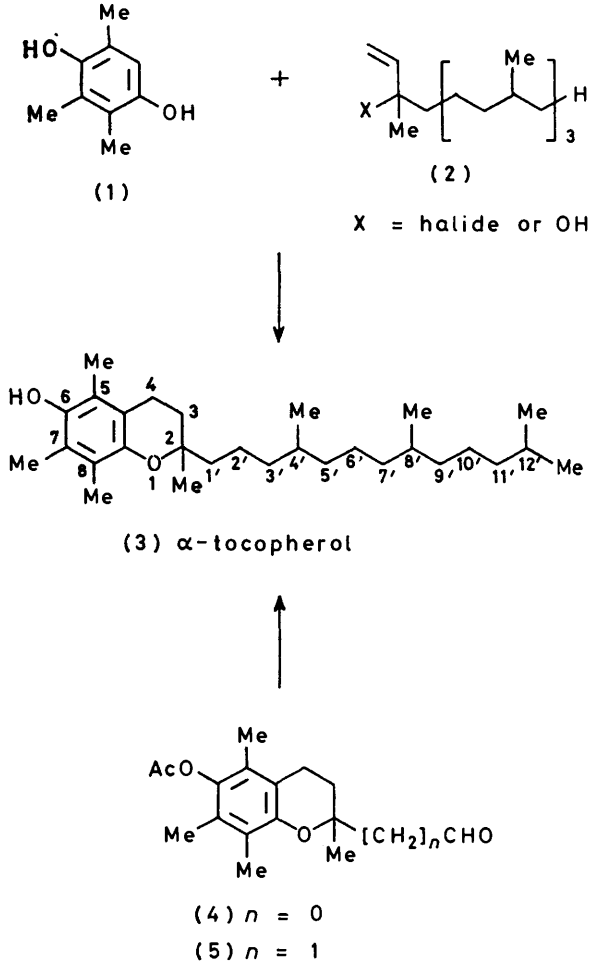
The Synthesis of α-Tocopherol *via* 2-(Sulphinylmethyl)chromans [1]

By **Jaap M. Akkerman, Henk de Koning,* and Henderikus O. Huisman,** Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, Amsterdam, The Netherlands

2,5,7,8-Tetramethyl-2-[(phenylthio)methyl]chroman-6-ol, (6) was synthesized from trimethylhydroquinone (1) and 3-methyl-4-(phenylthio)buten-3-ol (12). Acetylation of (6) and subsequent oxidation gave 6-acetoxy-2,5,7,8-tetramethyl-2-[(phenylsulphinyl)methyl]chroman (9). This was converted to the known α-tocopherol precursor 6-acetoxy-2,5,7,8-tetramethylchroman-2-carbaldehyde (4) by Pummerer reaction, hydrolysis, and re-acetylation. An attempted more direct synthesis of α-tocopherol *via* alkylation of 6-(methoxymethoxy)-2,5,7,8-tetramethyl-2-[(phenylsulphonyl)methyl]chroman (12) with hexahydrofarnesyl bromide led to ring opening and subsequent *O*-alkylation.

THE preparation of 2-substituted 2-methylchromans and the control of their functionalization and stereochemistry is important in the total synthesis of α-tocopherol (3).† The classical approach to the synthesis of α-tocopherol

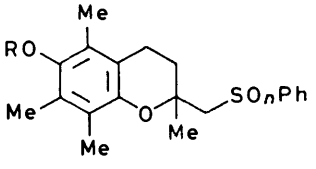


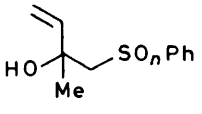
involves the Lewis acid-catalysed reaction of trimethylhydroquinone (1) with isophytol (or its halide) (2).[3] An alternative approach comprises the synthesis *via* the formylchromans [(4) and (5)], to which the side-chain is attached by a Wittig reaction.[4a,b] We wish to report a novel synthesis of the 2-formylchroman (4) by using chroman-sulphur compounds (6) and (8). We have also investigated a more direct coupling of the side-chain halide with the α-lithio-salts of the chroman-sulphur compounds (10) and (11).

† α-Tocopherol [2] is the biologically most active substance of the eight compounds with ' Vitamine E activity ' isolated by Evans in 1922.

RESULTS AND DISCUSSION

Initial attempts to synthesize the chroman-sulphoxide (8), making use of the isoprenoid building block (13) (recently described by our group [5]) were not successful. Coupling of the hydroxy-sulphoxide (13) and trimethyl-





(6) n = 0 R = H
(7) n = 0 R = Ac
(8) n = 1 R = H
(9) n = 1 R = Ac
(10) n = 1 R = CH_2OMe
(11) n = 2 R = CH_2OMe

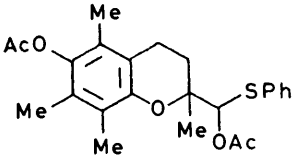
(12) n = 0
(13) n = 1

hydroquinone (1) with boron trifluoride–ether or tin(IV) tetrachloride as catalyst, did not lead to the expected chroman-sulphoxide (8) but to the corresponding chroman-sulphide (6),‡ which was isolated in moderate yield. Obviously the combination of a sulphoxide and a Lewis acid with an easily oxidizable hydroquinone is an ideal redox system.[6]

Another approach, synthesis of the sulphoxide *via* the corresponding sulphide (6), proved to be more successful. The required hydroxy-sulphide (12) was prepared in quantitative yield by reaction of 1,2-isoprene oxide [7] and benzenethiol with a catalytic amount of sodium.[8] Condensation of the hydroxy-sulphide (12) with trimethylhydroquinone (1) and boron trifluoride–ether afforded the chroman-sulphide (6) in excellent yield. Before oxidation of the sulphide, the phenolic hydroxy-

‡ Though i.r. and ^1H n.m.r. spectra of this product did not allow a distinction between sulphoxide and sulphide, the structure was corroborated by mass spectra of the acetates (7) and (9), described below.

group in (6) was protected by reaction with acetic anhydride in pyridine, providing the acetate (7). The sulphide moiety in (7) was then oxidized with *N*-bromosuccinimide in dioxan–water according to Tagaki's procedure [9] to give the chroman-sulphoxide (9) in high yield. Though information from i.r. and ^{1}H n.m.r. spectra was insufficient, structural proof for (7) and (9) followed from their mass spectra, which had molecular ions at *m/e* 370 and 386, respectively. Characteristic losses of $PhSCH_2^{\bullet}$ and $PhSOCH_2^{\bullet}$, respectively, leading to *m/e* 247, followed by loss of hydrogen to *m/e* 245, formed additional evidence for the proposed structures. The sulphoxide (9) also loses $OH^{\bullet}$, leading to *m/e* 369. The mixture of diastereoisomers of the sulphoxide (9) [caused by the presence of the chiral centres at C(2) and sulphur] could be separated after recrystallization from light petroleum (b.p. 60—80 °C), furnishing the two diastereoisomeric racemates, (*RR*/*SS*) and (*SR*/*RS*), m.p. 102—108 and 141—143 °C, respectively. ^{1}H N.m.r. spectra of the two isomers displayed absorptions of the C(2)-methyl protons at δ 1.45 (higher-melting isomer) and 1.66 (lower-melting isomer).*



(14)

In order to complete the synthesis of (4), the mixture of sulphoxides (9) was subjected to the modified Pummerer reaction of Iriuchijima *et al.*[10] After heating for 7 h at 135 °C in acetic anhydride–sodium acetate, the monothio-acetal (14) was isolated in excellent yield. This could readily be hydrolysed with 5% sodium hydroxide in ethanol and subsequently acetylated to give the 6-acetoxychroman-2-carbaldehyde (4) in good yield.

The synthesis of α-tocopherol from (4) was described by Mayer *et al.*: [4a] Wittig reaction with (hexahydrofarnesyl)triphenylphosphonium bromide was followed by hydrogenation and hydrolysis. If [(3*R*,7*R*)-hexahydrofarnesyl]triphenylphosphonium bromide (15) is used in the Wittig reaction, this route leads to the formation of (2*RS*,4′*R*,8′*R*)-α-tocopherol. Because the *R*-configuration at C-2 is important for biological activity [2] we are currently investigating the application of optically active sulphoxides which, together with the possibility to separate diastereoisomers of (9), would lead to the synthesis of the optically active (2*S*)-formylchroman (4).[4a]

Attempted alkylation of α-sulphur-stabilized carbanions, as a more direct route to α-tocopherol, appeared to be unsuccessful. Table 1 shows the results of quenching experiments with D_2O after treating the chroman-sulphide (6), -sulphoxide (10) and -sulphone (11) with n-butyl-lithium. Compounds (10), and (11) were prepared from the sulphide (6) by refluxing (6) in dimethoxymethane–dichloromethane with toluene-*p*-sulphonic acid in the presence of molecular sieves,[11] followed by subsequent oxidation with 1 or 2 mol. equiv.

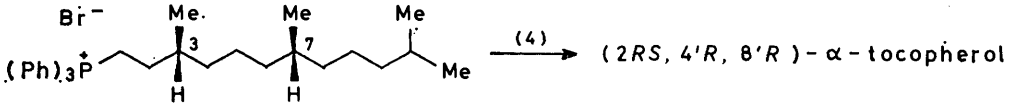
TABLE 1

Quenching experiments with D_2O

Compound	n-BuLi/mol equiv.	Solvent	Temperature (°C)	% D
(6)	2.2	THF [a]	−50	0 [d]
(6)	2.2	THF–HMPT [b]	−50	0 [d]
(6)	2.2	THF–TMEDA [c]	0	0 [d]
(10)	1.1	THF–HMPT	−50	20 [d]
(11)	1.1	THF	−50	100 [e]
(11)	1.1	THF–HMPT	0	100 [e]

[a] THF = Tetrahydrofuran. [b] HMPT = hexamethylphosphorotriamide. [c] TMEDA = *NNN′N′*-tetramethylethylenediamine. [d] Calculated from mass spectra. [e] Calculated from ^{1}H n.m.r. spectra.

of *m*-chloroperbenzoic acid at 0 °C. The sulphide (6) does not form any lithio-salt at all; both the α-position to sulphur and the benzylic positions were not deuteriated. The sulphoxide (10) is deuteriated for 20% at the α-position and only the sulphone (11) is completely monodeuteriated to produce (20). These observations are surprising; from the literature [12] it is known that α-lithio-salts of sulphoxides are easily formed by treatment with n-butyl-lithium, while α-lithio-sulphides are easily prepared with n-butyl-lithium in combination with diazabicyclo[2.2.2]octane [13] or *NNN′N′*-tetramethylethylenediamine.[14]



Reaction of the α-lithio-salt (16) of the sulphone (11) with alkyl halides always led to ring opening and subsequent *O*-alkylation to produce (18), in which the double bond is isomerized † from the α,β- to the β,γ-position (Table 2). The *C*-alkylated product (19) could never be detected. Replacement of n-butyl-lithium by lithium di-isopropylamide or sodium hydride only enhanced the yield of (18). Starting material was recovered quantitatively upon using tetrahydrofuran without hexamethylphosphorotriamide as solvent.

These results indicate a hardly attainable α-position to the sulphide, the sulphoxide, and also the sulphone group in (6), (10), and (11), respectively. Apparently

* The same phenomenon was observed by Nederlof *et al.*[5] in the case of the diastereoisomers of the β-hydroxy-sulphoxide (13), showing absorptions of the C(2)-methyl proton at δ 1.38 and 1.57.

† Isomerization of α,β-unsaturated sulphones and sulphoxides to the β,γ-compounds under basic conditions is often observed; see *e.g.* ref. 15.

TABLE 2

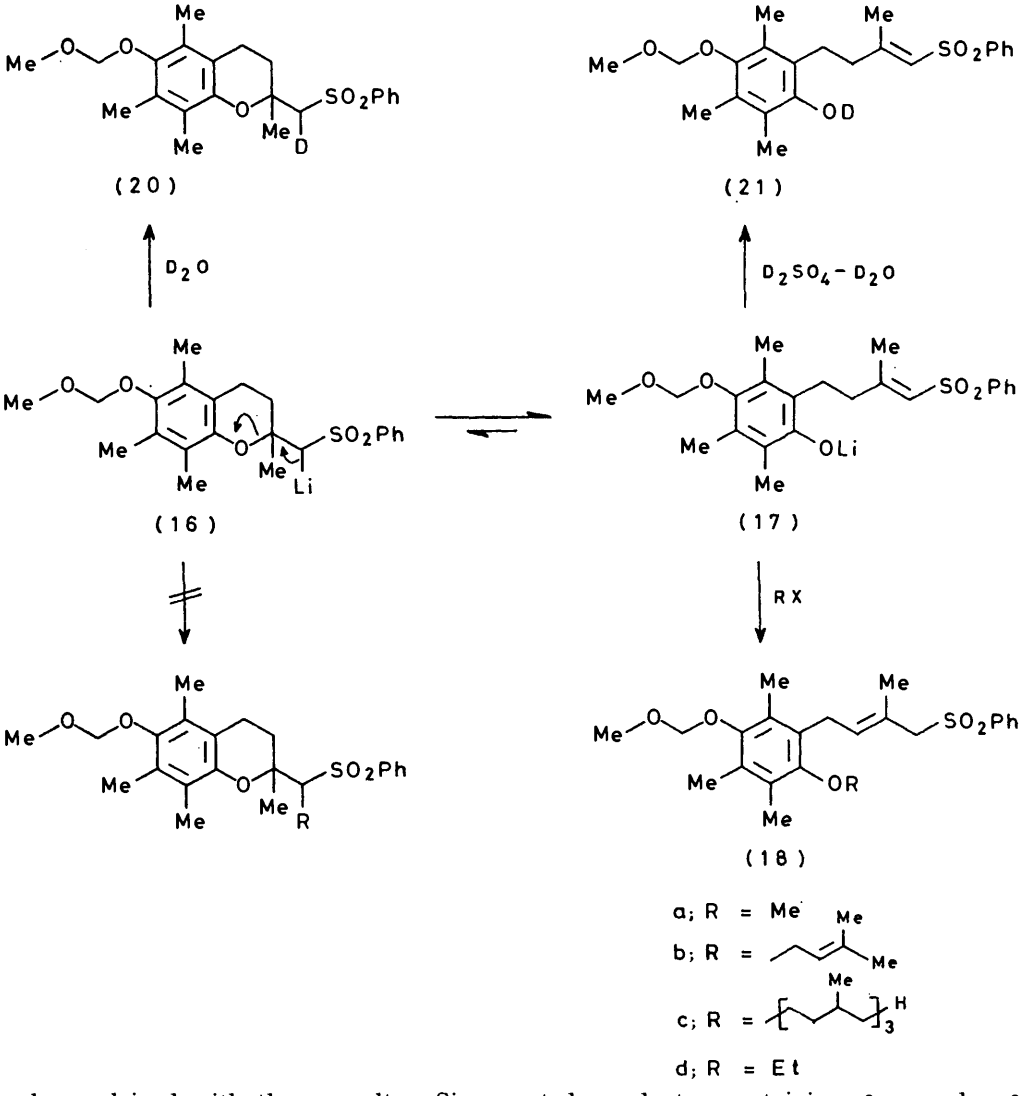
Alkylation of (11)

Base	Solvent	Temperature (°C)	RX	Yield (%) (11)	(19)	(18)
Bu^nLi	HMPT–THF	0	MeI	28	0	28 (18a) [b]
Bu^nLi	HMPT–THF	0	$CMe_2{=}CHCH_2Br$	0	0	60 (18b)
Bu^nLi	HMPT–THF	0	$H{-}[CH_2CHMe(CH_2)_2]_3{-}Br$	30	0	24 (18c)
Bu^nLi	THF	−50	$H{-}[CH_2CHMe(CH_2)_2]_3{-}Br$	100	0	0 (18c)
LDP [a]	THF–HMPT	0	EtBr	0	0	65 (18d)
NaH	THF–HMPT	20	EtBr	40	0	40 (18d) [b]
NaH	THF–HMPT	−25	EtBr	40	0	40 (18d) [b]

[a] Lithium di-isopropylamide. [b] (11) and (18a, d) could not be separated; yields were calculated from ^1H n.m.r.

the α-lithio-sulphone (16) is able to open the ring as shown. Subsequently the lithio-salt (17) is alkylated leading to (18). The quenching experiments on the lithio-salts of (6), (10), and (11) with deuterium oxide leading to the α,β-unsaturated sulphone (21). No β,γ-isomer was isolated.

Upon attempted alkylation of the sulphoxide (10) *O*-alkylation was observed in low yield. In the *O*-alkyl-



(Table 1) can be explained with these results. Since deuterium oxide is not able to replace the lithium ion in open structure (17), the equilibrium between (16) and (17) is completely shifted backwards to the α-deuteriated sulphone (20). Quenching with D_2SO_4 in D_2O confirmed this supposition, because we then observed replacement of the lithium in (17) by deuterium for 90%, ated products, containing β,γ- and α,β-unsaturated sulphoxides,* partial substitution on the sulphoxide leading to the corresponding n-butyl sulphoxides, has occurred.† These observations support the supposition

* See footnote † on p. 2125.

† Similar substitutions were observed by Durst *et al.*[16]

of a hardly attainable α-position to the sulphoxide moiety in (10).

EXPERIMENTAL

All reactions with Lewis acids, Bu^nLi, NaH, and LDP were carried out under nitrogen in carefully dried glassware. Bu^nLi (Merck, 2.0—1.3 mmol ml^{-1} in hexane, depending on batch) was added with a syringe through a septum. THF was freshly distilled from $LiAlH_4$; HMPT was distilled from CaH_2 and stored over molecular sieves. Thin layer chromatography (t.l.c.) was performed on Merck silica gel 60 F_{254} plates. ^1H N.m.r. spectra were recorded on a Varian HA-100 spectrometer, i.r. spectra on a Unicam SP 200 spectrometer, and mass spectra with an A.E.I. MS-9 instrument. Elemental analyses, performed by Mr. H. Pieters of this laboratory, were only obtained from crystalline samples.

6-Acetoxy-2,5,7,8-tetramethylchroman-2-carbaldehyde (4).—The monothioacetal (14) (77 mg, 0.18 mmol) was dissolved in ethanol (2 ml). Under nitrogen, 5% sodium hydroxide in water (0.6 ml, 0.7 mmol) was added. The mixture was stirred at room temperature for 1.5 h and neutralized with 5% sulphuric acid. After extraction with ether, drying, and evaporation a red oil (56 mg) was isolated, which was dissolved in pyridine (1 ml) and acetic anhydride (0.15 ml). After 16 h the mixture was thoroughly evaporated (with toluene) to give a brown oil (61 mg). T.l.c. on silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (5 : 1)] yielded the acetoxyaldehyde (4) as a yellow oil (32 mg, 65%). The i.r. and n.m.r. data agreed with those reported by Mayer *et al.*[4a]

2,5,7,8-Tetramethyl-2-[(phenylthio)methyl]chroman-6-ol (6).—(a) *From 2-methyl-1-(phenylsulphinyl)but-3-en-2-ol* (13). To a stirred solution of the trimethylhydroquinone (1) (360 mg, 2.37 mmol) and the hydroxy-sulphoxide (13) (500 mg, 2.38 mmol) in nitromethane (25 ml, distilled and dried over molecular sieves) at 85 °C, $SnCl_4$ (540 μl, 4.8 mmol) was injected through a septum. After the mixture had been stirred for 2 h it was cooled and poured onto ice. Extraction with chloroform, washing with a 5% NaOH solution, and then water, drying, and evaporation gave a red residue. Column chromatography on silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (25 : 1—1 : 1)] yielded the chroman-sulphide (6) (270 mg, 35%) as a yellow oil. A sample was crystallized from nitromethane at −25 °C, m.p. 71.5—74 °C.

(b) *From 2-methyl-1-(phenylthio)but-3-en-2-ol* (12). To a stirred solution of trimethylhydroquinone (1) (1.52 g, 10 mmol) and boron trifluoride–ether (1.4 ml, 11 mmol) in nitromethane (30 ml, distilled and dried) at 85 °C, the hydroxy-sulphide (12) (1.95 g, 10 mmol) dissolved in nitromethane (20 ml), was added during 15 min. After 1 h the dark red-brown mixture was cooled and then saturated $NaHCO_3$ solution (20 ml) was added. Vigorous stirring during 15 min afforded a yellow solution to which chloroform (30 ml) was added. After separation, the water layer was washed with chloroform and the combined organic layers were dried and evaporated until some nitromethane (±10 ml) was still left. The dark green residue was cooled overnight (−25 °C) to give the crystalline hydroxychroman-sulphide (6) (2.74 g, 84%). Crystallization of the mother-liquor in nitromethane yielded a second crop of (6) (0.27 g, 9%) (Found: C, 73.1; H, 7.3; S, 9.7. $C_{20}H_{24}O_2S$ requires C, 73.12; H, 7.37; S, 9.76%); $\nu_{max.}$($CHCl_3$) 3 700, 1 590, 1 460, and 1 080 cm^{-1}; δ($CDCl_3$) 7.5—7.0 (5 H, m, Ph), 4.22 (1 H, s, OH), 3.15 (2 H, s, CH_2SPh), and 1.35 [3 H, s, C(2)-Me]; *m/e* 328 (42%, M^+), 218 (M − PhSH, 20), 205 (M − $PhSCH_2$, 100), 203 (205 − H_2, 49), and 110 (PhSH, 35).

1,2-Isoprene Oxide.—Synthesis was according to Reist *et al.*,[7] modified as suggested by Eletti-Bianchi *et al.*[17] Isoprene bromohydrin, synthesized from isoprene and *N*-bromosuccinimide, was distilled (b.p. 60—80 °C, 10 mmHg) and subsequently distilled from powdered NaOH (b.p. 70—75 °C, 76 mmHg). Separation of the water layer and drying over $MgSO_4$ afforded 1,2-isoprene oxide in 70% yield from isoprene.

6-Acetoxy-2,5,7,8-tetramethyl-2-[(phenylthio)methyl]-chroman (7).—The hydroxychroman-sulphide (6) (95 mg, 0.29 mmol) was dissolved in pyridine (1 ml) and acetic anhydride (0.15 ml). After 16 h the mixture was evaporated thoroughly (finally with toluene) to give a reasonably pure sample of the acetate (7) (106 mg, 95%) as a yellow oil. Preparative t.l.c. on silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (2 : 1)] yielded a clear oil (83 mg) which slowly crystallized. Recrystallization from light petroleum afforded white crystals, m.p. 72.5—75 °C (Found: C, 71.2; H, 7.0; O, 13.1; S, 8.7. $C_{22}H_{26}O_3S$ requires C, 71.32; H, 7.07; O, 12.96; S, 8.65%); $\nu_{max.}$($CHCl_3$) 1 750, 1 460, 1 370, 1 230, 1 200, and 1 075 cm^{-1}; δ($CDCl_3$) 7.5—7.1 (5 H, m, Ph), 3.17 (2 H, s, CH_2SPh), 2.28 (3 H, s, $MeCO_2$), and 1.37 [3 H, s, C(2)-Me]; *m/e* 370 (32%, M^+), 328 (M − C_2H_2O, 20), 247 (M − $PhSCH_2$, 80), 245 (247 − H_2, 4), 205 (328 − $PhSCH_2$, 100), and 203 (205 − H_2, 64).

6-Acetoxy-2,5,7,8-tetramethyl-2-[(phenylsulphinyl)methyl]-chroman (9).—To a stirred solution of the chroman-sulphide (7) (1.04 g, 2.8 mmol) in dioxan–water (7 : 3, 50 ml) *N*-bromosuccinimide (0.55 g, 3.1 mmol; recrystallized from water and stored in a refrigerator) was added.[9,*] After 10 min the orange solution was extracted with ether. Washing of the organic layer with water and a saturated $NaHCO_3$ solution, drying, and evaporation afforded a yellow residue. Column chromatography through silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (10 : 1—1 : 1)] yielded the crude chroman-sulphoxide (9) (1.07 g) as a yellow oil. Crystallization from light petroleum (b.p. 60—80 °C) (200 ml) gave after 16 h at room temperature, and then one week at −25 °C, respectively, two crystalline fractions (I and II) consisting of the two diastereoisomeric pairs of racemates. According to its n.m.r. spectrum fraction I (m.p. 141—143 °C; 0.49 g, 45%) is enriched to 95% with one of the racemates (racemate A).† Fraction II (m.p. 102—108 °C; 0.53 g, 49%) is 80% enriched with the second racemate (B). Racemate A (Found: C, 68.2; H, 6.7; S, 8.4. $C_{22}H_{26}O_4S$ requires C, 68.36; H, 6.78; S, 8.30%); $\nu_{max.}$($CHCl_3$) 1 750, 1 450, 1 375, 1 200—1 240, 1 085 (S=O), 1 075, 1 030 (S=O), and 1 020 cm^{-1}; δ($CDCl_3$) 7.4—7.7 (5 H, m, Ph), 3.06 (2 H, s, CH_2SOPh ‡), 2.28 (3 H, s, $MeCO_2$), and 1.45 [3 H, s, C(2)-Me]; *m/e* 386 (28%, M^+), 369 (M − OH, 60, m^* = 352.7), 344 (M − C_2H_2O, 16), 260 (M − PhSOH, 10), 219 (260 − C_2H_2O, 52), 259 (M − PhSO − H_2, 26), 247 (M − $PhSOCH_2$, 22), 205 (247 − C_2H_2O, 30), 203 (205 − H_2, 62), and 191 (219 − C_2H_5, m^* = 166.6, 100). Racemate B δ($CDCl_3$) 7.4—7.7

* Oxidation with *m*-chloroperbenzoic acid was unsuccessful.

† No attempts have been made to reveal the relative configuration.

‡ N.m.r. spectra in hexadeuteriobenzene display an AB system.

(5 H, m, Ph), 2.98 (2 H, AB system, δ_A 2.92, δ_B 3.03, J_{AB} 12 Hz, CH_2SOPh), 2.28 (3 H, s, $MeCO_2$), and 1.66 [3 H, s, C(2)-Me]; other data were identical to those of racemate A.

6-*Methoxymethoxy*-2,5,7,8-*tetramethyl*-2-[(*phenylsulphinyl*)*methyl*]*chroman* (10).—The synthesis was by oxidation, with *m*-chloroperbenzoic acid, of 6-methoxymethoxy-2,5,7,8-tetramethyl-2-[(phenylthio)methyl]chroman. This compound was prepared in quantitative yield from the corresponding alcohol (6) according to Yardley and Fletcher.[11] To a solution of the chroman-sulphide ether (326 mg, 0.88 mmol) in ether (10 ml) which was cooled at −40 °C, *m*-chloroperbenzoic acid (180 mg, 0.88 mmol) dissolved in dichloromethane (15 ml) was added very slowly. The mixture was set aside overnight in the refrigerator. After evaporation of the solvents, the residue was dissolved in chloroform (10 ml), washed with a saturated $NaHCO_3$ solution (3 × 10 ml), and then water, dried, and evaporated. Preparative t.l.c. on silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (2 : 1)] yielded the chroman-sulphoxide ether (10) as a yellow oil (254 mg, 74%). The corresponding sulphone (11) was also isolated (40 mg, 11%). Preparation of the sulphoxide (10) by oxidation of the sulphide with *N*-bromosuccinimide, as previously mentioned for the corresponding acetates, provided (10) in 70% yield after t.l.c. Separation of the diastereoisomeric racemates could not be achieved; $\nu_{max.}$($CHCl_3$) 1 460, 1 240, 1 210, 1 160, 1 085 (S=O), 1 060, 1 030 (S=O), and 975 cm^{-1}; δ($CDCl_3$) 7.4—7.7 (5 H, m, Ph), 4.85 (2 H, s, OCH_2O), 3.58 (3 H, s, MeO), 3.07 (s, CH_2SOPh), and 3.06 (AB system, δ_A 3.10, δ_B 3.01, J_{AB} 11 Hz, CH_2SOPh *), and 1.67 and 1.47 [3 H, s, C(2)-Me *]; *m/e* 388 (7%, M^+), 344 (M − CH_2H_4O, 2), 219 (344 − PhSO, 13), 217 (219 − H_2, 100), 218 (344 − PhSOH, 22), 205 (344 − $PhSOCH_2$, 3), 203 (205 − H_2, 18), 343 (M − C_2H_5O, 1), 217 (343 − PhSOH, *m** = 137.3, 100), and 371 (M − OH, 4).

6-*Methoxymethoxy*-2,5,7,8-*tetramethyl*-2-[(*phenylsulphonyl*)*methyl*]*chroman* (11).—The synthesis was performed as described for (10) using 2 mol. equiv. of *m*-chloroperbenzoic acid. T.l.c. on silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (2 : 1)] yielded a colourless oil (100%) which slowly crystallized from light petroleum (b.p. 60—80 °C), m.p. 73—81 °C; $\nu_{max.}$($CHCl_3$) 1 450, 1 310 (SO_2), 1 300 (SO_2), 1 200, 1 150 (SO_2), 1 075, and 975 cm^{-1}; δ($CDCl_3$) 7.8—8.0 (m, 2 aromatic H), 7.4—7.6 (m, 3 aromatic H), 4.90 (2 H, s, OCH_2O), 3.63 (3 H, s, MeO), 3.43 (2 H, AB, δ_A 3.52, δ_B 3.34, J_{AB} = 14 Hz, CH_2SO_2Ph), and 1.65 [3 H, s, C(2)-Me]; *m/e* 404 (34%, M^+), 359 (M − C_2H_5O, *m** = 319, 48), 217 (359 − $PhSO_2H$, *m** = 131.2, 100), 175 (217 − C_3H_6, 19), and 203 (359 − $PhSO_2Me$, 30).

2-*Methyl*-1-(*phenylthio*)*but*-2-*en*-1-*ol* (12).—This was synthesized according to the method of Zaitseva and Al'bitskaya.[8] The reaction time was extended from 6—12 h to 70 h. The crude yellow oil (100%) needed no further purification (g.l.c. on 8% Carbowax, temperature 175 °C).

6-*Acetoxy*-2-[*acetoxy*(*phenylthio*)*methyl*]-2,5,7,8-*tetramethylchroman* (14).—A mixture of the diastereoisomeric chroman-sulphoxides (9) (64 mg, 0.165 mmol) and anhydrous sodium acetate (64 mg, 0.78 mmol) was dissolved in acetic anhydride (3 ml). The mixture was slowly heated to 135 °C. Subsequent heating for 7 h, cooling, and evaporation of the solvent by distillation with toluene gave a brown residue, which was purified through a silica gel filter [1 g SiO_2, light petroleum (b.p. 60—80 °C)–ethyl acetate (10 : 1, 50 ml)]. The monothioacetal (14) was isolated as a yellow oil (65 mg, 92%). A sample was crystallized from light petroleum (b.p. 60—80° C) (m.p. 120—123 °C) (Found: C, 67.2; H, 6.6; O, 18.7; S, 7.5. $C_{24}H_{28}O_5S$ requires C, 67.26; H, 6.59; O, 18.67; S, 7.48%); $\nu_{max.}$($CHCl_3$) 1 750, 1 375, 1 240, 1 200, 1 075, and 1 020 cm^{-1}; δ($CDCl_3$) 7.5—7.1 (5 H, m, Ph), 6.42 and 6.33 (1 H, 2 × s, CH(OAc)SPh *), 2.28 (3 H, s, $MeCO_2$), and 1.44 and 1.40 [3 H, 2 × s, C(2)-Me *].

Quenching Experiments (*Table* 1).—The chroman compounds (6), (10), or (11) (110—60 mg, *ca.* 0.3 mmol) were dissolved in THF (4 ml), THF with HMPT (5 ml; 3 : 2), or THF (4 ml) with TMEDA (2 mol. equiv.). The solution was cooled either to 0 or to −50 °C and then Bu^nLi was slowly injected. After 0.5 h D_2O (3—5 mol. equiv.) was added and the cooling bath was removed. The mixture was poured into water (2—3 ml) and extracted with ether (3 × 5 ml). When HMPT or TMEDA were used, the organic layers were washed with water (5 × 5 ml). The crude products, isolated after drying and evaporation, needed no further purification. The percentage deuteriation of (6) and (10) was calculated from the value of $(M + 1)/M$ in the mass spectra; the deuteriation of (11) was determined from the intensity of the $PhSO_2CH_2$ absorption at δ 3.43 in the n.m.r. spectra.

Alkylation of (11) (*Table* 2).—The anion of the chroman-sulphone (11) was prepared with Bu^nLi (1.1 mol. equiv.) as described for the quenching experiments. When LDP or NaH were used (11) (0.3 mmol) was dissolved in THF–HMPT (3 ml; 2 : 1) and subsequently added to a solution of LDP [1.1 mol. equiv. of Bu^nLi added to 1.1 mol. equiv. of di-isopropylamine dissolved in THF–HMPT (2 ml; 1 : 1)] or NaH [1.1 mol. equiv. washed with dry pentane and dissolved in THF–HMPT (2 ml; 1 : 1)]. The mixture was stirred for 0.5 h, then the alkyl halide (1.0—1.5 mol. equiv.) was injected and allowed to react at room temperature for 3 h. The mixture was poured into water (2—3 ml) and extracted with ether (3 × 5 ml). The organic extracts were washed with water (5 × 5 ml). Preparative t.l.c. on silica gel [light petroleum (b.p. 60—80 °C)–ethyl acetate (5 : 1)] afforded the *O*-alkylated product (18) (24—60%); (18a); $\nu_{max.}$($CHCl_3$) 1 450, 1 315, and 1 160 cm^{-1}; δ($CDCl_3$) 7.9—8.0 (m, 2 aromatic H), 7.5—7.7 (m, 3 aromatic H), 5.40 (1 H, t, *J* 7 Hz, vinyl H), 4.83 (2 H, s, OCH_2O), 4.03 (2 H, s, CH_2SO_2Ph), 3.57 (3 H, s, $MeOCH_2$), 3.50 (3 H, s, *Me*OAr), 2.81 (2 H, d, *J* 7 Hz, CH_2Ar), 2.11, 2.09, and 2.03 (9 H, 3 × s, Ar*Me*), and 1.78 (3 H, s, *Me*-allyl); *m/e* 418 (M^+, 8%), 277 (M − $PhSO_2$, 5), 276 (M − $PhSO_2H$, 11), 231 (376 − C_2H_5O, 47), and 94 (PhOH, 100).

Quenching with D_2SO_4.—The α-lithio-salt (16) of the sulphone (11) (0.3 mmol), prepared in THF as mentioned previously, was quenched with D_2SO_4 (1.0 mmol) in D_2O (3 ml). The usual work-up, with water, allowing slow exchange of deuterium with the phenolic OH, furnished a clear yellow oil. The ^1H n.m.r. spectrum indicated a mixture of the αβ-unsaturated sulphone (21) (90%) and the sulphone (11) (10%; 0% D). Purification on silica gel caused ring-closure of (21), leading to starting material (11); $\nu_{max.}$($CHCl_3$) 3 400, 1 630, 1 310, 1 160, and 1 100 cm^{-1}; δ($CDCl_3$) 7.8—8.0 (m, 2 aromatic H), 7.4—7.7 (m, 3 aromatic H), 6.14 and 6.22 [1 H, 2 × s, vinyl-H (*Z* and *E*, respectively, 2 : 1)], and 1.85 and 2.04 [3 H, 2 × s, allyl-*Me* (*E* and *Z*, respectively)].

* Two pairs of enantiomers.

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