J_{11A,11B}$	$J_{11a,11B}$
endo	3.4	4.0–3.7	3.6–3.5	5.8–5.3	8.9–8.2	1.9–1.3	17.1–14.0	6.9–6.0
exo	3.0–2.8		3.2–3.1	10.7–10.1	10.7–9.8	7.1–6.4		12.3–10.7

[†] Selected ^{1}H NMR absorptions of 4-{1-[(1*S*-*exo*)-2-bornylsulfonyl]vinyl}-1,2-dihydro-7-methoxynaphthalene: δ_H 7.17 (d, $J_{5,6}$ 9.1, H-5), 6.73 (br s, H-8), 6.71 (dd, $J_{6,8}$ 2.8, H-6), 6.53 and 5.91 (two s, H_2-2″), 6.26 (t, $J_{2,3}$ 4.7, H-3), 3.80 (s, OMe), 3.16 (br t, $J_{2',3'}$ 8.7, H-2′), 1.23 (s, H_3-10′), 1.10 (s, H_3-8′), 0.85 (s, H_3-9′).

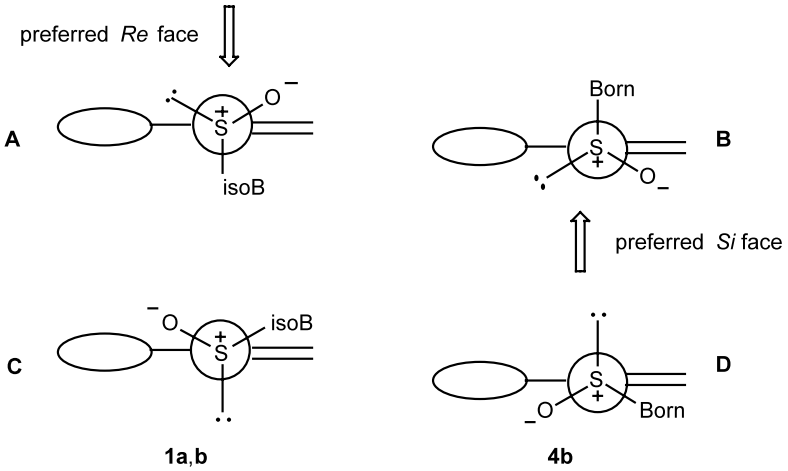
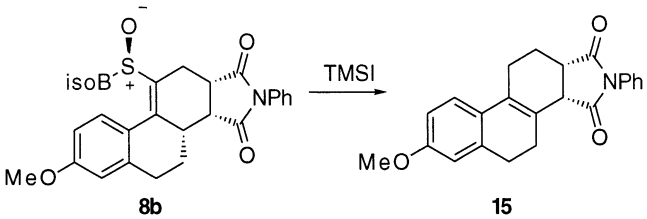


Figure 2. Preferred conformations **A** [(R_S)-dienes **1a** and **1b**] and **B** [(S_S)-diene **4b**], compared to their less populated conformations **C** and **D**, respectively, in the DA *endo* approach with NPM.



Scheme 3.

of modified 16-azasteroids (Scheme 3). (3a*S*,11a*S*)-7-Methoxy-2,3,3a,4,5,10,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione **15** may be the thermodynamically favored product of reduction and dehydration of an intermediate carbonyl compound transiently formed by TMSI-promoted conversion of α,β-unsaturated sulfoxide **8b**.[12]

3. Conclusions

In conclusion, we have constructed enantiopure 16-azasteroid derivatives **8–14** in a few simple steps. DA reactions of sulfinyldienes **1–4** with NPM occur under thermal conditions very slowly but with notable stereoselection, giving in each case just one of the two *endo* adducts in high yield. Further transformation of the major cycloadducts led to the formation of modified azasteroids. These results open the way for the setting up of stereocontrolled syntheses of further estrone-like compounds and corroborate the role that sulfinyldienes can fulfil within the synthetic chemistry.[2–4,10]

4. Experimental

Solvents were purified according to standard procedures. All reactions were monitored by TLC on commercially available precoated plates (Aldrich silica gel 60 F 254) and the products were visualized with vanillin [1 g dissolved in MeOH (60 mL) and conc. H_2SO_4 (0.6 mL)]. Silica gel used for column chromatography was Aldrich 60. Melting points were recorded on a microscopic apparatus and are uncorrected. Mass spectra were measured by Electron Impact (EI, 70 eV) or Fast Atom Bombardment (FAB, *m*-nitrobenzyl alcohol as matrix) with a Finnigan MAT 90 instrument. Optical rotations were measured for $CHCl_3$ solutions on a Jasco P-1030 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$ solutions with $SiMe_4$ as internal standard: *J* values are given in Hz; the attributions are supported by Attached Proton Test (APT) and homodecoupling experiments; proton and carbon indexes, marked with (′), pertain to isoborneol or bornyl moieties; the symbol (″) identifies vinyl nuclei in dienes **1–4** and phenyl nuclei in compounds **8–15**. Cycloadduct ratios were established by integration of well-separated proton signals of the diastereoisomers in the crude adduct mixtures and are listed in Table 1.

4.1. 1,2-Dihydro-4-{1-[(1*S*)-isoborneol-10-sulfinyl]-vinyl}naphthalenes 1 and 2

A solution of the sulfoxides **5** (sulfur epimeric mixture, 0.35 g, 1.37 mmol) dissolved in mixed xylenes (1 mL) was added to a solution of enyne **7** (4.11 mmol) in mixed xylenes (1.2 mL). The reaction mixture was maintained at 130°C in oil bath until the reaction appeared complete by TLC (after about 90 min). The solvent was then removed under reduced pressure and the crude reaction mixture separated in its components by column chromatography. When the acceptor of (1*S*)-isoborneol-10-sulfenic acid was 1,2-dihydro-4-ethynylnaphthalene **7a**,[8] two dienes were obtained by elution with light petroleum increasing the amount of EtOAc, from 5 up to 20%. **(R_S)-1,2-Dihydro-4-{1-[(1*S*)-isoborneol-10-sulfinyl]vinyl}naphthalene 1a** was first eluted and was isolated as a colorless oil, 45% yield, $[\alpha]_D^{23}$ +19.4 (*c* 0.0083); ^1H NMR: δ_H 7.3–7.2 (m, ArH), 6.20 (dd, $J_{2,3}$ 5.7 and 3.7, H-3), 6.20 and 5.92 (two s, H_2-2″), 4.12 (dd, $J_{2',3'}$ 8.1 and 4.4, H-2′), 2.97 and 2.52 (AB system, $J_{10'A,10'B}$ 13.4, H_2-10′), 2.9–2.2 (m, H_2-1,2), 1.8–0.8 (m, H_2-3′,5′,6′, H-4′), 1.02 (s, H_3-8′), 0.64 (s, H_3-9′); ^{13}C NMR: δ_C 151.56 (C-1″), 136.21

(C-4), 132.78 and 132.27 (C-4a,8a), 130.19 (C-8), 128.04 (C-7), 127,90 (C-3), 126.69 (C-5), 124.61 (C-6), 118.37 (C-2″), 76.94 (C-2′), 54.08 (C-10′), 51.31 (C-1′), 48.06 (C-7′), 45.06 (C-4′), 38.40 (C-3′), 30.79 and 27.02 (C-5′,6′), 27.66 and 23.09 (C-1,2), 20.29 and 19.79 (C-8′,9′); MS/FAB: *m/z* (%) 357 (M+1, 67), 339 (17), 155 (51), 135 (100). Anal. calcd for $C_{22}H_{28}O_2S$: C, 74.12; H, 7.92. Found: C, 74.08; H, 7.87%. The next eluting band afforded **(S_S)-1,2-dihydro-4-{1-[(1*S*)-isoborneol-10-sulfinyl]vinyl}naphthalene 2a** isolated as a colorless oil, 15% yield, $[\alpha]_D^{25}$ −53.0 (*c* 0.0101); ^{1}H NMR: δ_H 7.3–7.2 (m, ArH), 6.27 (dd, $J_{2,3}$ 6.1 and 3.3, H-3), 6.19 and 5.97 (two s, H_2-2″), 3.95 (dd, $J_{2',3'}$ 6.1 and 5.3, H-2′), 3.24 and 2.37 (AB system, $J_{10'A,10'B}$ 13.8, H_2-10′), 2.8–2.2 (m, H_2-1,2), 1.8–0.8 (m, H_2-3′,5′,6′, H-4′), 0.94 (s, H_3-8′), 0.73 (s, H_3-9′). From the thermolysis of **5** in the presence of 1,2-dihydro-4-ethynyl-7-methoxynaphthalene **7b**[9] the following products were obtained after chromatographic separation performed as reported above. The more mobile epimer was **(R_S)-1,2-dihydro-4-{1-[(1S)-isoborneol-10-sulfinyl]vinyl}-7-methoxynaphthalene 1b**, isolated as a yellow oil in 45% yield, $[\alpha]_D^{20}$ +2.8 (*c* 0.0066); ^{1}H NMR: δ_H 7.20 (d, $J_{5,6}$ 8.2, H-5), 6.75 (br s, H-8), 6.73 (dd, $J_{6,8}$ 2.7, H-6), 6.17 and 5.90 (two s, H_2-2″), 6.06 (dd, $J_{2,3}$ 6.0 and 3.6, H-3), 4.12 (m, H-2′), 3.82 (s, OMe), 2.96 and 2.54 (AB system, $J_{10'A,10'B}$ 13.3, H_2-10′), 2.8–2.2 (m, H_2-1,2), 1.9–1.0 (m, H_2-3′,5′,6′, H-4′), 1.03 (s, H_3-8′), 0.65 (s, H_3-9′); ^{13}C NMR: δ_C 159.28 (C-7), 151.83 (C-1″), 138.11 (C-4), 132.41 (C-8a), 127.46 (C-3), 125.97 (C-5), 125.29 (C-4a), 117.99 (C-2″), 114.22 (C-8), 111.05 (C-6), 76.94 (C-2′), 55.27 (OMe), 54.08 (C-10′), 51.31 (C-1′), 48.03 (C-7′), 45.06 (C-4′), 38.40 (C-3′), 30.80 and 27.02 (C-5′,6′), 28.20 and 23.04 (C-1,2), 20.30 and 19.80 (C-8′,9′); MS/FAB: *m/z* (%) 387 (M+1, 92), 369 (24), 233 (50), 201 (28), 185 (100). Anal. calcd for $C_{23}H_{30}O_3S$: C, 71.47; H, 7.82. Found: C, 71.40; H, 7.87%. Then **(S_S)-1,2-dihydro-4-{1-[(1S)-isoborneol-10-sulfinyl]vinyl}-7-methoxynaphthalene 2b** eluted and isolated as a yellow oil in 15% yield, $[\alpha]_D^{20}$ −24.8 (*c* 0.0042); ^{1}H NMR: δ_H 7.21 (d, $J_{5,6}$ 8.3, H-5), 6.72 (br s, H-8), 6.71 (dd, $J_{6,8}$ 2.6, H-6), 6.15 and 5.93 (two s, H_2-2″), 6.12 (dd, $J_{2,3}$ 6.2 and 3.3, H-3), 3.95 (m, H-2′), 3.80 (s, OMe), 3.25 and 2.35 (AB system, $J_{10'A,10'B}$ 13.7, H_2-10′), 2.8–2.2 (m, H_2-1,2), 1.8–1.0 (m, H_2-3′,5′,6′, H-4′), 0.95 (s, H_3-8′), 0.73 (s, H_3-9′); ^{13}C NMR: δ_C 159.26 (C-7), 152.51 (C-1″), 138.35 (C-4), 132.99 (C-8a), 127.62 (C-3), 126.26 (C-5), 125.11 (C-4a), 117.92 (C-2″), 114.09 (C-8), 111.02 (C-6), 76.82 (C-2′), 55.23 (OMe), 53.71 (C-10′), 51.37 (C-1′), 48.29 (C-7′), 44.68 (C-4′), 40.02 (C-3′), 31.51, 28.20, 27.30 and 22.96 (C-1,2,5′,6′), 20.31 and 20.11 (C-8′,9′); MS/FAB: *m/z* (%) 387 (M+1, 95), 369 (35), 233 (76), 185 (100).

4.2. 4-{1-[(1*S*-*exo*)-2-Bornylsulfinyl]vinyl}-1,2-dihydro-7-methoxynaphthalenes 3b and 4b

A solution of the sulfoxides **6** (sulfur epimeric mixture, 0.19 g, 0.8 mmol) in toluene (2 mL) were added to a solution of enyne **7b** (2.4 mmol) in toluene (1.3 mL). The reaction mixture was heated under reflux (110°C) in an oil bath until the reaction appeared complete by TLC (after about 90 min). The solvent was then removed under reduced pressure and the crude reaction mixture separated in its components by column chromatography, eluting with light petroleum containing increasing amount of EtOAc from 5% up to 20%. The **(R_S)-epimer 3b** was first eluted and was isolated as a yellow oil in 21% yield, $[\alpha]_D^{20}$ +5.9 (*c* 0.0122); ^{1}H NMR: δ_H 7.19 (d, $J_{5,6}$ 8.1, H-5), 6.73 (br s, H-8), 6.71 (dd, $J_{6,8}$ 2.6, H-6), 6.05 (dd, $J_{2,3}$ 5.8 and 3.6, H-3), 6.02 and 5.81 (two s, H_2-2″), 3.81 (s, OMe), 2.55 (dd, $J_{2',3'}$ 9.9 and 7.5, H-2′), 2.8–2.2 (m, H_2-1,2), 1.8–1.0 (m, H_2-3′,5′,6′, H-4′), 0.97 (s, H_3-8′), 0.89 (s, H_3-10′), 0.81 (s, H_3-9′); ^{13}C NMR: δ_C 159.07 (C-7), 151.64 (C-1″), 137.96 (C-4), 133.05 (C-8a), 127.37 (C-3), 126.03 (C-5), 125.53 (C-4a), 117.73 (C-2″), 113.97 (C-8), 110.89 (C-6), 66.77 (C-2′), 55.13 (OMe), 49.89 (C-1′), 46.71 (C-7′), 45.19 (C-4′), 39.21, 28.25, 27.29, 25.39 and 23.00 (C-1,2,3′,5′,6′), 20.31 and 19.48 (C-8′,9′), 13.21 (C-10′); MS/FAB: *m/z* (%): 371 (M+1, 8), 234 (10), 137 (100). Less mobile was the **(S_S)-epimer 4b**, isolated as a yellow oil in 43% yield, $[\alpha]_D^{20}$ +37.7 (*c* 0.0116); ^{1}H NMR: δ_H 7.28 (d, $J_{5,6}$ 7.9, H-5), 6.73 (br s, H-8), 6.72 (dd, $J_{6,8}$ 2.9, H-6), 6.20 (dd, $J_{2,3}$ 6.2 and 3.7, H-3), 6.18 and 5.88 (two s, H_2-2″), 3.81 (s, OMe), 2.63 (dd, $J_{2',3'}$ 9.3 and 6.5, H-2′), 2.8–2.2 (m, H_2-1,2), 1.8–1.0 (m, H_2-3′,5′,6′, H-4′), 1.24 (s, H_3-10′), 0.89 (s, H_3-8′), 0.84 (s, H_3-9′); ^{13}C NMR: δ_C 158.92 (C-7), 152.87 (C-1″), 138.50 (C-4), 134.35 (C-8a), 127.53 (C-3), 126.34 (C-5), 125.58 (C-4a), 119.52 (C-2″), 113.98 (C-8), 110.93 (C-6), 75.89 (C-2′), 55.21 (OMe), 50.21 (C-1′), 47.76 (C-7′), 45.02 (C-4′), 39.04 (C-3′), 32.13 and 27.02 (C-5′,6′), 28.13 and 23.04 (C-1,2), 20.08 and 19.49 (C-8′,9′), 13.88 (C-10′); MS/FAB: *m/z* (%): 371 (M+1, 12), 234 (10), 137 (100). Anal. calcd for $C_{23}H_{30}O_2S$: C, 74.55; H, 8.16. Found: C, 74.60; H, 8.10%.

4.3. General procedure for the DA cycloadditions of dienes 1a, 1b and 4b with NPM

A solution of diene (0.18 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added to NPM (190 mg, 1.1 mmol) dissolved in the same solvent (1.5 mL). The reaction mixture was stirred at 40°C under nitrogen until the diene was completely consumed, as verified by TLC monitoring (light petroleum/EtOAc 1:1). The solvent was removed under vacuum and the crude mixture was column chromatographed. Times and yields are shown in Table 1.

4.3.1. Cycloaddition of diene 1a. The elution of the chromatographic column with light petroleum containing increasing amount of EtOAc, from 10 up to 30%, afforded the following products, reported in order of raising retention times. Two *exo* cycloadducts **(3a*R**,3b*R**,11a*S**,R_S)-10-[(1*S*)-isoborneol-10-sulfinyl]-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-diones 10a** and **11a** were eluted first. The more mobile ***exo* adduct** was isolated as white crystals, mp 114–116°C, 27% yield; ^{1}H NMR: δ_H 7.5–6.8 (m, ArH), 4.13 (m, H-2′), 3.86 (dd, $J_{11A,11a}$ 6.4, $J_{11A,11B}$ 16.1, H_A-11), 3.66 and 2.62 (AB system, $J_{10'A,10'B}$ 13.1, H_2-10′), 3.21 (ddd, $J_{3a,11a}$ 9.8, $J_{11a,11B}$ 12.3, H-11a), 2.92 (t, $J_{3a,3b}$ 10.1, H-3a), 2.9–2.6 and 2.0–1.2 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.20 (s, H_3-8′), 0.88 (s, H_3-9′); ^{13}C NMR: δ_C 176.46 and 176.38 (C-1,3), 143.76 (C-10),

141.29 (C-9b), 136.86 (C-9a), 131.48 (C-1″), 130.53 and 129.50 (C-7,9), 129.29, 128.89 and 126.47 (C-2″-6″), 128.31 (C-6), 125.57 (C-8), 130.30 (C-5a), 77.00 (C-2′), 52.54 (C-10′), 51.74 (C-1′), 48.36 (C-7′), 45.57, 41.77 and 40.90 (C-3a,3b,11a), 45.13 (C-4′), 38.46 (C-3′), 31.08 and 27.02 (C-5′,6′), 29.91, 27.27 and 23.45 (C-4,5,11), 20.63 and 20.12 (C-8′,9′). The less mobile ***exo* adduct** was obtained as white crystals, mp 110–112°C, 27% yield; ^{1}H NMR: δ_H 7.5–6.9 (m, ArH), 4.11 (m, H-2′), 4.02 (dd, $J_{11A,11a}$ 7.1, $J_{11A,11B}$ 14.0, H_A-11), 3.54 and 2.57 (AB system, $J_{10'A,10'B}$ 13.2, H_2-10′), 3.17 (ddd, $J_{3a,11a}$ 9.9, $J_{11a,11B}$ 10.7, H-11a), 3.02 (t, $J_{3a,3b}$ 10.2, H-3a), 2.9–2.5 and 2.0–1.2 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.15 (s, H_3-8′), 0.86 (s, H_3-9′); ^{13}C NMR: δ_C 177.17 and 176.77 (C-1,3), 144.57 (C-10), 141.62 (C-9b), 136.85 (C-9a), 131.54 (C-1″), 130.89 (C-5a), 130.50 and 129.60 (C-7,9), 129.24, 128.80 and 126.47 (C-2″-6″), 127.68 (C-6), 125.45 (C-8), 76.66 (C-2′), 52.79 (C-10′), 51.65 (C-1′), 48.33 (C-7′), 45.06 (C-4′), 42.03, 40.86 and 38.68 (C-3a,3b,11a), 38.44 (C-3′), 31.01 and 27.18 (C-5′,6′), 27.24, 25.79 and 20.42 (C-4,5,11), 20.59 and 19.99 (C-8′,9′). Finally **(3a*R*,3b*S*,11a*S*,R_S)-10-[(1*S*)-isoborneol-10-sulfinyl]-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione 8a** was eluted as white crystals, mp 209–210°C, 40% yield; ^{1}H NMR: δ_H 7.8–6.7 (m, ArH), 4.04 (dd, $J_{2',3'}$ 8.1 and 4.2, H-2′), 4.00 (dd, $J_{11A,11a}$ 1.8, $J_{11A,11B}$ 17.1, H_A-11), 3.59 (ddd, $J_{3a,11a}$ 8.9, $J_{11a,11B}$ 6.9, H-11a), 3.44 (dd, $J_{3a,3b}$ 5.8, H-3a), 3.29 and 2.17 (AB system, $J_{10'A,10'B}$ 13.0, H_2-10′), 3.0–1.0 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.04 (s, H_3-8′), 0.64 (s, H_3-9′); ^{13}C NMR: δ_C 176.66 and 175.83 (C-1,3), 142.16 (C-10), 141.32 (C-9b), 136.70 (C-9a), 131.60 (C-1″), 130.49 (C-5a), 129.51 and 128.59 (C-7,9), 129.14, 129.08 and 126.45 (C-2″-6″), 128.41 (C-6), 126.33 (C-8), 76.74 (C-2′), 53.08 (C-10′), 51.45 (C-1′), 48.14 (C-7′), 45.01 (C-4′), 43.44, 41.29 and 41.10 (C-3a,3b,11a), 38.49 (C-3′), 30.51 and 26.98 (C-5′,6′), 30.32, 24.32 and 20.96 (C-4,5,11), 20.34 and 19.90 (C-8′,9′). Anal. calcd for $C_{32}H_{35}NO_4S$: C, 72.56; H, 6.66. Found: C, 72.17; H, 6.55%.

4.3.2. Cycloaddition of diene 1b. The elution from the chromatographic column with light petroleum containing increasing amount of EtOAc, from 20 up to 50%, afforded the following products, here reported in order of raising retention times. Two *exo* cycloadducts **(3a*R**,3b*R**,11a*S**,R_S)-10-[(1*S*)-isoborneol-10-sulfinyl]-7-methoxy-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-diones 10b** and **11b** were first eluted. The more mobile ***exo* adduct** was isolated as white crystals, mp 113–115°C, 19% yield, $[\alpha]_D^{20}$ +199.0 (*c* 0.0032); ^{1}H NMR: δ_H 7.5–6.8 (m, ArH), 4.14 (dd, $J_{2',3'}$ 8.1 and 4.0, H-2′), 3.86 (s, OMe), 3.81 (dd, $J_{11A,11a}$ 6.4, $J_{11A,11B}$ 16.5, H_A-11), 3.67 and 2.60 (AB system, $J_{10'A,10'B}$ 13.2, H_2-10′), 3.20 (ddd, $J_{3a,11a}$ 9.9, $J_{11a,11B}$ 12.1, H-11a), 2.89 (t, $J_{3a,3b}$ 10.2, H-3a), 2.9–2.6 and 1.9–1.2 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.20 (s, H_3-8′), 0.89 (s, H_3-9′); ^{13}C NMR: δ_C 176.55 and 176.44 (C-1,3), 160.51 (C-7), 143.65 (C-10), 143.18 (C-9b), 133.86 (C-5a), 132.10 (C-9), 131.51 (C-1″), 129.24, 128.82 and 126.46 (C-2″-6″), 123.15 (C-9a), 113.66 (C-6), 110.95 (C-8), 76.62 (C-2′), 55.39 (OMe), 52.38 (C-10′), 51.67 (C-1′), 48.33 (C-7′), 45.68, 41.84 and 40.81 (C-3a,3b,11a), 45.12 (C-4′), 38.44 (C-3′), 31.14 and 27.04 (C-5′,6′), 30.21, 27.26 and 23.37 (C-4,5,11), 20.62 and 20.08 (C-8′,9′); MS/FAB: *m*/*z* (%) 560 (M+1, 70), 543 (10), 406 (100), 390 (35), 241 (40), 210 (80). Then the less mobile ***exo* adduct** was obtained as white crystals, mp 105–110°C, 21% yield, $[\alpha]_D^{20}$ +131.8 (*c* 0.0036); ^{1}H NMR: δ_H 7.5–6.7 (m, ArH), 4.11 (dd, $J_{2',3'}$ 8.1 and 3.7, H-2′), 3.98 (dd, $J_{11A,11a}$ 7.1, $J_{11A,11B}$ 14.2, H_A-11), 3.85 (s, OMe), 3.53 and 2.53 (AB system, $J_{10'A,10'B}$ 13.2, H_2-10′), 3.16 (ddd, $J_{3a,11a}$ 10.0, $J_{11a,11B}$ 11.6, H-11a), 2.99 (t, $J_{3a,3b}$ 10.3, H-3a), 2.9–2.7 and 2.0–1.2 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.15 (s, H_3-8′), 0.86 (s, H_3-9′); ^{13}C NMR: δ_C 177.20 and 176.82 (C-1,3), 160.58 (C-7), 144.40 (C-10), 143.42 (C-9b), 134.37 (C-5a), 131.94 (C-9), 131.57 (C-1″), 129.19, 128.73 and 126.46 (C-2″-6″), 123.62 (C-9a), 113.23 (C-6), 110.75 (C-8), 76.64 (C-2′), 55.39 (OMe), 52.73 (C-10′), 51.57 (C-1′), 48.28 (C-7′), 45.05 (C-4′), 42.12, 40.94 and 38.70 (C-3a,3b,11a), 38.44 (C-3′), 31.05 and 27.23 (C-5′,6′), 27.49, 25.57 and 20.33 (C-4,5,11), 20.58 and 19.97 (C-8′,9′); MS/FAB: *m*/*z* (%) 560 (M+1, 55), 543 (10), 406 (100), 388 (40), 241 (35), 210 (65). **(3a*R*,3b*S*,11a*S*,R_S)-10-[(1*S*)-Isoborneol-10-sulfinyl]-7-methoxy-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione 8b** was isolated as white crystals, mp 133–135°C, 48% yield, $[\alpha]_D^{20}$ +51.4 (*c* 0.0079); ^{1}H NMR: δ_H 7.5–6.7 (m, ArH), 4.05 (dd, $J_{2',3'}$ 8.1 and 4.2, H-2′), 3.93 (dd, $J_{11A,11a}$ 1.8, $J_{11A,11B}$ 15.6, H_A-11), 3.80 (s, OMe), 3.56 (ddd, $J_{3a,11a}$ 8.8, $J_{11a,11B}$ 6.9, H-11a), 3.42 (dd, $J_{3a,3b}$ 5.6, H-3a), 3.31 and 2.19 (AB system, $J_{10'A,10'B}$ 13.0, H_2-10′), 3.0–1.0 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.06 (s, H_3-8′), 0.68 (s, H_3-9′); ^{13}C NMR: δ_C 176.79 and 175.91 (C-1,3), 160.31 (C-7), 143.24 (C-10), 142.48 (C-9b), 133.56 (C-5a), 131.61 (C-1″), 130.76 (C-9), 129.01, 128.50 and 126.45 (C-2″-6″), 123.22 (C-9a), 113.46 (C-6), 111.78 (C-8), 76.71 (C-2′), 55.25 (OMe), 52.74 (C-10′), 51.40 (C-1′), 48.11 (C-7′), 44.96 (C-4′), 43.49, 41.05 and 40.92 (C-3a,3b,11a), 38.43 (C-3′), 30.59 and 26.97 (C-5′,6′), 30.46, 24.18 and 20.95 (C-4,5,11), 20.38 and 19.87 (C-8′,9′); MS/FAB: *m*/*z* (%) 560 (M+1, 65), 543 (10), 406 (100), 390 (20), 241 (25), 210 (70). Anal. calcd for $C_{33}H_{37}NO_5S$: C, 70.81; H, 6.66. Found: C, 70.72; H, 6.58%. Finally **(3a*S*,3b*R*,11a*R*,R_S)-10-[(1*S*)-isoborneol-10-sulfinyl]-7-methoxy-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione 9b** eluted and isolated as an oil in 5% yield; ^{1}H NMR: δ_H 7.4–6.5 (m, ArH), 4.08 (dd, $J_{2',3'}$ 8.0 and 3.8, H-2′), 3.84 (s, OMe), 3.75 (dd, $J_{11A,11a}$ 1.9, $J_{11A,11B}$ 16.4, H_A-11), 3.64 (ddd, $J_{3a,11a}$ 8.8, $J_{11a,11B}$ 6.0, H-11a), 3.64 and 2.12 (AB system, $J_{10'A,10'B}$ 13.7, H_2-10′), 3.45 (dd, $J_{3a,3b}$ 5.7, H-3a), 3.0–1.2 (m, H-3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.08 (s, H_3-8′), 0.51 (s, H_3-9′); MS/FAB: *m*/*z* (%) 560 (M+1, 30), 543 (7), 406 (100), 390 (20), 241 (20).

4.3.3. Cycloaddition of diene 4b. Elution of the chromatographic column with light petroleum containing increasing amount of EtOAc, from 20 up to 50%, afforded the following products, here reported in order of raising retention times. Two *exo* cycloadducts **(3a*R**,3b*R**,11a*S**,S_S)-10-[(1*S*-*exo*)-2-bornylsulfinyl]-7-methoxy-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth-**

[2,1-*e*]isoindole-1,3(1*H*)-diones 13b and **14b** were first eluted. The more mobile ***exo* adduct** was isolated as a colorless oil, 13% yield; ^{1}H NMR: δ_H 7.8–6.7 (m, ArH), 3.81 (s, OMe), 3.72 (dd, $J_{11A,11a}$ 6.8, $J_{11A,11B}$ 15.6, H_A-11), 3.09 (ddd, $J_{3a,11a}$ 10.5, $J_{11a,11B}$ 11.6, H-11a), 2.94 (t, $J_{3a,3b}$ 10.5, H-3a), 2.9–2.5 and 1.9–1.0 (m, H-2′,3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.19 (s, H_3-10′), 0.80 (s, H_3-8′), 0.50 (s, H_3-9′); ^{13}C NMR: δ_C 177.06 and 176.76 (C-1,3), 159.99 (C-7), 145.76 (C-10), 143.18 (C-9b), 133.03 (C-5a), 131.73 (C-9), 131.49 (C-1″), 129.22, 128.79 and 126.44 (C-2″-6″), 124.25 (C-9a), 112.72 (C-6), 111.46 (C-8), 70.35 (C-2′), 55.33 (OMe), 49.29 (C-1′), 47.45 (C-7′), 44.84 (C-4′), 42.77, 40.20 and 38.72 (C-3a,3b,11a), 38.81 (C-3′), 32.79 and 27.13 (C-5′,6′), 27.77, 26.48 and 21.30 (C-4,5,11), 20.03 and 18.59 (C-8′,9′), 13.61 (C-10′); MS/FAB: *m*/*z* (%) 544 (M+1, 60), 407 (100), 390 (80). Then the less mobile ***exo* adduct** was obtained as a colorless oil, 18% yield; ^{1}H NMR: δ_H 7.9–6.7 (m, ArH), 3.97 (dd, $J_{11A,11a}$ 6.6, $J_{11A,11B}$ 15.4, H_A-11), 3.82 (s, OMe), 3.23 (dt, $J_{3a,11a}=J_{11a,11B}$ 10.7, H-11a), 2.84 (t, $J_{3a,3b}$ 10.7, H-3a), 2.8–2.5 and 1.7–1.0 (m, H-2′,3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.20 (s, H_3-10′), 0.79 (s, H_3-8′), 0.55 (s, H_3-9′); ^{13}C NMR: δ_C 176.91 and 176.59 (C-1,3), 160.08 (C-7), 145.79 (C-10), 143.06 (C-9b), 132.82 (C-5a), 131.96 (C-9), 131.62 (C-1″), 129.13, 128.66 and 126.44 (C-2″-6″), 123.06 (C-9a), 113.01 (C-6), 111.65 (C-8), 71.43 (C-2′), 55.28 (OMe), 49.23 (C-1′), 47.60 (C-7′), 44.99, 41.34 and 41.09 (C-3a,3b,11a), 44.70 (C-4′), 38.74 (C-3′), 31.95 and 27.02 (C-5′,6′), 30.22, 26.89 and 21.03 (C-4,5,11), 19.98 and 18.84 (C-8′,9′), 13.56 (C-10′); MS/FAB: *m*/*z* (%) 544 (M+1, 15), 407 (30), 390 (25), 137 (100). Finally **(3a*S*,3b*R*,11a*R*,S_S)-10-[(1*S*-*exo*)-2-bornylsulfinyl]-7-methoxy-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione 12b** eluted and isolated as white crystals, mp 204–205°C, 64% yield, $[\alpha]_D^{24}$ +27.1 (*c* 0.0373); ^{1}H NMR: δ_H 7.8–6.6 (m, ArH), 3.85 (dd, $J_{11A,11a}$ 1.3, $J_{11A,11B}$ 15.1, H_A-11), 3.77 (s, OMe), 3.50 (ddd, $J_{3a,11a}$ 8.2, $J_{11a,11B}$ 6.8, H-11a), 3.39 (dd, $J_{3a,3b}$ 5.3, H-3a), 2.8–1.0 (m, H-2′,3b,4′, H_B-11, H_2-3′,4,5,5′,6′), 1.19 (s, H_3-10′), 0.76 (s, H_3-8′), 0.45 (s, H_3-9′); ^{13}C NMR: δ_C 176.53 and 175.78 (C-1,3), 160.19 (C-7), 145.34 (C-10), 143.00 (C-9b), 131.66 (C-5a), 131.58 (C-1″), 131.09 (C-9), 129.02, 128.45 and 126.53 (C-2″-6″), 123.26 (C-9a), 113.21 (C-6), 111.87 (C-8), 70.94 (C-2′), 55.28 (OMe), 49.16 (C-1′), 47.61 (C-7′), 44.65 (C-4′), 43.21, 41.42 and 40.95 (C-3a,3b,11a), 38.59 (C-3′), 31.95 and 27.06 (C-5′,6′), 31.05, 24.19 and 21.19 (C-4,5,11), 19.95 and 18.73 (C-8′,9′), 13.43 (C-10′); MS/FAB: *m*/*z* (%) 544 (M+1, 30), 407 (25), 390 (60), 137 (100). Anal. calcd for $C_{33}H_{37}NO_4S$: C, 72.90; H, 6.86. Found: C, 72.58; H, 6.77%.

4.4. X-Ray analysis of (3a*S*,3b*R*,11a*R*,S_S)-10-[(1*S*-*exo*)-2-bornylsulfinyl]-7-methoxy-2,3,3a,3b,4,5,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione 12b

The space group of the orthorhombic $C_{33}H_{37}NO_4S$ crystal (from EtOAc, $M=543.73$) was $P2_12_12_1$ with $a=10.558(2)$, $b=14.7990(10)$, $c=19.014(2)$ Å. Other crystal parameters were as follows: $V=2970.9(7)$ Å^3, $Z=4$, $d_{calcd}=1.216$ g/cm^3. The structure, solved by direct methods (SIR-97),[13] was subsequently completed by a combination of least squares technique and Fourier syntheses and refined by the full-matrix least squares technique (SHELXTL PLUS) based on *F*.[14] The H atoms were included in the refinement following the 'riding model' with a unique common fixed isotropic displacement parameter. The structure refinement, with all anisotropic non-H atoms, reached $R(F)=0.050$ including a parameter for extinction correction into the last cycles. The Flack enantiomorph parameter converged to the final value of –0.03(9), which characterizes the assigned absolute configuration.[15] The final Fourier difference maps revealed no significant residual (<0.01 e Å^{-3}). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 172145. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.5. (3a*S*,11a*S*)-7-Methoxy-2,3,3a,4,5,10,11,11a-octahydro-2-phenylnaphth[2,1-*e*]isoindole-1,3(1*H*)-dione 15

TMSI (0.06 mL, 0.4 mmol) was added to a solution of the cycloadduct **8b** (90 mg, 0.16 mmol) in $CHCl_3$ (1.5 mL) under an argon atmosphere with stirring. The reaction, monitored by TLC, appeared complete after 90 min. Then MeOH (5 mL) was added and stirring was maintained for a further 30 min. After evaporation of the solvent under reduced pressure, purification of the crude product by column chromatography with light petroleum/EtOAc 95:5 as eluent afforded **15** as a low-melting solid, (29 mg, 50%), $[\alpha]_D^{24}$ +32.4 (*c* 0.0326); ^{1}H NMR: δ_H 7.5–6.7 (m, ArH), 3.80 (s, OMe), 3.69 (d, $J_{3a,11a}$ 8.5, H-3a), 3.33 (dt, $J_{11a,11A}=J_{11a,11B}$ 5.3, H-11a), 2.9–2.3 (m, H_2-4,5,10, H_A-11), 1.94 (m, H_B-11); ^{13}C NMR: δ_C 178.18 and 175.50 (C-1,3), 158.72 (C-7), 137.41 (C-5a), 131.91 (C-1″), 131.24 and 128.31 (C-3b,9b), 129.04, 128.43 and 126.38 (C-2″-6″), 124.23 (C-9a), 123.58 (C-9), 113.52 (C-6), 111.08 (C-8), 55.28 (OMe), 45.72 (C-3a), 40.07 (C-11a), 28.50, 27.33, 21.93 and 21.75 (C-4,5,10,11); MS/EI: *m*/*z* (%) 359 (M, 100), 213 (11), 212 (62), 211 (16), 197 (11), 165 (10).

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