

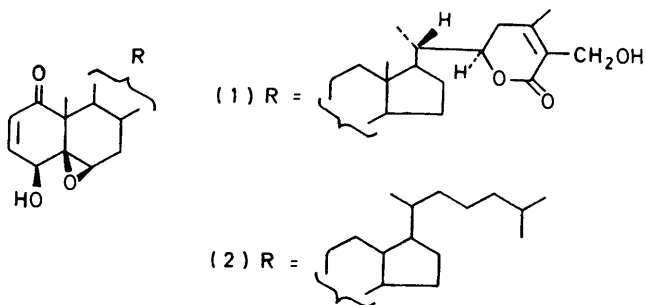
## Synthetic Studies of Withanolides. Part 2.† Synthesis of 4 $\alpha$ ,5 $\beta$ -Epoxy-4 $\alpha$ ,5,6,7,8,8 $\alpha$ -hexahydro-4 $\beta$ -hydroxy-8 $\alpha$ $\beta$ -methyl-naphthalen-1(4H)-one and Related Compounds

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The title compound, a simple AB ring moiety of withaferin A, and its seven isomers, were synthesized *via* octahydro-4 $\alpha$ -hydroxy-5-(phenylthio)-8 $\alpha$ -methyl-naphthalen-1(2H)-ones [(5a) and (5b)]. The key steps in the synthesis involve either 1,2-phenylthio-migration, or dehydration reactions of (5a) and (5b).

WITHAFERIN A (1), an anti-tumour plant metabolite, contains two biologically active sites, the epoxide enone system of rings AB, and the unsaturated lactone group in the side-chain.<sup>1</sup> It was recently reported that 5,6 $\beta$ -epoxy-4 $\beta$ -hydroxy-5 $\beta$ -cholest-2-en-1-one (2), which possesses the same AB ring functionalities as withaferin A,



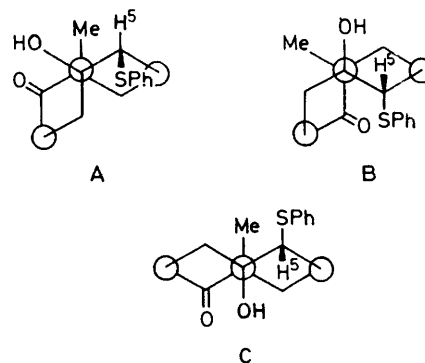
also has anti-tumour activity.<sup>2</sup> We report here a stereoselective synthesis of 4 $\alpha$ ,5 $\beta$ -epoxy-4 $\alpha$ ,5,6,7,8,8 $\alpha$ -hexahydro-4 $\beta$ -hydroxy-8 $\alpha$  $\beta$ -methyl-naphthalen-1(4H)-one (16b), a simple AB ring moiety of (1) and (2), and its regio- and stereo-isomers [(15a—d) and (16a, c, d)] which were prepared for structure-activity relationship studies. The synthetic route is shown in Schemes 1 and 2.

### RESULTS AND DISCUSSION

The key intermediates were octahydro-4 $\alpha$ ,5 $\beta$ -hydroxy-8 $\alpha$  $\beta$ -methyl-5 $\alpha$ -(phenylthio)naphthalen-1(2H)-one (5a) and its isomer, the 4 $\alpha$ -hydroxy-5 $\beta$ -phenylthio-derivative (5b). Epoxidation of enone (3), which was obtained from Wieland–Miescher ketone by the method of Dawson *et al.*,<sup>3</sup> with *m*-chloroperbenzoic acid (*m*-CPBA) afforded a mixture of two epoxides (4a) and (4b) in the ratio 2 : 1, and these were separated by silica gel column chromatography. Treatment of (4a) with thiophenol in the presence of Al<sub>2</sub>O<sub>3</sub> gave a vicinal hydroxy-sulphide (5a) and similar treatment of (4b) gave (5b). As this ring-opening reaction proceeded stereo- (*trans*) and regio-specifically,<sup>4</sup> the  $\beta$ - and  $\alpha$ -epoxide must give the corresponding *cis*- (conformer A or B) and *trans*-

† Part 1 is ref. 2.

naphthalenone (conformer C), respectively. Configurational assignments of (5a) and (5b) were based on the n.m.r. data (Table 1). The spectra indicated that the half-height widths ( $W_{1/2}$ ) of the H<sup>5</sup> signals of (5a) (16 Hz) and (5b) (7 Hz) were compatible with their axial and equatorial nature, respectively. Furthermore, the solvent effect on the hydroxy-protons of sulphides and sulphoxides [(5a), (5b), (19a), and (19b), and (19b')] ‡ in deuteriochloroform (CDCl<sub>3</sub>) and [<sup>2</sup>H<sub>6</sub>]dimethyl sulphoxide ([<sup>2</sup>H<sub>6</sub>]DMSO) solutions, indicated the presence of intramolecular hydrogen bonding between the hydroxy-proton and sulphoxide oxygen in (19a) [(19a):  $\Delta = \delta(\text{CDCl}_3) - \delta([\text{}^2\text{H}_6]\text{DMSO}) = -0.07$ ; (5a), (5b), and (19b), and (19b'):  $\Delta = -2.89$  to  $-2.30$ ].<sup>6</sup> Since it seems that the hydrogen bond can only be formed by the *cis* conformer A, it follows that the ring junction in (5a) must be *cis*, and that in (5b) *trans*. Therefore, the epoxides (4a) and (4b) have the  $\beta$ - and  $\alpha$ -configuration, respectively.



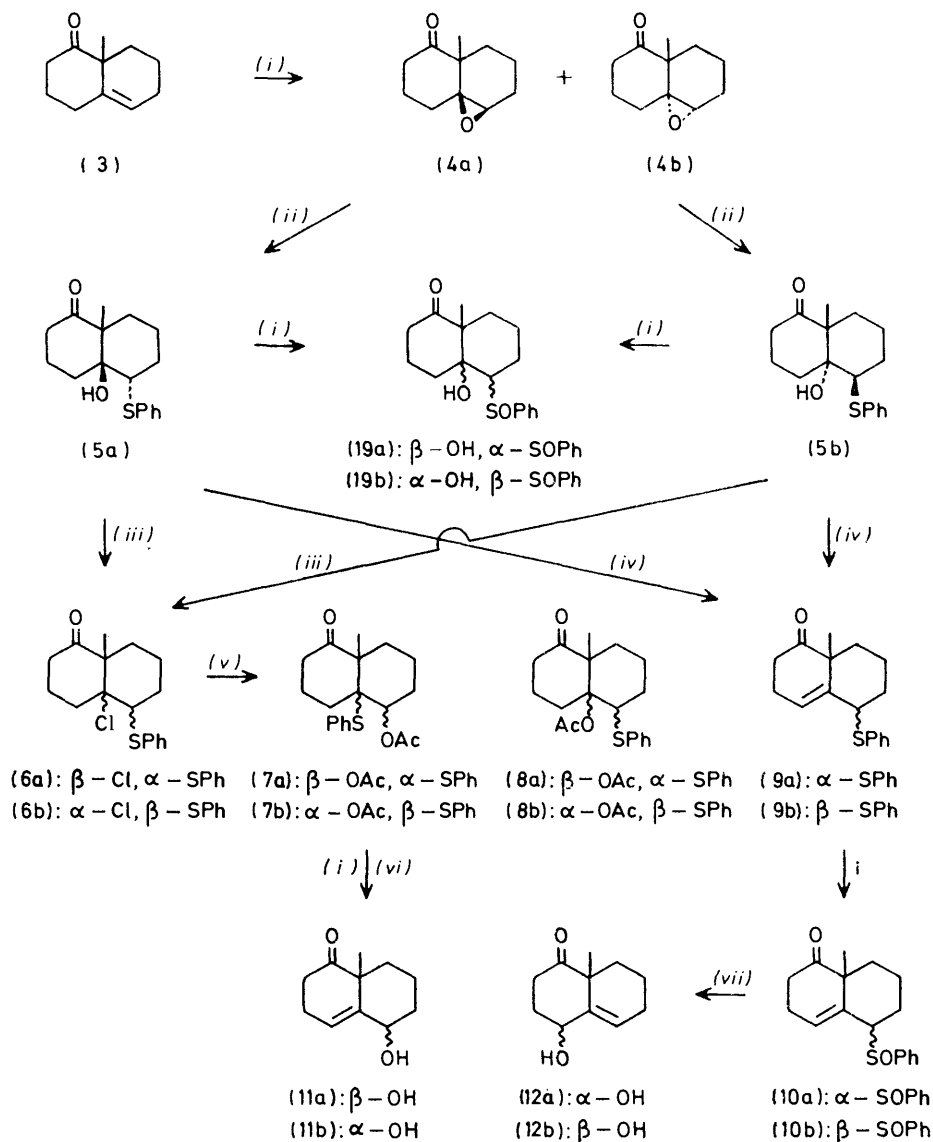
These key intermediates (5a) and (5b) were transformed stereo- and regio-selectively into 5-hydroxy-enones [(11a) and (11b)] and the 4-hydroxy-isomers [(12a) and (12b)]. It was found that 1,2-phenylthio (PhS) migration and dehydration reactions of (5a) and (5b) were useful for these transformations. A few 1,2-PhS migration reactions have been reported previously,<sup>7</sup>

‡ Oxidation of (5a) with *m*-CPBA gave the sulphoxide (19a) as a single product, but similar reaction of (5b) gave a mixture of two isomeric sulphoxides (19b) and (19b') probably due to configuration at sulphur.<sup>5</sup>

but we are not aware of previous examples having the corresponding ring junction substituents to these sulphides.

When (5a) was treated with a solution of sulphuric acid-acetic anhydride-acetic acid ( $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ ), known as a regiospecific *syn*-dehydration reagent,<sup>8</sup> a mixture of three compounds was obtained; a PhS migration product (7a), a C-4a substitution product

using thionyl chloride. These results are summarised in Table 2. Phenylthio-migration products (7a) and (7b) were successfully obtained from the chloro-sulphides in good yields, accompanied by small amounts of C-4a substitution products. Elimination product (9b) could be obtained in high yield either by dehydration of (5b) with toluene-*p*-sulphonic acid or by dehydrochlorination of (6b) with 1,5-diazabicyclo[3.4.0]non-5-ene (DBN),



SCHEME 1 (i) *m*-CPBA; (ii)  $\text{PhSH-Al}_2\text{O}_3$ ; (iii)  $\text{SOCl}_2$ ; (iv)  $\text{TsOH}$  or  $\text{H}_2\text{SO}_4$ ; (v)  $\text{AcOK}$  or  $\text{AcOAg}$ ; (vi) aqueous  $\text{KOH}$ ; (vii)  $\text{C}_5\text{H}_{11}\text{N}$

(8a), and an elimination product (9a). Analogous treatment of the *trans*-isomer (5b) afforded a similar mixture of three products, (7b), (8b), and (9b). Attempts were made to prepare the PhS migration products and the elimination products more conveniently from either the hydroxy-sulphides or their corresponding chlorosulphides [(6a) and (6b)]. The latter were obtained in good yields by chlorination of (5a) and (5b)

whereas (9a) was only produced in poor yield from (5a) or (6a) under similar elimination conditions. Their stereochemical assignments were deduced by comparing n.m.r. data with those of the hydroxy-sulphides (5a) and (5b) (Table 1). As the half-height widths of the the  $\text{H}^5$  signal of (6a), (7b), (8a), and (9a) were *ca.* 15–18 Hz, and those of (6b), (7a), (8b), and (9b) were *ca.* 6–7 Hz, the former protons are axial in *cis* conformer A, and

the latter equatorial in *trans* conformer C. Although the detailed mechanism has not been studied, it is probable that the PhS migration occurs through the formation of an intermediate phenylthiiranium ion<sup>7</sup> (D or E), which suffers nucleophilic attack at either the

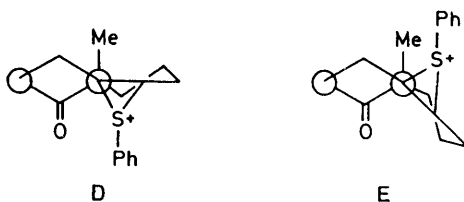
oxide, the *syn*-elimination and the allyl sulphoxide-sulphenate rearrangement reaction. By oxidation with *m*-CPBA followed by *syn*-elimination, (7a) and (7b) were transformed into 5-acetoxy-enones, which were treated with aqueous potassium hydroxide to afford 5 $\beta$ -hydroxy-

TABLE 1  
Spectral data of naphthalen-1(2*H*)-ones

Compound	<sup>1</sup> H N.m.r. (δ)				ν(C=O)/cm <sup>-1</sup>	M <sup>+</sup>
	4-H, W <sub>1</sub> (J/Hz)	5-H, W <sub>1</sub> (J/Hz)	Me	Others		
(4a)		2.98 (t, 3)	1.22		1 708	180.1137 <sup>a</sup>
(4b)		3.33 (t, 2)	1.30		1 708	180.1150 <sup>a</sup>
(5a)		3.33, 16 (10, 4)	1.17	OH 2.33 <sup>b</sup>	1 692	290.1326 <sup>c</sup>
(5a')		3.82, 7 (m)	1.48		1 692	290.1347 <sup>c</sup>
(5b)		3.17, 7 (m)	1.33	OH 1.55 <sup>b</sup>	1 691	290.1324 <sup>c</sup>
(19a)		3.05, 16 (12, 4)	1.13	OH 4.93 <sup>b</sup>	1 704	306.1262 <sup>d</sup>
(19b)		2.70, 7 (m)	1.58	OH 2.28 <sup>b</sup>	1 708	Anal <sup>e</sup>
(19b')			1.53	OH 2.09 <sup>b</sup>	1 708	Anal <sup>e</sup>
(6a)		3.57, 15 (10, 5)	1.30		1 710	308.0981 <sup>f</sup>
(6b)		3.53, 6 (m)	1.43		1 710	308.1003 <sup>f</sup>
(7a)		5.08, 7 (t, 3)	1.45	AcO 1.97	1 737,	332.1431 <sup>g</sup>
					1 705	
(7b)		5.17, 15 (10, 5)	1.35	AcO 1.56	1 736,	332.1455 <sup>g</sup>
					1 710	
(8a)		4.20, 17 (10, 4)	1.20	AcO 1.82	1 727,	332.1444 <sup>g</sup>
					1 704	
(8b)		4.47, 7 (t, 3)	1.37	AcO 1.90	1 730,	332.1497 <sup>g</sup>
					1 710	
(9a)	6.00 (m)	3.82, 18 (d, 12)	1.30		1 710	272.1221 <sup>h</sup>
(9b)	5.38 (t, 3)	3.97, 7 (m)	1.53		1 710	272.1242 <sup>h</sup>
(10a)	6.25 (m)	3.05, 16 (m)	1.18			
(10b)	4.68 (t, 4)	3.23, 6 (m)	1.37			
(10b')	5.78 (t, 3)	3.23, 6 (m)	1.52			
(11a)	5.68 (t, 3)	4.28, 6 (m)	1.43		1 687	180.1147 <sup>a</sup>
(11b)	5.80 (m)	4.23, 18 (d, 11)	1.20		1 689	180.1410 <sup>a</sup>
(12a)	5.63, 7 (m)	4.30 (m)	1.43		1 706	180.1158 <sup>a</sup>
(12b)	4.53, 18 (d, 11)	5.73 (m)	1.23	2.95 (m) <sup>i</sup>	1 706	180.1134 <sup>a</sup>

<sup>a</sup> C<sub>11</sub>H<sub>16</sub>O<sub>2</sub> requires *M*, 180.1150. <sup>b</sup> Measured in [<sup>2</sup>H<sub>6</sub>]DMSO [(5a) 4.63; (5b), 4.48; (19a), 5.00; (19b), 4.72; (19b'), 4.55]. C<sub>17</sub>H<sub>22</sub>O<sub>2</sub>S requires *M*, 290.1340. <sup>c</sup> C<sub>17</sub>H<sub>22</sub>O<sub>3</sub>S requires *M*, 306.1289. <sup>d</sup> Found: (19b), C, 66.65; H, 7.25%. (19b'), C, 66.45; H, 7.2%. Calc. for C<sub>17</sub>H<sub>22</sub>O<sub>3</sub>S: C, 66.64; H, 7.24%. <sup>e</sup> C<sub>17</sub>H<sub>21</sub>CIOS requires *M*, 308.1001. <sup>f</sup> C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>S requires *M*, 332.1446. <sup>g</sup> C<sub>17</sub>H<sub>20</sub>OS requires *M*, 272.1234. <sup>h</sup> 2 $\beta$ -Proton.

C-5 or C-4a carbon to generate the PhS migration product or the C-4a substitution product. The desired stereoelectronic requirement for facile formation of the thiiranium ion, *i.e.* an *anti*-periplanar arrangement of PhS and Cl, is present in sulphide (6b) where the *trans* ring junction favours the process (conformer C $\rightarrow$ E).



In contrast, the isomeric sulphide (6a) has a *cis* ring junction in which the corresponding groups are both preferentially located equatorially (conformer A). It is probably due to this conformational difference that the PhS migration of sulphide (6b) occurs more readily than that of the isomer (6a).

Phenylthio-migration and elimination compounds (7a), (7b), (9a), and (9b) were converted into four regio- and stereo-isomeric hydroxy-enones [(11a), (11b), (12a), and (12b)] by the application of two useful reactions of sulph-

oxide (11a) [54% yield from (7a)] and 5 $\alpha$ -hydroxy-enone (11b) [53% yield from (7b)], respectively. 4 $\alpha$ -Hydroxy-enone (12a) and 4 $\beta$ -hydroxy-isomer (12b) were

TABLE 2

Yields of phenylthio-migration products (II), C-4a substitution products (III), and elimination products (IV) from sulphides (I)

(I)	Method <sup>a</sup>	Product distribution Compound (Yield %)			
		(II)	(III)	(IV)	(I) <sup>b</sup>
(5a)	A	(7a) (17)	(8a) (27)	(9a) (36)	(85)
	B			(9a) (6)	
(5b)	A	(7b) (5)	(8b) (23)	(9b) (50)	(95)
	B			(9b) (95)	
(6a)	C	(7a) (75)	(8a) (10)	(9a) (9)	(54)
	D	(7a) (11)		(9a) (16)	
	E			(9a) (trace)	
(6b)	C'	(7b) (57)	(8b) (29)	(9b) (trace)	(91)
	D'	(7b) (73)	(8b) (8)		
	E'			(9b) (67) <sup>c</sup>	

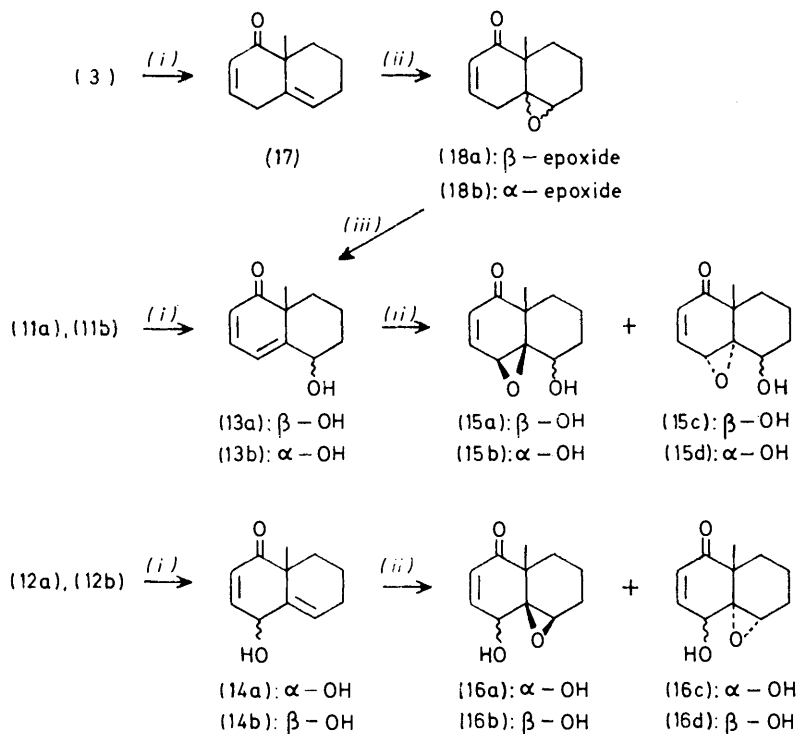
<sup>a</sup> See in Experimental section. <sup>b</sup> Unchanged. <sup>c</sup> Compound (3) was obtained in 27% yield.

obtained from elimination products (9a) and (9b) by oxidation with *m*-CPBA followed by allyl sulphoxide-sulphenate rearrangement using piperidine as a thio-philic reagent.<sup>9</sup> The 5 $\beta$ -sulphoxide was observed as a

mixture of two isomers [(10b) and (10b')] in the ratio 2 : 1 from the n.m.r. spectrum, probably due to configuration at sulphur<sup>5</sup> (Me protons,  $\delta$  1.37 and 1.52; 4-proton,  $\delta$  4.68 and 5.78), but the 5 $\alpha$ -sulphoxide (10a) seemed to be a single compound by n.m.r. and t.l.c. analyses (Me protons,  $\delta$  1.18; 4-H,  $\delta$  6.25). Retention of configuration of (11a), (11b), (12a), and (12b) was confirmed by the n.m.r. half-height widths of the 4-H or 5-H signals (Table 1). Hydroxy-enones [(11a), (11b), (12a), and (12b)] were readily transformed into the corresponding hydroxy-dienones [(13a), (13b), (14a), and (14b)] in 52–78% yields by the Reich-Sharpless procedure.<sup>10</sup>

torial  $\alpha$ -hydroxy-groups. That is, (13a) showed 5-H at  $\delta$  4.40 ( $W_{\frac{1}{2}}$  6 Hz), indicative of an equatorial hydrogen, whereas (13b) showed 5-H at  $\delta$  4.31 ( $W_{\frac{1}{2}}$  15 Hz), indicative of an axial hydrogen. Furthermore, allylic 1,3-coupling<sup>13</sup> of 4-H with 2-H was negligible in (14b), indicating the quasi-equatorial nature of 4-H, whereas it was significant (2 Hz) in (14a), indicating its quasi-axial nature.

Configurational assignments of these hydroxy-epoxides were based on a comparative n.m.r. analysis (Table 3). For the 4,4a-epoxides (15a–d), the 2-H signal in each case appeared as a doublet of doublets due



SCHEME 2 (i) LDA, PhSeBr, and H<sub>2</sub>O<sub>2</sub>; (ii) *m*-CPBA; (iii) aqueous NaOH

Compounds (13a) and (13b) were also obtained by base-induced rearrangement of 4a,5-epoxy-enones (18a) and (18b), which were obtained from (3) *via* dienone (17). As the epoxides were opened with retention of configuration,<sup>11</sup> (18a) and (18b) were determined to be the  $\beta$ - and  $\alpha$ -epoxide, respectively.

Epoxidation of each hydroxy-dienone with *m*-CPBA gave a mixture of two epoxides, which could be separated by silica gel column chromatography. Though  $\beta$ -epoxides were obtained as major products in every reaction, higher stereoselectivity was observed in the reaction of  $\beta$ -hydroxy-dienones (13a) and (14b) ( $\beta/\alpha$ -epoxide > 5) than in that of  $\alpha$ -hydroxy-isomers (13b) and (14a) ( $\beta/\alpha$ -epoxide = 1–1.5). This selectivity may be ascribed to the participation of the neighbouring  $\beta$ -hydroxy-group,<sup>12</sup> since the 4-H and 5-H signals *gem* to the hydroxy-group suggested that (13a) and (14b) had axial  $\beta$ -hydroxy-groups but (13b) and (14a) had equa-

to allylic coupling with 4-H, and the 8a-Me signals of  $\beta$ -epoxides (15a) and (15b) appeared at lower field than those of the corresponding  $\alpha$ -isomers (15c) and (15d), probably due to deshielding by the 1-oxo-function. For the 4a,5-epoxides (16a–d), their stereochemistry was deduced by comparing n.m.r. data with those of the 4-deoxy-analogues (18a) and (18b).  $\beta$ -Epoxides (16a), (16b), and (18a) showed the 8a-Me signals at higher field than the corresponding  $\alpha$ -isomers (16c), (16d), and (18b). These relevant n.m.r. signals showed fair agreement with those of (2) and its isomers.<sup>2</sup>

Hydroxy-epoxides (15a), (15d), (16b), and (16c) had no inhibitory effect against Sarcoma 180 ascites tumour.

#### EXPERIMENTAL

The i.r. spectra were recorded on a JASCO IR-G spectrometer and mass spectra on a JEOL-OISG spectrometer. The n.m.r. spectra were obtained in CDCl<sub>3</sub> with tetra-

methylsilane as an internal standard, unless otherwise stated. Column chromatography was performed using silica gel (Wakogel C-200). Thin layer chromatography (t.l.c.) was carried out on pre-coated plates of silica gel (E. Merck). Organic extracts were dried over magnesium sulphate. The usual work-up refers to dilution with water, extraction with an organic solvent, washing to neutrality, drying, filtration, and evaporation under vacuum. Ether refers to diethyl ether, IPE to diisopropyl ether, DMF to *NN*-dimethylformamide, THF to tetrahydrofuran, and LDA to lithium di-isopropylamide. The purity of *m*-CPBA was 85%.

4 $\alpha$ ,5 $\beta$ - and 4 $\alpha$ ,5 $\alpha$ -Epoxyoctahydro-8 $\alpha$  $\beta$ -methyl-naphthalen-1(2H)-one (4a) and (4b).—Enone (3) (4.92 g, 30 mmol) in

same method, 4 $\alpha$ -chloride (6b) was obtained from (5b) in 96.4% yield as a single product, m.p. 111–112 °C.

*Phenylthio-migration and Elimination Reaction of Hydroxy-sulphides (5a) and (5b) or Chloro-sulphides (6a) and (6b).*—(A) The hydroxy-sulphide (1 mmol) was treated with a solution (2 ml) of H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH (25 mg–1.6 g–10 ml) at room temperature for 4 h.

(B) The hydroxy-sulphide (1 mmol) was treated with *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>OH·H<sub>2</sub>O (40 mg) in benzene (5 ml) at room temperature for 24 h.

(C, C') The chloro-sulphide (1 mmol) was treated with silver acetate (335 mg) in acetonitrile (20 ml) at 50 °C for 62 h in a dark room (C'; at room temperature for 24 h).

(D, D') The chloro-sulphide (1 mmol) was treated with

TABLE 3  
Spectral data of naphthalen-1(4H)-ones

Compound	<sup>1</sup> H N.m.r. ( $\delta$ )					$\nu$ (C=O)	M <sup>+</sup>
	2-H (J/Hz)	3-H (J/Hz)	4-H (J/Hz)	5-H (J/Hz)	Me		
(13a)	5.93 (10)	6.84 (10, 6)	6.03 (6)	4.40 <sup>a</sup>	1.43	1 657	178.1004 <sup>b</sup>
(13b)	5.90 (10)	6.95 (10, 6)	6.28 (6)	4.31 <sup>a</sup>	1.22	1 657	178.0995 <sup>b</sup>
(14a)	5.75 (10, 2)	6.72 (10, 2)	4.97 (m)	5.83 (m)	1.18	1 680	178.0999 <sup>b</sup>
(14b)	5.85 (10)	6.78 (10, 5)	4.53 (5)	5.77 (m)	1.38	1 677	178.1008 <sup>b</sup>
(15a)	5.87 (10, 1)	6.92 (10, 4)	3.22 (4, 1)	3.47	1.50	1 656	194.0945 <sup>c</sup>
(15b)	5.92 (10, 1)	6.95 (10, 4)	3.74 (4, 1)	3.34	1.32	1 673	194.0943 <sup>c</sup>
(15c)	5.92 (10, 1)	6.95 (10, 4)	3.72 (4, 1)	4.07	1.32	1 676	194.0934 <sup>c</sup>
(15d)	5.92 (10, 1)	6.95 (10, 4)	3.74 (4, 1)	3.98	1.17	1 687	194.0932 <sup>c</sup>
(16a)	5.95 (10, 2)	6.82 (10, 2)	4.82 (m)	3.58 (m)	1.17	1 678	194.0944 <sup>c</sup>
(16b)	6.05 (10)	6.82 (10, 5)	3.78 (5)	3.17	1.35	1 679	194.0942 <sup>c</sup>
(16c)	5.81 (10, 2)	6.65 (10, 2)	4.60 (t, 2)	3.38 (m)	1.30	1 683	194.0952 <sup>c</sup>
(16d)	5.93 (10)	6.70 (10, 5)	3.67 (5)	3.18 (m)	1.43	1 679	194.0949 <sup>c</sup>
(17)	5.80 (10, 3, 1)	6.75 (10, 5, 3)	2.70 (dd) <sup>d</sup>	4.47 (s)	1.17	1 658	161.0976 <sup>e</sup>
(18a)	5.97 (10, 3, 1)	6.80 (10, 6, 2)	3.00 (dt)	3.02 (m)	1.17	1 676	178.0979 <sup>b</sup>
(18b)	5.90 (10, 3, 1)	6.78 (10, 5, 3)	3.83 (dt)	3.02 (m)	1.25	1 672	178.0997 <sup>b</sup>

<sup>a</sup> Half-height widths; (13a), 6 Hz; (13b), 15 Hz. <sup>b</sup> C<sub>11</sub>H<sub>14</sub>O<sub>3</sub> requires *M*, 178.0993. <sup>c</sup> C<sub>11</sub>H<sub>14</sub>O<sub>3</sub> requires *M*, 194.0942. <sup>d</sup> The other 4-H,  $\delta$  3.25 (dq). <sup>e</sup> C<sub>11</sub>H<sub>14</sub>O requires *M*, 161.0966.

chloroform (160 ml) was treated with *m*-CPBA (6.70 g, 33 mmol) at 0 °C for 5 h and then filtered. The usual work-up (chloroform extraction) provided a crude product (6.02 g) containing two epoxides. Chromatography on silica gel [toluene-ethyl acetate (95:5)] gave the  $\beta$ -epoxide (4a) (2.39 g, 54.2%) as an oil. Further elution gave the  $\alpha$ -epoxide (4b) (2.39 g, 42.2%) as an oil.

*Octahydro-4 $\alpha$  $\beta$ -hydroxy-5 $\alpha$ -phenylthio- and Octahydro-4 $\alpha$  $\alpha$ -hydroxy-5 $\beta$ -phenylthio-8 $\alpha$  $\beta$ -methyl-naphthalen-1(2H)-one (5a) and (5b).*—According to the procedure reported by Posner and Rogers,<sup>4</sup> (4a) (1.80 g, 10 mmol) was treated in ether (100 ml) for 20 min with W-200-N alumina (76 g) doped with thiophenol (3.1 ml) to give a crude product. Chromatography on silica gel [toluene-ethyl acetate (80:20)] gave two isomeric hydroxy-sulphides, 1.93 g (66.7%) of (5a), m.p. 150–151 °C (IPE-hexane) and 99 mg (3.4%) of the 5 $\beta$ -hydroxy-4 $\alpha$  $\alpha$ -phenylthio-isomer (5a<sup>1</sup>), m.p. 177–178 °C (IPE-hexane). A similar treatment of (4b) gave (5b) in 72.7% yield, m.p. 142–143 °C (IPE-hexane).

4 $\alpha$  $\beta$ -Chloro-octahydro-5 $\alpha$ -phenylthio- and 4 $\alpha$  $\alpha$ -Chloro-octahydro-5 $\beta$ -phenylthio-8 $\alpha$  $\beta$ -methyl-naphthalen-1(2H)-one (6a) and (6b).—Hydroxy-sulphide (5a) (1.45 g, 5 mmol) was allowed to react in pyridine (5 ml) with thionyl chloride (0.5 ml) at 0 °C for 1 h. The usual work-up (ethyl acetate extraction) gave a crude product, which recrystallized from IPE-hexane to afford the 4 $\alpha$  $\beta$ -chloride (6a) (1.14 g, 73.6%), m.p. 120–121 °C. The filtrate was chromatographed on silica gel [toluene-ethyl acetate (95:5)] to give (6a) (48 mg, 3.1%) and enone (9a) (307 mg, 22.6%) as an oil. By the

potassium acetate (293 mg) in DMF (40 ml) at 50 °C for 92 h (D'; at room temperature for 24 h).

(E, E') The chloro-sulphide (1 mmol) was treated with DBN (2 ml) in benzene (2 ml) at 60 °C for 24 h (E'; for 10 h).

Each crude product, after the usual work-up, was chromatographed on silica gel [toluene-ethyl acetate (97:3)] to give the phenylthio-migration product or elimination product. Yields and product distribution are summarized in Table 2. Physical data are as follows: (7a) m.p. 105–106 °C; (7b), 123–124 °C; (8a), oil; (8b), 116–117 °C; (9a), oil; (9b), oil.

3,5,6,7,8,8a-Hexahydro-5 $\beta$ - and -5 $\alpha$ -hydroxy-8 $\alpha$  $\beta$ -methyl-naphthalen-1(2H)-one (11a) and (11b).—A solution of *m*-CPBA (213 mg, 1.05 mmol) in chloroform (20 ml) was added to a solution of the 5 $\beta$ -acetate (7a) (332 mg, 1 mmol) in chloroform (20 ml) at 0 °C and the resulting solution was stirred for 3 h. The usual work-up (chloroform extraction) provided a crude 5 $\beta$ -acetoxy-enone (250 mg). The crude oil was treated with 2N aqueous potassium hydroxide (3.5 ml) in DMF (10 ml) at room temperature for 2 h. After the usual work-up (ethyl acetate extraction), the residue was chromatographed on silica gel [toluene-ethyl acetate (70:30)] to give 5 $\beta$ -hydroxy-enone (11a) [98 mg, 54.4% from (7a)], m.p. 67–68 °C (IPE-hexane). In the same way, the 5 $\alpha$ -hydroxy-enone (11b) was obtained from (7b) in 53% yield, m.p. 77–78 °C (IPE-hexane).

3,4,6,7,8,8a-Hexahydro-4 $\alpha$ - and -4 $\beta$ -hydroxy-8 $\alpha$  $\beta$ -methyl-naphthalen-1(2H)-one (12a) and (12b).—A solution of *m*-

CPBA (213 mg, 1.03 mmol) in chloroform (20 ml) was added to a solution of (9b) (272 mg, 1 mmol) in chloroform (10 ml) at 0 °C and the resulting solution was stirred for 2 h. The usual work-up (chloroform extraction) provided a crude product, showing two spots on t.l.c. [chloroform-methanol (98 : 2)  $R_F$  0.29 and 0.16]. Each compound was isolated by preparative t.l.c.: (10b) (upper band; oil) and (10b') (lower band; oil). After standing in  $CDCl_3$  for 2 days, both n.m.r. spectra of the two purified compounds showed a mixture of (10b) and (10b') in the ratio 2 : 1. This ratio was the same as that of the crude product. The crude product, chlorobenzene (3 ml), and piperidine (1.5 ml) was stirred at 60 °C for 40 min. After the usual work-up (ethyl acetate extraction), chromatography on silica gel [toluene-ethyl acetate (70 : 30)] afforded the 4 $\beta$ -hydroxy-enone (12b) [158 mg, 87.8% yield from (9b)] as an oil. In the same way, (9a) was converted into (10a) as a single sulphoxide, which provided the 4 $\alpha$ -hydroxy-isomer (12a) [92.7% yield from (9a)] as an oil.

6,7,8,8a-Tetrahydro-5-hydroxy-8a-methylnaphthalen-1(5H)-ones [(13a) and (13b)] and the Regioisomeric 4-Hydroxy-naphthalen-1(4H)-ones [(14a) and (14b)].—(a) From the hydroxy-enones (11a), (11b), (12a), and (12b). A solution of (11a) (180 mg, 1 mmol) in THF (7 ml) was added at -60 to -70 °C under nitrogen to a solution of LDA (2.2 mmol) and stirred for 1 h. To this solution was added phenylselenenyl bromide (1.1 mmol) in THF (8 ml) at the same temperature and stirring was continued for 2.5 h. The resulting reaction mixture was poured into aqueous ammonium chloride (50 ml) and extracted with ether. The ether extract was washed with 1N hydrochloric acid, aqueous sodium hydrogencarbonate, and water. After drying with magnesium sulphate, evaporation of solvent gave a yellow residue. This residue in THF (10 ml) was treated with 30% aqueous hydrogen peroxide (0.5 ml) at room temperature for 1 h. After the usual work-up (ether extraction), a crude product was chromatographed on silica gel [toluene-ethyl acetate (60 : 40)] to provide (13a) (140 mg, 77.8%) as an oil. Other compounds also obtained as oils: (13b), 72.5%; (14a), 60.2%; and (14b), 51.8%.

(b) From the epoxy-enones (18a) and (18b). Compound (18a) (180 mg, 1 mmol) was treated with 15% aqueous sodium hydroxide (0.9 ml) in dioxan (8 ml) under reflux for 4 h. The usual work-up (ether extraction) gave a crude oil, which was chromatographed on silica gel to afford (13a) (139 mg, 77.2%). Compound (13b) was also obtained from (18b) in 62.3% yield.

4 $\alpha$ ,5-Epoxy-4 $\alpha$ ,5,6,7,8,8a-hexahydro-5- and -4-hydroxy-8a-methylnaphthalen-1(4H)-ones (15a-d) and (16a-d).—Epoxidation of (13a) with *m*-CPBA (1.02 equiv.) in chloroform at room temperature gave a mixture of two epoxides. Chromatography on silica gel [toluene-ethyl acetate (70 : 30)] afforded the  $\beta$ -epoxide (15a) (81% yield), m.p. 107–108 °C, and the  $\alpha$ -epoxide (15c) (12% yield), m.p. 77–79 °C. By the same method, other epoxides were obtained as follows: (15b) (58% yield, oil) and (15d) (39% yield), m.p. 82–83 °C from (13b); (16b) (76% yield), m.p. 66–68 °C, and (16d) (15% yield, oil) from (14b); (16a) (53%

yield, oil) and (16c) (39% yield), m.p. 121–122 °C from (14a).

4 $\alpha$ ,5 $\beta$ - and 4 $\alpha$ ,5 $\alpha$ -Epoxyhexahydro-8a $\beta$ -methylnaphthalen-1(4H)-one (19a) and (19b).—According to a similar procedure described in the preparation of (13a), (3) was transformed into the dienone (17) (71.5% yield), b.p. 173–175 °C at 2 mmHg, using LDA (1.1 equiv.) and phenylselenenyl bromide (1.1 equiv.). Treatment of (17) with *m*-CPBA in chloroform at 0 °C for 5 h gave a crude product containing two epoxides. Chromatography on silica gel [toluene-ethyl acetate (90 : 10)] provided  $\beta$ -epoxide (18a) (51.2% yield, oil) and the  $\alpha$ -epoxide (18b) (46.8% yield, oil).

Oxidation of Hydroxy-sulphides (5a) and (5b) with *m*-CPBA.—A solution of *m*-CPBA (100 mg, 0.5 mmol) in chloroform (10 ml) was added to a solution of (5a) (145 mg, 0.05 mmol) in chloroform (3 ml) at 0 °C and stirred for 2 h. The usual work-up (chloroform extraction) gave sulphoxide (19a) (139 mg, 90.8%), m.p. 193–194 °C (chloroform-IPE). Similar treatment of (5b) with *m*-CPBA gave a mixture of two sulphoxides. Preparative t.l.c. [toluene-ethyl acetate (70 : 30)] gave (19b) (lower band; 41.1% yield), m.p. 163–164 °C and (19b') (upper band; 22.5% yield), m.p. 163–164 °C.

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