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44. Synthesis of Vitamin A via Sulfones: A C₁₅ Sulfone Route

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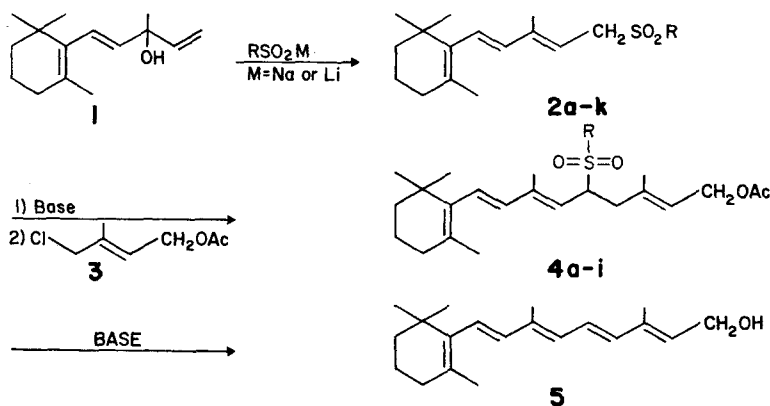
(4. XII. 75)

Summary. A synthesis of vitamin A has been achieved by alkylating a β -ionylidene-ethyl (C₁₅) aromatic sulfone with 1-acetoxy-3-chloromethyl-2-butene (C₅) followed by elimination of the corresponding sulfinic acid.

In recent years the application of sulfones to the synthesis of natural products has increased considerably [1]. This increased interest stems from the recognition that sulfones can stabilize anions [2], may be removed reductively [3] and, where appropriate, may be eliminated to form olefins [4]. One recent application of sulfones, which prompted our interest in this area, is an elegant synthesis of retinoic acid by Julia *et al.* [5]

In this paper we describe a direct synthesis of vitamin A alcohol (5) by the series of reactions outlined in Scheme 1.

Scheme 1

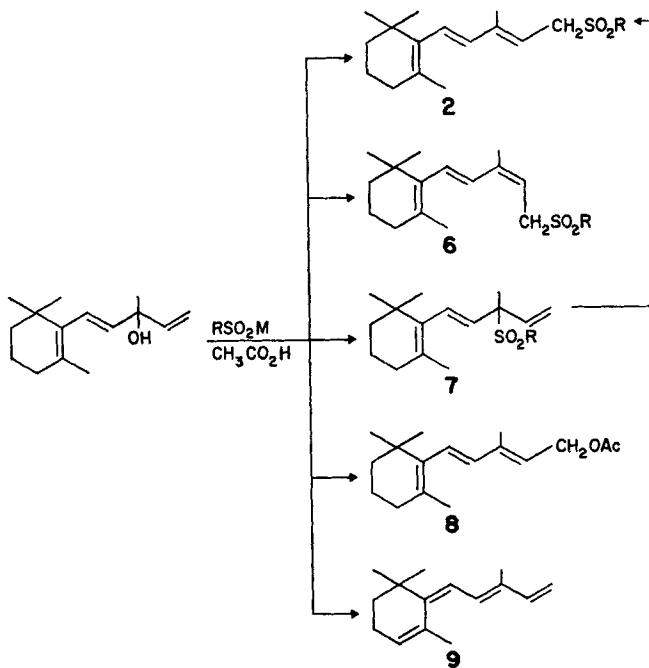


Reaction of vinyl- β -ionol (**1**) [6] with the lithium or sodium salt of a sulfinic acid, essentially as described by *Julia* [5], gave the C_{15} -sulfones **2** (a-k)¹⁾ which on alkylation with 1-acetoxy-3-chloromethyl-2-butene (**3**) [7] afforded the C_{20} -sulfones **4** (a-i); certain of these on base treatment furnished vitamin A (**5**). Table I lists the C_{15} - and C_{20} -sulfones which were used in the present study.

It was recognized at the onset that a major problem in this synthesis would be the elimination of the sulfinic acid from the C_{20} -sulfone. To this end we have explored some of the factors which were expected to influence the elimination reaction, namely electronic and steric factors associated with the sulfone group, as well as the effect of various bases and solvents.

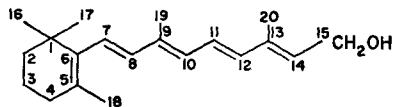
Preparation of C_{15} -Sulfones. – The C_{15} -sulfones **2** were conveniently prepared [5] by reacting vinyl- β -ionol (**1**) with the sodium or lithium salt of the sulfinic acid [8] in acetic acid. In general there was a rapid disappearance of starting material with the initial formation of several products, however, as the reaction proceeded, one of these was further converted into the all-*trans* primary sulfone which becomes the main product.

Scheme 2



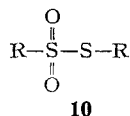
By terminating the reaction at an early stage it was possible to isolate the primary all-*trans*- and $\Delta^{9,10}$ -*cis*-sulfones, **2** and **6** respectively (see Scheme 2). In addition, the

¹⁾ Numbering system: C_{15} and C_{20} refer to the isoprenoid skeleton.



acetate **8** and the tetraene hydrocarbon **9** were also isolated in quantities which appear to depend on the strength of the sulfinic acid used. In certain cases we were also able to isolate compounds for which we tentatively assign the tertiary sulfone structure **7** (see later).

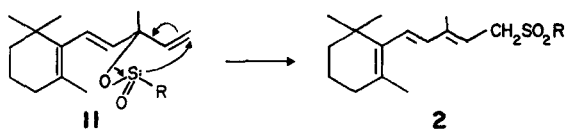
Interestingly, although the salts of sulfinic acids in acetic acid are known to disproportionate giving products for which the sulfone-sulfide structure **10** has been



proposed [9], we were unable to identify any of these in the preparation of the C₁₅-sulfones. These compounds were, however, readily obtained according to [9].

The mixture of C₁₅-sulfones produced was usually separable by chromatography (column or thin-layer) and the individual isomers were readily identified by their characteristic ¹H-NMR. spectra. Thus, the C_{7,8} protons appeared as a singlet at *ca.* δ 6.0 in the all-*trans* isomer, but at lower fields in the Δ^{9,10}-*cis* isomer. The tertiary sulfone, in addition to showing the expected *ABX* pattern for the vinyl group, also exhibited an *AB* quartet for the C_{7,8} protons.

It has already been mentioned that an intermediate is apparently involved in the formation of the C₁₅-sulfones. This observation led us to entertain the possibility that this reaction might proceed *via* a [2,3]-sigmatropic rearrangement [10] of an allylic sulfinate ester **11**.



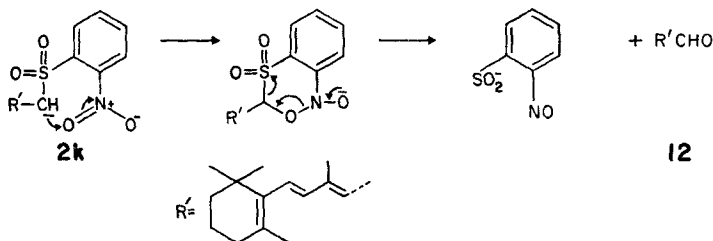
Examination of the reaction mixture for the preparation of **2b** led to the isolation of a substance, C₂₂H₃₀O₃S, whose NMR. properties were compatible with either the sulfinate **11** or the tertiary sulfone **7b**. However, this compound had IR. bands

Table 1

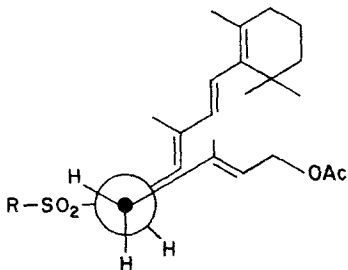
Compound	R	Compound	R	Compound	R
2a and 4a		2e and 4e		2h and 4h	
2b, 4b and 7b		2f and 4f		2i and 4i	
2c and 4c		2g and 4g		2j	
2d and 4d				2k	

(1130 and 1300 cm^{-1}) which are characteristic of sulfones and was quite stable to conditions which are known to convert allylic sulfinate esters into sulfones [11]. It appears that the material we have isolated is the tertiary sulfone **7b**, rather than the sulfinate **11**. Treatment of the isolated material with acetic acid at room temperature gave the primary sulfone **2b**.

Preparation of C₂₀-Sulfones 4. – Alkylation of the C₁₅-sulfones with the chloro-ester **3** was readily accomplished in most cases using potassium *t*-butoxide, sodium hydride or dimsyl sodium with THF, DMF or DMSO as solvent. No alkylation occurred with the nitro compounds **2j** and **2k** and, in the case of sulfone **2k**²), an aldehyde **12** was formed possibly by an internal oxidation of the anion by the nitro group:



From a study of the ^1H -NMR. spectra it was possible to obtain some information concerning the conformation of the C_{20} -sulfones. All the C_{20} -sulfones displayed the C(12) methylene protons as a pair of doublets centered at *ca.* δ 2.7 (geminal coupling, $J = 14$ Hz) which were modified by unequal coupling to the proton at C(11): the low field doublet appeared as an unresolved quartet ($J = 4$ Hz) in most cases, whereas the high field doublet gave a well defined quartet with a coupling constant of 10 Hz. From these coupling constants the preferred rotamer of the C_{20} -sulfones would appear to be the one in which the groups are nearly eclipsed:



Another noteworthy feature in the ^1H -NMR. spectra of the C_{20} -sulfones was the exceptionally high field (δ 1.15–1.40) at which the C(9) methyl group occurred, this was particularly evident in compounds **4a**, **4b**, **4c** and **4h**.

Elimination to form Vitamin A. — Of crucial importance to any synthesis of the vitamin from a C₂₀-sulfone is a satisfactory elimination procedure which should

2) We are most grateful to Dr. *A. Fischli*, Hoffmann-La Roche Inc., Basel, for a supply of this material.

not only give the product in high yield, but should also give a high preponderance of the all-*trans* isomer.

Previous studies [4] on the elimination reaction of sulfones, which did not have an activating group to assist in the process, indicate that vigorous conditions were required. Our aim was therefore to utilize the electronic and steric effects present in the substituted sulfones **4a–i**, in conjunction with an appropriate base, to facilitate the elimination process.

Somewhat surprisingly, we found no significant difference in the yield of vitamin A when the various C₂₀-sulfones were subjected to base treatment (KOH in aqueous *n*-butanol, 100–120°). Indeed, the best yield of product was obtained with the unsubstituted phenyl sulfone **4a**. With the trichloro-derivative **4f**, the *para* chlorine atom was displaced by methoxide to give the sulfone **13**, whereas with sodium acetate in refluxing DMF the *retro* product **14** was formed; **14** was also formed when the *t*-butyl derivative was refluxed in DMF.

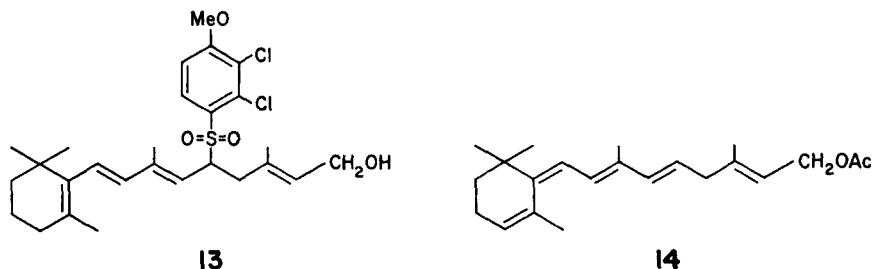


Table 2. Base Treatment of Sulfone **4a**

Base (M) ^a /Solvent	Temp. (°C)/ Time (h)	Yield (%) of Vitamin A Acetate						
		UV.		HPLC ^b		13- <i>cis</i> <i>retro</i>	others	total
		<i>trans</i>	9/9, 13- <i>cis</i> ^c	13- <i>cis</i>	<i>retro</i>			
NaOMe (10)/ <i>n</i> -BuOH	80/4	–	29	1	4	2	–	36
NaOMe (10)/ <i>n</i> -BuOH	80/12	–	63	8	1	5	–	77
NaOEt (10)/EtOH	80/10	–	58	7	1	–	1(11- <i>cis</i>)	67
NaOEt (10)/EtOH	80/13	83	73	7	1	7	–	88
NaOEt (20)/EtOH	80/4	–	47	5	1	–	–	53
<i>t</i> -BuOK (4)/THF	25/16	5	5	1	–	–	–	6
<i>t</i> -BuOK (2)/DMSO	80/16	trace	–	–	–	–	–	–
<i>t</i> -BuOK (2)/ <i>t</i> -BuOH	80/16	19	–	–	–	–	–	–
NaNH ₂ (10)/liq. NH ₃ / <i>i</i> -PrOH	– 33/4	0	–	–	–	–	–	–
NaNH ₂ (10)/Pyridine	100/20	0	–	–	–	–	–	–
KOH (25)/ <i>n</i> -BuOH (5)/H ₂ O (1)	120/4	–	26	7	1	–	1(11- <i>cis</i>)	35
NaOH (5)/DMF	25/72	< 5	–	–	–	–	–	–
NaOH (5)/HMPA	25/72	< 5	–	–	–	–	–	–
Piperidine	106/5	0	–	–	–	–	–	–
Piperidine Acetate	106/4	0	–	–	–	–	–	–

^a) M = mol of the base per mol of sulfone.

^b) High pressure liquid chromatography.

^c) No separation between 9- and 9,13-di-*cis* isomers.

As the substituted aromatic sulfones did not appear to offer an advantage in the elimination reaction, we directed our attention to the effect of various solvents and bases on the phenyl sulfone **4a**. The results obtained from this study are given in Table 2. It can be seen from Table 2 that a high yield (88%) of vitamin A (assayed as its acetate), with a fairly high all *trans*-content (73%), was obtained when **4a** was refluxed with a large excess of sodium ethoxide in ethanol. It is also apparent from Table 2 that the best yields were obtained when protic solvents were employed, in accordance with the need to protonate the anion which is formed at C(11).

The facility with which we were able to effect the β -elimination reaction on the C₂₀-sulfone **4a**, without assistance from an activating group (*cf.* the synthesis of retinoic acid [5]), provides a fairly efficient synthesis of vitamin A from the readily available vinyl- β -ionol (**1**) and the chloro-ester **3**. In addition, it should be noted that since the sulfinic acid (as a salt) used in preparing the C₁₅-sulfones is regenerated in the final step it is, in principle, recoverable.

Experimental Part

All operations involving polyenes were carried out in an inert atmosphere (argon or nitrogen).

¹H-NMR. spectra were determined in CDCl₃ with tetramethyl silane as internal standard; chemical shifts are expressed in δ values (ppm). Unless otherwise indicated, IR. and UV. spectra were determined in chloroform and ethanol solutions respectively. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected.

Identification of the isomers of vitamin A acetate was achieved by high pressure liquid chromatography (HPLC.) using the following conditions: silica gel coated with β , β -oxydipropionitrile (ODPN) at 200 psi. with heptane/ODPN 28:72 as eluent. These conditions were developed by Dr. M. Vecchi, Physical Chemistry Department, Hoffmann-La Roche Inc. (Basle) to whom we express our gratitude. We are also grateful to the following members of our department: Dr. W. Benz (MS.), Dr. F. Scheidl (Microchem.), Dr. C. G. Scott (HPLC.), Dr. V. Toome (UV.), Mr. S. Traiman (IR.) and Dr. T. H. Williams (NMR.) for their invaluable assistance.

General Work-Up Procedure. This implies dilution with water followed by extraction into ether, washing with brine, drying over anhydrous MgSO₄ and evaporation.

Preparation of C₁₅-Sulfones. – 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-benzene-sulfonyl-trans,trans-penta-1,3-diene (**2a**). A mixture of 23.85 g vinyl- β -ionol (**1**, 92.2% pure as estimated by GLC.) and 20.0 g of sodium phenylsulfinate (Aldrich, 96% pure) in 125 ml of acetic acid was stirred at 25° for 70 h and then evaporated *in vacuo* at 50°. The residue was stirred with 250 ml of water and 250 ml of ether for 30 min, the organic phase was separated, washed with 200 ml of NaHCO₃ (5%) followed by saturated brine (3 $\times$ 300 ml), dried (MgSO₄) and evaporated to give 35.7 of a pale brown gum. This was dissolved in 50 ml of hexane, left at –15° overnight and decanted. The residue was then crystallized from methanol (overnight, –15°) to give 20.1 g (58%) of **2a** as virtually colorless crystals, m.p. 57–59°. – UV. ($\lambda_{\max}$ (ϵ)): 272 (15,350), 265 (14,920), 240 (13,420), and 227 (16,500) nm. – IR.: 1620, 1590, 1315, 1160, 1080 and 985 cm⁻¹. – NMR.: 0.98 (s, 6 H); 1.44 (s, 3 H); 1.66 (s, 3 H); 3.95 (d, *J* = 7, 2 H); 5.40 (t, *J* = 7 Hz, 1 H); 6.03 (s, 2 H); 7.58 (m, 3 H), and 7.87 (d $\times$ d, *J* = 7 and 2 Hz, 2 H). – MS. (*m/e*): 344 (0.05), 329 (0.01) and 203 (100).

C₂₁H₂₈O₂S (344.5) Calc. C 73.21 H 8.19 S 9.31% Found C 73.33 H 7.90 S 9.31%

Examination of the mother liquor and hexane wash by preparative-scale TLC. (silica gel, ether/hexane 1:1) led to the isolation of:

a) the *tetraene* **9** (14%), b.p. 68–70°/0.05 Torr (Kugelrohr). – UV. ($\lambda_{\max}$ (ϵ)): 325 (48,340); 312 (61,900) and 300 (51,400) nm. – IR.: 1600, 990 and 890 cm⁻¹. – NMR.: 1.0 (s, 3 H); 1.05 (s, 3 H); 1.29 (s, 6 H); 1.85 (m, 4 H), and 5.0–7.1 (m, 6 H). – MS. (*m/e*): 202.

C₁₅H₂₂ (202.3) Calc. C 89.04 H 10.96% Found C 88.84 H 11.10%

b) the *acetate* **8** (6%). – UV. ($\lambda_{\max}$ (ε)): 267 (7,825) and 230 (10,250) nm. – IR.: 1725, 1120 and 960 cm^{-1} . – NMR.: 1.0 (s, 6 H); 1.68 (s, 3 H); 1.87 (s, 3 H); 2.05 (s, 3 H); 4.72 (d, $J = 7$ Hz, 2 H); 5.54 (t, $J = 7$ Hz, 1 H); 6.00 (d, $J = 16$ Hz, 1 H), and 6.20 (d, $J = 16$ Hz, 1 H). – MS. (m/e): 262.

$\text{C}_{17}\text{H}_{26}\text{O}_2$ (262.4) Calc. C 77.82 H 9.99% Found C 77.53 H 9.98%

c) the *cis-sulfone* **6a** (ca. 5%) as a gum. – NMR.: 0.90 (s, 6 H); 1.52 (s, 3 H); 1.88 (s, 3 H); 3.94 (d, $J = 7$ Hz, 2 H); 5.30 (t, $J = 7$ Hz, 1 H); 5.90 (d, $J = 16$ Hz, 1 H); 6.20 (d, $J = 16$ Hz, 1 H); 7.55 (m, 3 H); 7.85 (m, 2 H). – MS. (m/e): 344 (0.1), 203 (100).

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(*p*-methoxybenzenesulfonyl)-trans, trans-1, 3-pentadiene (**2b**). A mixture of 15.4 g of the lithium salt of *p*-methoxybenzene sulfinic acid [8] and 9.7 g of vinyl- β -ionol in 44 ml of acetic acid was stirred at RT. for 3 h and then worked up to give 13.0 g of crude product. Chromatography on 400 g of silica gel with increasing amounts of ether in hexane gave:

a) the *tertiary sulfone* **7b** (1.9 g), m.p. 79–81° (from hexane). – IR. (nujol): 1136, 1300 and 970 cm^{-1} . – NMR.: 1.00 (s, 6 H); 1.60 (s, 3 H); 1.70 (br. s, 3 H); 3.90 (s, 3 H); 5.20 (d, $J = 17$ and 10 Hz, 2 H); 5.60 (d, $J = 16$ Hz, 1 H); 6.10 (d, $J = 16$ Hz, 1 H); 6.20 (d, $J = 17$ and 10 Hz, 1 H); 6.90 (d, $J = 9$ and 4 Hz, 2 H) and 7.73 (d, $J = 9$ and 4 Hz, 2 H).

$\text{C}_{22}\text{H}_{30}\text{O}_3\text{S}$ (374.5) Calc. C 70.55 H 8.07 S 8.56% Found C 70.44 H 7.81 S 8.42%

b) the *primary sulfone* **2b** (2.93 g), m.p. 69–71° (from hexane). – IR. (nujol): 1280 and 1125 cm^{-1} . – NMR.: 1.00 (s, 6 H); 1.50 (s, 3 H); 1.65 (s, 3 H); 3.80 (s, 3 H); 3.90 (d, $J = 9$ Hz, 2 H); 5.40 (t, $J = 9$ Hz, 1 H); 6.00 (s, 2 H); 6.90 (d, $J = 9$ Hz, 2 H) and 7.55 (d, $J = 9$ Hz, 2 H).

$\text{C}_{22}\text{H}_{30}\text{O}_3\text{S}$ (374.5) Calc. C 70.55 H 8.07 S 8.56% Found C 70.44 H 7.81 S 8.42%

The primary sulfone **2b** was formed when **7b** was treated with acetic acid.

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(*o*-methoxybenzenesulfonyl)-1, 3-pentadiene **2c**. A mixture of 8 g of vinyl- β -ionol, 12.5 g of lithium *o*-methoxybenzene sulfinate in 50 ml of acetic acid was stirred at RT. for 2 h. Work-up of the reaction mixture gave 14 g of crude sulfone **2c** which was purified by chromatography on 250 g of silica gel with ether/hexane 1:1 and 2:1 as eluents. Removal of the solvents gave 6.5 g of **2c** as a gum. – NMR. 0.95 (s, 6 H); 1.55 (s, 3 H); 1.65 (s, 3 H); 3.95 (s, 3 H); 4.00 (d, $J = 8$ Hz, 2 H); 5.20 (t, $J = 8$ Hz, 1 H); 5.90 (s, 2 H); 7.0–7.6 (m, 4 H).

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(2,4-dimethoxybenzenesulfonyl)-trans, trans-1, 3-pentadiene (**2d**). To a solution of 4.1 g of sodium carbonate in 20 ml of water was added 5.35 g of 2,4-dimethoxybenzene sulfinic acid [8]. The mixture was evaporated to dryness at 45° and the residue stirred with 4.5 g of vinyl- β -ionol in 25 ml of acetic acid for 20 h. Work-up of the reaction followed by chromatography on 500 g of silica gel with ether/hexane 6:4 furnished 6.3 g of sulfone **2d** as an oil. – NMR.: 0.93 (s, 6 H); 1.65 (s, 3 H); 1.80 (s, 3 H); 3.80 (s, 3 H); 3.90 (d, $J = 7$ Hz, 2 H); 3.91 (s, 3 H); 5.30 (t, $J = 7$ Hz, 1 H); 5.96 (s, 2 H); 6.44 and 7.75 (m, 3 H).

$\text{C}_{22}\text{H}_{32}\text{O}_4\text{S}$ (404.5) Calc. C 68.28 H 7.97 S 7.93% Found C 68.18 H 8.07 S 7.82%

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(*p*-chlorobenzenesulfonyl)-trans, trans-1, 3-pentadiene (**2e**). A mixture of 3.3 g vinyl- β -ionol and 3.3 g of sodium *p*-chlorobenzene sulfinate [8] was stirred at RT. for 2 days. Work-up of the reaction mixture followed by crystallization from hexane gave the sulfone **2e**, m.p. 99–101°. – NMR.: 1.00 (s, 6 H); 1.50 (s, 3 H); 1.60 (s, 3 H); 3.85 (d, $J = 8$ Hz, 2 H); 5.25 (t, $J = 8$ Hz, 1 H); 5.95 (s, 2 H); 7.40 (d, $J = 8$ Hz, 2 H) and 7.75 (d, $J = 8$ Hz, 2 H).

$\text{C}_{21}\text{H}_{27}\text{ClO}_2\text{S}$ (378.6) Calc. C 66.56 H 7.18 Cl 9.35 S 8.14%
Found „ 66.49 „ 6.88 „ 9.35 „ 8.41%

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(2,3,4-trichlorobenzenesulfonyl)-trans, trans-1, 3-pentadiene (**2f**). A mixture of 6.6 g of vinyl- β -ionol and 10 g of sodium 2,3,4-trichlorobenzene sulfinate in 30 ml of acetic acid was stirred at RT. for 24 h and worked up. Crystallization from hexane gave 9.8 g of **2f**, m.p. 105–107°. – NMR. (CCl_4): 1.00 (s, 6 H); 1.5 (s, 3 H); 1.70 (s, 3 H); 4.10 (d, $J = 8$ Hz, 2 H); 5.20 (t, $J = 8$ Hz, 1 H); 6.00 (br. s, 2 H); 7.45 (d, $J = 7$ Hz, 1 H); 7.85 (d, $J = 7$ Hz, 1 H).

$\text{C}_{21}\text{H}_{25}\text{Cl}_3\text{SO}_2$ (447.9) Calc. C 56.32 H 5.63 Cl 23.75 S 7.16%
Found „ 56.36 „ 5.76 „ 23.76 „ 7.28%

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(p-nitrobenzenesulfonyl)-trans,trans-1,3-pentadiene (2j). A mixture of 1.2 g of sodium *p*-nitrobenzene sulfinate [8] and 1.2 g of vinyl- β -ionol in 10 ml of acetic acid was stirred at RT. for 24 h. Work-up gave 1.78 g of **2j** as an unstable substance m.p. 126–128° (from ether). – NMR.: 1.00 (s, 6 H); 1.50 (s, 3 H); 1.65 (s, 3 H); 4.0 (d, $J = 8$ Hz, 2 H); 5.30 (t, $J = 8$ Hz, 1 H); 6.00 (s, 2 H); 8.00 (d, $J = 7$ Hz, 2 H); 8.40 (d, $J = 7$ Hz, 2 H).

$C_{21}H_{27}NO_4S$	Calc.	C 64.76	H 6.99	N 3.60	S 8.23%
(389.4)	Found	64.64	7.02	3.60	8.26%

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(p-cyanobenzenesulfonyl)-trans,trans-1,3-pentadiene (2g). A mixture of 0.57 g of sodium *p*-cyanobenzene sulfinate [8] and 0.5 g of vinyl- β -ionol in 5 ml of acetic acid was stirred at RT. for 16 h. Work-up followed by crystallization from ether gave **2g**, m.p. 114–115°.

$C_{22}H_{27}NO_2S$	Calc.	C 71.51	H 7.37	N 3.79	S 8.68%
(369.4)	Found	71.20	7.20	3.66	8.39%

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(2,4,6-trimethylbenzenesulfonyl)-trans,trans-1,3-pentadiene (2h). A mixture of 11.5 g of 2,4,6-trimethylbenzene sulfonic acid [8], 5 g of sodium acetate and 11.0 g of vinyl- β -ionol in 100 ml of acetic acid was stirred at RT. for 24 h. Work-up of the reaction followed by crystallization from hexane gave 13.05 g of **2h**, m.p. 84–86°. – NMR.: 1.00 (s, 6 H); 1.45 (s, 3 H); 1.60 (s, 3 H); 2.25 (s, 3 H); 2.60 (s, 6 H); 3.90 (d, $J = 8$ Hz, 2 H); 5.30 (t, $J = 8$ Hz, 1 H); 6.00 (s, 2 H); 6.90 (s, 2 H).

$C_{24}H_{34}O_2S$ (386.51)	Calc.	C 74.57	H 8.87	S 8.29%	Found	C 74.84	H 9.16	S 8.11%
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*1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-*t*-butylsulfonyl-trans,trans-1,3-pentadiene (2i)*. A mixture of 1.5 g of lithium *t*-butyl sulfinate [8] and 2.2 g of vinyl- β -ionol in 25 ml of acetic acid was stirred at RT. for 6 h. Work-up of the reaction followed by crystallization from hexane gave the sulfone **2i**, m.p. 81–82°. – NMR.: 1.00 (s, 6 H); 1.35 (s, 9 H); 1.70 (s, 3 H); 1.90 (s, 3 H); 3.65 (d, $J = 9$ Hz, 2 H); 5.50 (t, $J = 9$ Hz, 1 H); 6.05 (s, 2 H).

$C_{19}H_{32}O_2S$ (324.4)	Calc.	C 70.32	H 9.94	S 9.88%	Found	C 70.24	H 10.14	S 9.20%
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Preparation of C_{20} -Sulfones³⁾. – *3,7-Dimethyl-5-phenylsulfonyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4a)*. To a cooled (–7°), stirred slurry of 1.34 g of sodium hydride (washed with hexane) in 40 ml of anhydrous DMF was added a solution of 17.2 g of sulfone **2a** in 40 ml of anhydrous DMF at such a rate that the internal temperature was kept between –5° and –7°. The resulting deep red mixture was stirred at –5° for 15 min and treated with 8.1 g of the chloroester **3** in 40 ml of anhydrous DMF during 20 min. The mixture was stirred at 10° for 1 h and 15 min, poured into 250 ml of ice-cold sulfuric acid (4%) and extracted into 250 ml of ether. The extract was washed, dried (MgSO₄) and evaporated to give 23.2 g of an orange-colored gum. Two crystallizations from methanol gave 17.25 g (73%) of **4a** as virtually colorless prisms, m.p. 87–89°. – UV. (λ_{max} (ϵ)): 281 sh (15,200), 274 (16,000), 267 (15,580), 245 (13,760), 215 (23,720) nm. – IR.: 1735, 1620, 1590, 1445, 1305, 1240, 1140, 1080, 1025 and 985 cm^{–1}. – NMR.: 0.97 (s, 6 H); 1.26 (d, $J = 1$ Hz, 3 H); 1.65 (s, 6 H); 1.97 (s, 3 H); 2.40 (d $\times$ d, $J = 14$ and 11 Hz, 1 H); 3.00 (d $\times$ d, $J = 14$ and 3 Hz, 1 H); 4.01 (d $\times$ t, $J = 11$ and 3 Hz, 1 H); 4.50 (d, $J = 7$ Hz, 2 H); 5.08 (d, $J = 11$ Hz, 1 H); 5.37 (t, $J = 7$ Hz, 1 H); 5.60 (s, 2 H); 7.54 (m, 3 H); 7.81 (d $\times$ d, $J = 7$ and 2 Hz, 2 H). – MS. (m/e): 470 (0.01), 410 (0.1), 329 (100) and 269 (40).

$C_{28}H_{38}O_4S$ (470.6)	Calc.	C 71.45	H 8.14	S 6.81%	Found	C 71.45	H 8.14	S 6.85%
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3,7-Dimethyl-5-(p-methoxybenzenesulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4b). A solution of 187 mg of sulfone **2b** in 2 ml of THF was added to a suspension of 84 mg of potassium *t*-butoxide in 0.75 ml of THF at –20°, the mixture was stirred for 5 min and then treated with 120 mg of the chloroester **3**. The mixture was stirred at RT. for 15 min, worked up and chromatographed on silica to give 60 mg of starting material and 145 mg of **4b** as a gum. – NMR.: 1.00 (s, 6 H); 1.40 (s, 3 H); 1.70 (s, 6 H); 2.0 (s, 3 H); 2.50 (d $\times$ d, $J = 14$ and 10 Hz, 1 H); 3.0 (d $\times$ d, $J = 14$ and 4 Hz, 1 H); 3.90 (s, 3 H); 4.00 (d $\times$ t, $J = 10$ and 4 Hz, 1 H); 4.50 (d, $J = 7$ Hz, 2 H); 5.30 (m, 2 H); 6.0 (s, 2 H); 6.95 (d $\times$ d, $J = 8$ Hz, 2 H); 7.75 (d $\times$ d, $J = 8$ Hz, 2 H).

³⁾ All compounds are racemic.

3,7-Dimethyl-5-(*o*-methoxybenzenesulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4c). A solution of 3.9 g of **2c** in 40 ml of THF was cooled to -10° and treated with 13.3 ml of a 1.18M solution of dimsyl sodium in DMSO. The mixture was stirred for 4 min, cooled to -20° and treated with 2.6 g of the chloroester **3**. The reaction was allowed to warm to $+5^{\circ}$ during 30 min then worked up and purified by chromatography on silica gel (250 g). Elution with ether/hexane 1:1 and 4:1 gave 3.47 g of **4c** as an oil. – NMR. (CCl_4): 0.90 (s, 6 H); 1.45 (s, 3 H); 1.55 (s, 3 H); 1.65 (s, 3 H); 1.85 (s, 3 H); 2.40 ($d \times d$, $J = 14$ and 10 Hz, 1 H); 2.80 ($d \times d$, $J = 14$ and 4 Hz, 1 H); 4.00 (s, 3 H); 4.17 (m, 1 H); 4.35 (d, $J = 7$ Hz, 2 H); 5.05 (d, $J = 10$ Hz, 1 H); 5.25 (t, $J = 7$ Hz, 1 H); 5.85 (s, 2 H); 7.0–7.7 (m, 4 H).

$\text{C}_{29}\text{H}_{40}\text{O}_5\text{S}$ (500.6) Calc. C 69.57 H 8.05 S 6.40% Found C 69.67 H 8.15 S 6.08%

3,7-Dimethyl-5-(2,4-dimethoxybenzenesulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4d). A solution of 4.0 g of sulfone **2d** in 30 ml of THF was cooled to -40° and treated with 12 ml of a 1.0M solution of dimsyl sodium in DMSO. The solution was stirred at -30° for 5 min, treated with 1.9 g of chloroester **3** and allowed to react at 10° for 20 min. Work-up of the mixture followed by chromatography on 250 g of silica gel with ether/hexane 1:1 and 1:3 gave 3.9 g of **4d** as a gum. – NMR.: 1.0 (s, 6 H); 1.6 (s, 9 H); 2.0 (s, 3 H); 3.7 (s, 6 H); 4.5 (d, $J = 8$ Hz, 2 H); 5.2 (m, 2 H); 5.9 (s, 2 H); 6.4 (m, 2 H); 7.7 (d, 1 H).

$\text{C}_{30}\text{H}_{42}\text{O}_6\text{S}$ (530.6) Calc. C 67.89 H 7.98 S 6.04% Found C 68.25 H 8.03 S 6.14%

3,7-Dimethyl-5-(2,3,4-trichlorobenzenesulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4f). A solution of 894 mg of sulfone **2f** in 2 ml of THF was cooled to -10° and treated with 448 mg of potassium *t*-butoxide in 10 ml of THF. The mixture was stirred at this temperature for 5 min, treated with 650 mg of chloroester **3** and allowed to warm up to 5° during 25 min. Work-up followed by chromatography on silica gel with ether/hexane 1:5 gave 330 mg of the *trans*-sulfone **4f** as an oil. – NMR.: 1.00 (s, 6 H); 1.55 (s, 3 H); 1.60 (s, 3 H); 1.70 (s, 3 H); 2.0 (s, 3 H); 2.40 ($d \times d$, $J = 14$ and 10 Hz, 1 H); 3.00 ($d \times d$, $J = 14$ and 4 Hz, 1 H); 4.50 (d, $J = 7$ Hz, 2 H); 4.6 ($d \times t$, $J = 10$ and 4 Hz, 1 H); 5.1 (d, $J = 10$ Hz, 1 H); 5.35 (t, $J = 7$ Hz, 1 H); 5.90 (s, 2 H); 7.5 (d, $J = 8$ Hz, 1 H); 7.9 (d, $J = 8$ Hz, 1 H).

3,7-Dimethyl-5-(*p*-cyanobenzenesulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4g). A stirred solution of 3.69 g of sulfone **2g** in 50 ml of THF was treated with 2.24 g of potassium *t*-butoxide at -15° and the mixture stirred for a further 7 min. A solution of 3.24 g of chloroester **3** in 5 ml of THF was added, the mixture was stirred at 5° for 15 min and then worked up. Chromatography on 500 g of silica gel with ether/hexane 1:2 and 1:1 gave 2.17 g of **4g** as a gum. – NMR.: 1.00 (s, 6 H); 1.30 (s, 3 H); 1.70 (s, 6 H); 2.00 (s, 3 H); 2.50 ($d \times d$, $J = 14$ and 10 Hz, 1 H); 3.0 ($d \times d$, $J = 14$ and 4 Hz, 1 H); 4.1 ($d \times t$, $J = 10$ and 4 Hz, 1 H); 5.30 (m, 2 H); 6.00 (s, 2 H); 7.90 ($d \times d$, $J = 8$ Hz, 4 H).

$\text{C}_{29}\text{H}_{37}\text{O}_3\text{SN}$ (495.6) Calc. C 70.27 H 7.52 S 6.47% Found C 69.80 H 7.71 S 6.94%

3,7-Dimethyl-5-(2,4,6-trimethylbenzenesulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4h). A solution of 3.9 g of sulfone **2h** in 10 ml of DMF was added to a stirred slurry of 462 mg of sodium hydride (washed with hexane) at 0° and the mixture stirred for a further 10 min; 1.8 g of chloroester **3** was added and stirring continued at 10° for 30 min. Work-up of the mixture gave 5.2 g of crude product which was chromatographed on silica gel to give 4.0 g of **4h**. Crystallization from hexane gave an analytical sample, m.p. $67-74^{\circ}$. – NMR.: 1.00 (s, 6H); 1.15 (s, 3 H); 1.65 (s, 3 H); 1.70 (s, 3 H); 2.00 (s, 3 H); 2.30 (s, 3 H); 2.60 (s, 6 H); 2.60 ($d \times d$, $J = 14$ and 10 Hz, 1 H); 3.00 ($d \times d$, $J = 14$ and 4 Hz, 1 H); 4.05 ($d \times t$, $J = 10$ and 4 Hz, 1 H); 4.50 (d, $J = 7$ Hz, 2 H); 5.30 (m, 2 H); 5.95 (s, 2 H); 6.90 (s, 2 H).

$\text{C}_{31}\text{H}_{44}\text{O}_4\text{S}$ (512.6) Calc. C 72.66 H 8.65 S 6.25 Found C 72.87 H 8.48 S 6.17%

3,7-Dimethyl-5-(*t*-butylsulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,6,8-nonatrienyl acetate (4i). A stirred solution of 300 mg of sulfone **2i** in 2 ml of THF was cooled to -12° and treated with 225 mg of potassium *t*-butoxide. The mixture was cooled to -50° , treated with 330 mg of chloroester **3** in 0.5 ml of THF and allowed to warm to RT. during 20 min. Work-up of the reaction and chromatography of the product on 25 g of silica gave sulfone **4i** as an oil.

$\text{C}_{26}\text{H}_{42}\text{O}_4\text{S}$ (560.6) Calc. C 69.29 H 9.29 Found C 69.09 H 9.49

Treatment of Sulfone 2k with Base. A solution of 100 mg of sulfone **2k** in 2 ml of THF was treated with 3 ml of a 1.05M solution of dimsyl sodium in DMSO. The mixture was stirred at RT.

for 3 min and then worked up to give an oil. – NMR. (CCl_4): 1.06 (*s*, 3 H); 1.70 (*br. s*, 3 H); 2.30 (*s*, 3 H); 5.80 (*d*, $J = 8$ Hz, 1 H); 6.10 (*d*, $J = 16$ Hz, 1 H); 6.60 (*d*, $J = 16$ Hz, 1 H); 10.0 (*d*, $J = 8$ Hz, 1 H). The product was identified as 5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-*trans*-2,4-pentadienal, **12**.

Elimination to Form Vitamin A. – *From Sulfone 4a.* To a stirred solution of freshly prepared sodium ethoxide (from 29.9 g sodium and 600 ml of ethanol) was added 61.7 g of sulfone **4a**. The mixture was boiled under reflux for 16 h and worked up to give 41.3 g of crude vitamin A. This material was converted into the acetate by treating a cooled (5°) solution of the crude alcohol in 600 ml of hexane with 33.3 g of triethylamine and 30.6 g of acetic anhydride. The mixture was stirred at RT. for 16 h, cooled to -5° and treated dropwise with 200 ml of sodium carbonate (10%). Work-up of the reaction afforded 42.4 g of crude vitamin-A-acetate [UV.: λ_{max} 324 ($\epsilon = 38,100$) nm] which was crystallized from 50 ml of hexane at -15° (seeding necessary) to give 15.4 g of crystalline vitamin-A-acetate, m.p. $50\text{--}57^\circ$. – UV.: λ_{max} 325 ($\epsilon = 48,500$) nm. – NMR.: 1.00 (*s*, 6 H); 1.66 (*s*, 3 H); 1.86 (*s*, 3 H); 1.93 (*s*, 3 H); 2.00 (*s*, 3 H); 4.70 (*d*, $J = 7$ Hz, 2 H); 5.56 (*t*, $J = 7$ Hz, 1 H); 6.00 (*d*, $J = 7$ Hz, 1 H); 6.08 (*s*, 2 H); 6.22 (*d*, $J = 12$ Hz, 1 H); 6.60 ($\bar{d} \times \bar{d}$, $J = 12$ and 7 Hz, 1 H). – MS.: 328. HPLC. gave the following analysis: all-*trans* (95%), 9/9,13-dicis (1%) and 13-*cis* (3%).

The mother liquor from the above crystallization was evaporated to give a gum: UV.: λ_{max} 326 ($\epsilon = 30,030$) nm. – HPLC. gave the following analysis: all-*trans* (31%), 9/9,13-dicis (14%), 13-*cis* (9%) and 11-*cis* (4%).

From Sulfone 4h. A solution of 100 mg of sulfone **4h** in 1 ml of *n*-butanol was treated with 2 g of KOH and 0.7 ml of water and the mixture heated at 120° for 3 h. Isolation of the product followed by acetylation as described in the preceding experiment gave crude vitamin-A-acetate. – HPLC. gave the following analysis: all-*trans* (41%), 9,11-dicis (6%) and *retro* (9%).

Treatment of Sulfone 4f with Sodium Acetate. A solution of 200 mg of sulfone **4f** in 1.5 ml of DMF was refluxed with 200 mg of sodium acetate for 2 h. Work-up followed by preparative-scale TLC. afforded 60 mg of **14** as a gum. – NMR. (CCl_4): UV. λ_{max} 316 ($\epsilon = 26,100$) nm. – NMR. 1.10 (*s*, 3 H); 1.25 (*s*, 3 H); 1.70 (*s*, 3 H); 1.90 (*s*, 3 H); 2.00 (*s*, 3 H); 2.80 (*d*, $J = 6$ Hz, 2 H); 4.50 (*d*, $J = 7$ Hz, 2 H); 5.20 and 6.40 (*m*, 6 H).

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