Vitamin A Synthesis by Sulfone Alkylation–Elimination. C_{15} Halide, C_5 Hydroxy Sulfone Approach

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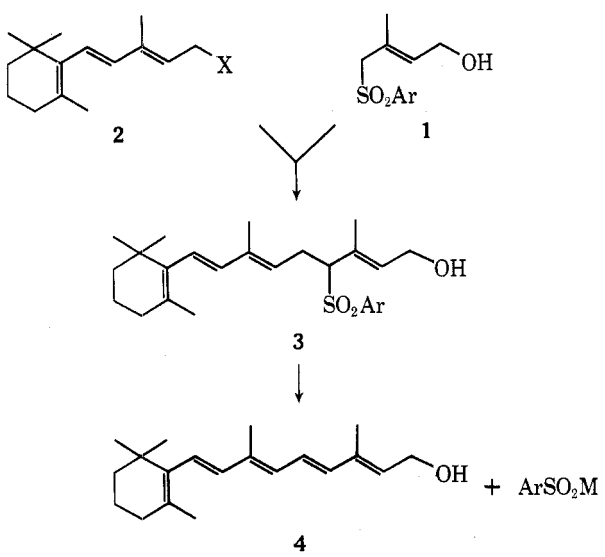
Condensation of 1-arylsulfonyl-2-methyl-4-hydroxy-2-butenes (**1**) with 1-chloro- and 1-bromo-3-methyl-5-(2,6,6-trimethylcyclohexen-1-yl)-penta-2,4-diene (**2**) to afford 1-hydroxy-3,7-dimethyl-4-arylsulfonyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,6,8-triene (**3**) and the subsequent elimination of sulfinic acid from **3** to give vitamin A alcohol has been studied. An efficient and stereoselective synthesis of halide **2** from vinyl-β-ionol (**14**) using HX in ether at low temperature has been achieved. The use of diethyl- and disilylamides with the *p*-tolyl sulfone compound **1b** and bromide **2b** gave **3b** in 83–84% isolated yield. Sodamide–ammonia–*tert*-butyl alcohol effected elimination of sulfinic acid in **3b** to afford, after acetylation, vitamin A acetate in 75% yield from **3b**. In a through process, crystalline, all-trans vitamin A acetate was obtained in 67–68 and 72–73% yield based on **14** and **1b**, respectively.

The alkylation of allylic sulfones and their subsequent 1,2 elimination to form olefins[1] is a synthetic method particularly suited to the synthesis of polyenes and vitamin A. This sequence was originally used by Julia to prepare the ester of vitamin A acid.[2] Because of the nutritional and commercial importance of all-trans vitamin A alcohol (β-retinol), strategic combinations of sulfone and halide directed toward the preparation of vitamin A alcohol have received great attention.[3] Approaches utilizing C_{13}[3b] and C_{15} sulfones[3c] and the appropriate halo alcohol partners have recently been described. An alternative in which the dianion of a C_5 hydroxy sulfone (**1**) is alkylated by a C_{15} halide (**2**) has now been studied in detail, and with appropriate choices of base, aryl sulfone, and C_{15} halide, this route affords a highly efficient and stereoselective synthesis of all-trans vitamin A (**4**) via the C_{20} hydroxy sulfone **3** (Scheme I).

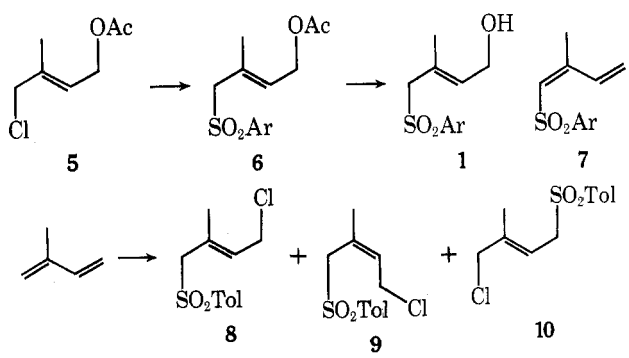
Scheme I



Results and Discussion

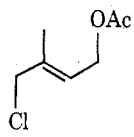
Preparation of C_5 Hydroxy Sulfones 1. Treatment of the isoprene hypochlorination product **5**[4] with sodium or lithium salts of sulfinic acids in warm dimethylformamide solution gives *trans*-acetoxy sulfones **6** in good yield (Table I). Reduction with $LiAlH_4$ or base hydrolysis affords the hydroxy sulfones **1** in high yield (Table II). The saponification, however, must be done under carefully controlled conditions to avoid elimination, particularly for the substituted sulfones.

Thus, phenyl sulfone **6a** was unaffected by sodium carbonate in 80% aqueous ethanol but was cleanly hydrolyzed in 80% aqueous methanol, as was tolyl sulfone **6b**. Under more basic conditions (potassium carbonate–95% aqueous methanol) **6a** gave hydroxy sulfone **1a** contaminated with 25% of diene **7a**. Saponification of the *p*-methoxyphenyl derivative **6c** (sodium carbonate, 80% aqueous ethanol) was slow, but stronger base (potassium carbonate) in the same solvent gave exclusively diene **7c**. The 2-pyridyl sulfone **6f** gave 20% diene **7b** even with sodium carbonate in 80% aqueous ethanol.



A second route to hydroxy sulfones was via solvolysis or acetolysis of halo sulfones (**8**) obtained from the copper(I)-catalyzed addition of sulfonyl halides to isoprene.[5] Thus, *p*-toluenesulfonyl chloride reacted with isoprene[6] to afford a mixture of chloro sulfones **8**, **9**, and **10** in 95% yield. The regio- and stereochemistry of the products of this reaction had not previously been rigorously established, and in the original report[5] **9** and **10** were not identified, so the structures of these adducts were proved by correlation with known compounds. *trans*-1-*p*-Toluenesulfonyl-4-acetoxy-2-methyl-2-butene (**6b**) was prepared from pure **8** by acetolysis and was identical with the product prepared from chloro acetate **5**. 1,4-Dichloro-2-methyl-2-butene reacted with sodium *p*-toluenesulfinate in ethanol to give a mixture of 1,4-disulfone and *trans*-1-*p*-toluenesulfonyl-3-methyl-4-chlorobut-2-ene. This latter compound displayed a methyl resonance in the NMR spectrum at 1.36 ppm (vs. 1.83 ppm in trans **8**) and was thus shown to be the compound which cocrystallizes with the desired trans **8** from ether. The crystallization mother liquors were repurified until the other compound, assumed to be the cis isomer **9**, was enriched to ca. 80% purity. The structure of this material was proved by correlation with *cis*- and *trans*-4-chlorosenecioic esters **11**[7] by displacement of the halide with *p*-toluenesulfinic acid to afford a cis/trans mixture of sulfone esters **12** from which a single isomer crystallized. Diisobutylaluminum hydride reduction of this crystalline compound followed by acetylation afforded the trans hydroxy and acetoxy sulfones **1b** and **6b**. Identical treatment of the mother liquors (80% cis isomer) afforded the cis acetoxy sulfone **13**.

Table I. Preparation and Properties of C_5 Acetoxy Sulfones

Method A: $ArSO_2Na$ (Li) +  → 6

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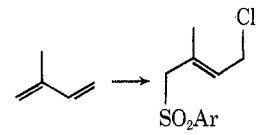
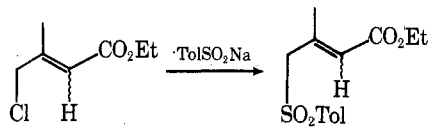
Method B: $ArSO_2Cl$ +  → 6

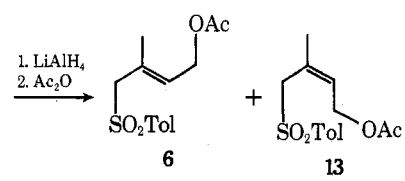
8

Compd	Ar	% yield A	% yield B	Mp, °C	NMR ($CDCl_3$), δ	Anal., found, %	
6a	C_6H_5	95[a]		93–94	7.95–7.45 (m, 5, aromatic), 5.22 (t, 1, J = 7 Hz, HC=C), 4.48 (d, 2, J = 7 Hz, CH_2OAc), 3.75 (s, 2, CH_2SO_2), 2.00 (s, 3, CH_3CO), and 1.83 ppm (s, 3, CH_3C=C)	C 58.14 S 11.86	H 6.32
6b	p-$CH_3C_6H_4$	95[a]	70[a]	56.5–59	7.71 and 7.31 (AA'XX', 4, J = 8 Hz, aromatic), 5.25 (t, 1, J = 7 Hz, HC=C), 4.48 (d, 2, J = 7 Hz, CH_2OAc), 3.74 (s, 2, CH_2SO_2), 2.43 (s, 3, CH_3Ar), 2.00 (s, 3, CH_3CO), and 1.80 ppm (s, 3, CH_3C=C)	C 59.72 S 11.25	H 6.31
6c	p-$OCH_3C_6H_4$	96[a]	61	55–56	7.70 and 6.95 (AA'XX', 4, J = 10 Hz, aromatic), 5.23 (t, 1, J = 7 Hz, HC=C), 4.45 (d, 2, J = 7 Hz, CH_2OAc), 3.83 (s, 3, OCH_3), 3.72 (s, 2, CH_2SO_2), 1.97 (s, 3, CH_3CO), and 1.82 ppm (s, 3, CH_3C=C)	C 56.41 S 10.67	H 6.08
6d	p-$N(CH_3)_2C_6H_4$	99[a]		82–84	7.60 and 6.62 (AA'XX', 4, J = 9 Hz, aromatic), 5.26 (t, 1, J = 7 Hz, HC=C), 4.49 (d, 2, J = 7 Hz, CH_2OAc), 3.68 (s, 2, CH_2SO_2), 3.04 [s, 6, $N(CH_3)_2$], 2.00 (s, 3, CH_3CO), and 1.81 ppm (s, 3, CH_3C=C)	C 57.74 N 4.45 S 10.09	H 6.72
6e	p-$CF_3C_6H_4$	86		Oil	8.12–7.50 (m, 4, aromatic), 5.22 (t, 1, J = 7 Hz, HC=C), 4.48 (d, 2, J = 7 Hz, CH_2OAc), 3.78 (s, 2, CH_2SO_2), 2.00 (s, 3, CH_3CO), and 1.88 ppm (s, 3, CH_3C=C)	C 49.77 S 9.71	H 4.68
6f		47		59–61	8.74–7.58 (m, 4, pyridine), 5.39 (t, 1, J = 7 Hz, HC=C), 4.49 (d, 2, J = 7 Hz, CH_2OAc), 4.09 (s, 2, CH_2SO_2), 1.98 (s, 3, CH_3CO), and 1.88 ppm (s, 3, CH_3C=C)	C 53.48 N 5.06	H 5.71

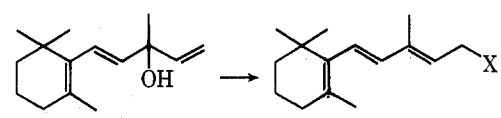
[a] Crude material, >95% pure by NMR.



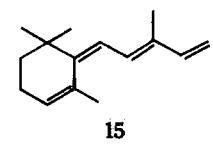
11 12



6 13



14 2a, X = Cl; b, X = Br



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Fortuitously, the cocrystallized mixture of 8 and 10 upon acetolysis with sodium acetate–acetic acid yields mainly trans acetate 6 which after saponification and crystallization gives pure hydroxy sulfone **1b** in 70% yield from the mixture of 8 and 10. The hydroxy sulfones 1 could also be obtained directly from chloro sulfone 8 by solvolysis with aqueous silver carbonate at room temperature.

Preparation of C_{15} Halides 2. Reaction of vinyl-β-ionol (14), readily available from β-ionone,[8] with phosphorus trihalides generally affords the corresponding C_{15} halide 2 in ca. 60% yield together with a substantial amount of the hydrocarbon 15.[2,9] We find that 14 is virtually quantitatively converted to the chloride **2a** or bromide **2b** by its reaction with ethereal HCl or HBr, respectively, at low temperature[10] and that these halides, while unstable at more than ca. 50% concentration at room temperature, are remarkably unaffected by base at low (−30 °C or below) temperature and are essentially inert to displacement by the lithium dialkyl- or disilylamides in THF at −70 °C. In addition, the stereochemistry (by NMR in CCl_4) about the trisubstituted double bond in these halides is >95% trans. By inference from the stereochemistry of the vitamin A produced (vide infra), the halides vary from 95 to 99% trans stereoisomer.

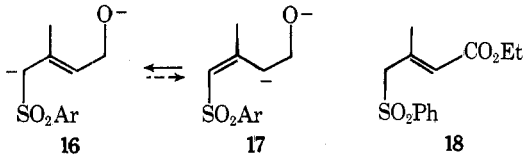
Alkylation Studies. Hydroxy sulfone 1 undergoes alkylation cleanly at the carbon α to the sulfonyl group, presumably owing to the displacement of the equilibrium between dianions 16 and 17 toward the more favorably charge-separated dianion 16. By contrast, the sulfone ester 18 was reported[2] to

Table II. Preparation and Properties of C_5 Hydroxy Sulfones 1

Method A: 6 $\xrightarrow[\text{aq MeOH}]{Na_2CO_3}$ 1 Method B: 6 $\xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$ 1

Compd	Ar	% yield A	% yield B	Mp, °C	NMR ($CDCl_3$), δ	Anal., found, %
1a	C_6H_5		97[a]	55–56.5	7.90–7.45 (m, 5, aromatic,), 5.34 (t, 1, J = 7 Hz, HC=C), 4.05 (d, 2, J = 7 Hz, CH_2OH), 3.75 (s, 2, CH_2SO_2), and 1.81 ppm (s, 3, CH_3C=C)	C 58.26 H 6.16 S 14.09
1b	p-$CH_3C_6H_4$	(69)[b]	97[a] (42.5)[c]	62.5–65	7.71 and 7.32 (AA'XX', 4, J = 8 Hz, aromatic,), 5.39 (t, 1, J = 7 Hz, HC=C), 4.07 (d, 2, J = 7 Hz, CH_2OH), 3.72 (s, 2, CH_2SO_2), 2.43 (s, 3, CH_3Ar), and 1.78 ppm (CH_3C=C)	C 60.16 H 6.88 S 13.19
1c	p-$OCH_3C_6H_4$		94[a] (60)[b]	45.5–47	7.67 and 7.25 (AA'BB', 4, J = 7 Hz, aromatic), 5.33 (t, 1, J = 7 Hz, HC=C), 4.03 (d, 2, CH_2OH), 3.70 (s, 2, CH_2SO_2), 2.75 (s, 1, OH), 2.33 (s, 3, CH_3Ar), and 1.75 ppm (s, 3, CH_3C=C)	C 56.02 H 6.29
1d	p-$N(CH_3)_2C_6H_4$		96[a] (60)[b]	160–164	7.65 and 6.62 (AA'XX', 4, J = 9 Hz, aromatic), 5.36 (t, 1, HC=C), 4.08 (d, 2, CH_2OH), 3.68 (s, 2, CH_2SO_2), 3.08 [s, 6, $N(CH_3)_2$], and 1.80 ppm (s, 3, CH_3C=C)	C 57.91 H 7.14 N 5.14 S 11.89
1e	p-$CF_3C_6H_4$		93[a]	63–68	8.17–7.54 (m, 4, aromatic), 5.33 (t, 1, J = 7 Hz, HC=C), 4.05, (d, 2, J = 7 Hz, CH_2OH), 3.78 (s, 2, CH_2SO_2), and 1.82 ppm (s, 3, CH_3C=C)	C 48.95 H 4.43 S 10.87 F 19.49
1f		53 (25)[b]		53–54	8.83–7.43 (m, 4, aromatic), 5.43 (t, 1, J = 7 Hz, HC=C), 4.03 (s, 2, CH_2SO_2), 4.02 (d, 2, J = 7 Hz, CH_2OH), and 1.75 ppm (s, 3, CH_3C=C)	C 52.97 H 5.63 N 6.21

[a] Crude product, >95% pure by NMR. [b] Overall yield of pure compound based on chloro acetate 5. [c] Overall yield of pure compound based on p-toluenesulfonyl chloride via chloro sulfone 8.



16 17 18

undergo almost exclusive γ-alkylation. The acetoxy sulfones 6 (precursors of 1) do not alkylate by either mode, but eliminate acetate rapidly under alkylation conditions to afford dienes 7.

The yield of C_{20} hydroxy sulfone 3 obtained in this reaction was found to depend to some extent upon the arylsulfonyl substituents and particularly upon the reaction conditions.

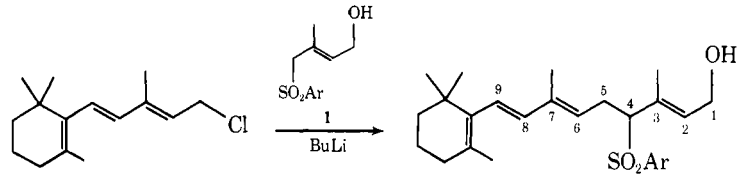
Substituent Variations (Table III). In initial studies, 2 equiv of n-butyllithium was added to a solution of the hydroxy sulfone in THF at −70 °C followed by slow, dropwise addition of the C_{15} chloride **2a** in ether. After 1 h at −70 °C and then warming to 0–25 °C, the reaction mixtures were quenched with water and extracted with ether. The crude products were chromatographed to give the substituted C_{20} sulfones **3.** The various substituted sulfones alkylated similarly to the phenyl sulfone **1a** except for the trifluoromethyl compound **1c** (low yield, **3c** unstable toward chromatography) and 2-pyridyl compound **1f** (eliminated to form diene **7f**). The somewhat higher yield observed with the dimethylamino compound **1d** may result from the amino group scavenging HCl from the decomposition of some excess C_{15} chloride prior to chromatography.

Since the p-tolyl (**1b**) and p-methoxy (**1c**) compounds gave the highest yields of vitamin A in the subsequent elimination step (vide infra), the alkylation of these two compounds was studied in detail with respect to base, halide, temperature, and mode of addition.

Alkylation with p-Tolyl Hydroxy Sulfone 1b. Variations of Base and C_{15} Halide (Table IV). In the alkylation of the p-tolyl hydroxy sulfone **1b** with the C_{15} chloride **2a** and n-butyllithium, unreacted **1b** was isolated after alkylation even though the dianion formation was complete at −70 °C (D_2O–DOAc exchange). Apparently, the rates of alkylation and base-promoted dehydrohalogenation of **2a** are similar at −70 °C. Higher reaction temperatures isomerized both C_5 and C_{20} sulfones. Thus, generation of the dianion **1c** with n-butyllithium at −20 °C in THF led to isomerization of the C_5 component prior to alkylation with C_{15} chloride **2a.** Similarly, formation of the dianion and alkylation at −70 °C followed by warming the mixture to room temperature overnight gave mainly the 2-cis C_{20} sulfone. No difference was seen between reactions run at −50 and −70 °C. Apparently, the dianion **1** has considerable stability toward cis/trans isomerization below −50 °C.

Because of its probable greater reactivity, the C_{15} bromide **2b** was substituted for the chloride **2a** in a butyllithium alkylation with little effect on the yield (33%). Changes in the base used, however, had a dramatic effect on the yield of sulfone in alkylation with the bromide **2b.** *Thus reaction of sulfone* **1b** *and bromide* **2b** *with 2 equiv of lithium diisopropylamide in tetrahydrofuran at −70 °C gave the desired C_{20} product* **3b** *in 83–84% yield.* Under the same conditions, chloride **2a** gave a 38% yield of product, while a mixture of chloride **2a** and 10 mol % of lithium bromide gave a 50% yield

Table III. Preparation of C_{20} Sulfones via C_{15} Chloride with Butyllithium



2a 3

Compd	Ar	Yield, %	Uv, λ_{max} (ϵ) Triene	Uv, λ_{max} (ϵ) Aryl	NMR ($CDCl_3$), δ	Anal., found, %
3a	C_6H_5	42	272–273 (16 800)	215 (18 200)	7.95–7.43 (m, 5, aromatic), 5.93 (s, 2, C_8 and C_9 vinyl H's), 5.33 (t, 1, J = 7 Hz, C_2 vinyl H), 5.17 (t, 1, J = 7 Hz, C_6 vinyl H), 4.03 (d, 2, J = 7 Hz, CH_2OH), 3.57 (m, 1, C_4 H), 2.83 (m, 2, C_5 CH_2), and 0.98 ppm (s, 6, *gem*-CH_3's)	C 72.77 H 8.47
3b	*p*-$CH_3C_6H_4$	41	262 (17 070)	228 (25 740)	7.70 and 7.30 (AA'XX', 4, J = 8 Hz, aromatic), 5.97 (s, 2, C_8 and C_9 vinyl H), 5.42 (t, 1, J = 6 Hz, C_2 vinyl H), 5.14 (t, 1, J = 7 Hz, C_6 vinyl H), 4.10 (d, 2, J = 6 Hz, CH_2OH), 3.56 (m, 1, C_4 H), 2.44 (s, 3, CH_3Ar), 1.77, 1.73, and 1.66 (3 s, 9, vinyl CH_3's), and 0.98 ppm (s, 6, *gem*-CH_3's)	C 73.51 H 8.95 S 6.79
3c	*p*-$OCH_3C_6H_4$	35–40	260 (16 515)	241–242 (24 625)	7.74 and 6.96 (AA'XX', 4, J = 8 Hz, aromatic), 5.96 (s, 2, C_8 and C_9 vinyl H), 5.31 (t, 1, J = 7 Hz, C_2 vinyl H), 5.12 (t, 1, J = 7 Hz, C_6 vinyl H), 4.06 (d, 2, J = 7 Hz, CH_2OH), 3.84 (s, 3, OCH_3), 3.50 (m, 1, C_4 H), 2.81 (m, 2, C_5 CH_2), 1.63, 1.71, 1.75 (3 s, 9, vinyl CH_3's), and 0.97 ppm (s, 6, *gem*-CH_3's)	C 71.29 H 8.35 S 6.51
3d	*p*-$N(CH_3)_2C_6H_4$	57		283–284 (35 600)	7.63 and 6.63 (AA'XX', 4, J = 9 Hz, aromatic), 5.96 (s, 2, C_8 and C_9 vinyl H), 5.41 (t, 1, J = 7 Hz, C_2 vinyl H), 5.15 (t, 1, J = 7 Hz, C_6 vinyl H), 4.10 (d, 2, J = 7 Hz. CH_2OH), 3.50 (m, 1, C_4 H), 3.03 [s, 6, $N(CH_3)_2$], and 0.99 ppm (s, 6, *gem*-CH_3's)	C 71.05 H 8.65 N 2.81 S 6.51
3e	*p*-$CF_3C_6H_4$	3.5	264–266	200–205	8.13–7.50 (m, 4, aromatic), 5.97 (s, 2, C_8 and C_9 vinyl H), 5.33 (t, 1, J = 7 Hz, C_2 vinyl H), 5.10 (t, 1, J = 7 Hz, C_6 vinyl H), 4.04 (d, 2, J = 7 Hz, CH_2OH), 3.57 (m, 1, C_4 H), and 0.99 ppm (s, 6, *gem*-CH_3's).	
3f		0				

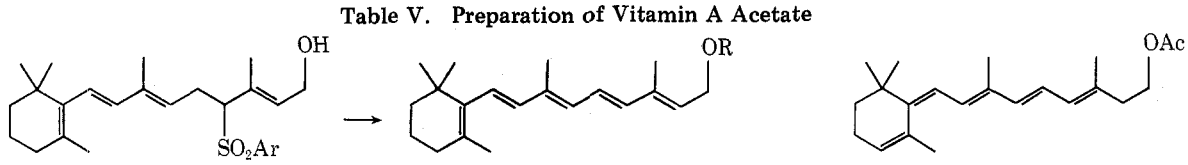
of product. Yields with other hindered amine bases were similarly high, regardless of the mode of addition (preformation of the dianion was unnecessary). These carefully defined working conditions for the tolyl sulfone **1b** were subsequently tried with the *p*-methoxyphenyl compound **1c** with a resulting 38% yield of adduct **3c**. Clearly the alkylation of C_5 hydroxy sulfones **1** is a reaction in which a delicate balance between rates of alkylation and dehydrohalogenation exists so that slight changes in the acidity of the sulfone[11] and its nucleophilicity due to substituent and medium effects can dramatically influence the product yield.

Elimination Step. Vitamin A Acetate Preparation (Table V). The elimination of sulfinic acid in **3** to afford vitamin A alcohol occurs smoothly and in high yield for the *p*-tolyl and *p*-methoxyphenyl sulfones **3b** and **3c** with an excess of sodamide (5 equiv) in liquid ammonia containing

Table IV. Alkylation of *p*-Tolyl Sulfone Ib with C_{15} Halides 2. Comparison of Bases

No.	Base	mmol	C_{15} halide,	mmol	C_5 sulfone, mmol	Mode of addition	Yield, %	
1	BuLi	26.0	Cl	19.7	13.0	Cl to dianion	41	
2	BuLi	9.5	Br	5.3	4.2	Base to substrates	33	
3	LDA	9.8	Cl	5.7	4.2	Base to substrates	31.5	
4	LDA	44.0	Br	25.0	21.0	Base to substrates	84	
5	LDA	44.0	Br	25.0	21.0	Rapid addition of Br to dianion	83	
6	LDA	9.8	Cl (+10 mol % LiBr)	5.7	4.2	Base to substrates	50	
7	$LiNEt_2$	19.7	Br	11.4	8.3	Base to substrates	68	
8	KO-*t*-Am	9.6	Br	5.5	4.2	Base to substrates	14.4	
9	$LiN(SiMe_3)_2$	19.0	Br	8.75	8.33	Base to substrates	74	(16% unreacted Ib)
10	$NaN(SiMe_3)_2$	11.5	Br	4.3	4.2	Base to substrates	62	(21% unreacted Ib)
11	$NaNH_2$	21.0	Br	15.8	8.3	Bromide to dianion	14.4	
12	NaC_6H_5	11.6	Br	5.40	4.15	Bromide to dianion	35	(43% unreacted Ib)

Table V. Preparation of Vitamin A Acetate



3 4 i

Compd	Ar	Conditions	Yields[a] (HPLC analysis)[12] 9-cis + 9,13-di-cis	11-cis	13-cis	Retro[b]	All-trans	Total
3a	C_6H_5	KOH, H_2O, *n*-BuOH, 120 °C	2	10			17	29
		$NaNH_2$, NH_3 anhydrous						0
		$NaNH_2$, NH_3, *t*-BuOH	4	2			45	51
3b	*p*-$CH_3C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH	3	1	0.2	4	67	75.2
3c	*p*-$OCH_3C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH	1		1	6	65	73
3d	*p*-$N(CH_3)_2C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH	2		1	4	50	57
3e	*p*-$CF_3C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH					1.4	1.5

[a] Of derived acetate; see Experimental Section. [b] Retro vitamin A = i. Found to be due to isomerization of vitamin A alcohol during prolonged reaction times in the elimination step.

tert-butyl alcohol. In the absence of alcohol, sulfone is recovered unchanged, suggesting that reprotonation of the acidic α-sulfonyl anion formed in a rapid initial step is essential. Substituent effects on the yield of vitamin A alcohol are observed (Table V), and although the yield is not a measure of reaction rate, the expected trend toward elimination of more acidic sulfinic acids faster and in higher yields is observed. Other alkaline conditions[3c] afford lower yields, and interestingly, the isomeric sulfones **3c** (sulfonyl at C_5) do not eliminate under sodamide–ammonia–*tert*-butyl alcohol conditions.

Crude vitamin A alcohol obtained from the elimination reaction was acetylated with acetic anhydride–triethylamine and the crude vitamin A acetate was analyzed by HPLC[12] to determine yields and isomeric composition. The results (Table V) show the crude reaction product to be surprisingly free of isomeric impurities. A small amount of "retro" vitamin A acetate observed in some cases was found to be due to prolongation of the reaction time after complete elimination. The low content of 9-cis/9,13-di-cis isomers reflects the stereochemical integrity of the C_{15} halide prepared by the above-described procedure.

The high yield in the alkylation and the very pure crude vitamin A acetate obtained by the elimination–acetylation procedure utilizing the *p*-tolyl sulfone **1b** suggested that the synthesis could be carried out without chromatographic purification of the intermediates. Indeed, alkylation of the crude C_{15} bromide **2b** with *p*-tolyl sulfone **1b** afforded the crude C_{20} sulfone **3b** which, after trituration with hexane and remove a small amount of C_{15} hydrocarbon by-product (**17**), was eliminated and acetylated to afford crude vitamin A acetate in an overall yield (by HPLC) of 67–68% based on vinyl-β-ionol (**14**) and 72–73% based on hydroxy sulfone **1b.**

By virtue of the high all-trans isomer content, the crude acetate crystallized from cold methanol in a very high weight yield. Crystalline samples were assayed by direct uv and Morton–Stubbs procedures[13] relative to the standard[14] for all-trans vitamin A acetate (2.906×10^6 IU/g). Thus, crystallization of the crude acetylation product from methanol afforded all-trans vitamin A acetate (assay 91.2–91.4%) in 63–65 and 67–70% overall yield based on vinyl-β-ionol (**14**) and hydroxy sulfone **1b,** respectively.

Experimental Section

Melting points were determined on a Kofler hot stage microscope and are uncorrected. Spectral measurements were performed on the following instruments: NMR, Varian T-60, HA-100, and XL-100 spectrometers using Me_4Si as internal standard and $CDCl_3$ as solvent; ir, Beckman IR 9 and Perkin-Elmer Model 621 and 237B spectrophotometers with $CHCl_3$ as solvent or as a liquid film; uv, Cary Model 14 and Perkin-Elmer Model 202 spectrophotometers with 2-propanol as solvent. Gas chromatographic analyses were performed on Hewlett-Packard Model 402B or 5721A instruments equipped with flame ionization detectors. High-pressure liquid chromatographic analyses (HPLC) were performed on apparatus constructed by members of our Physical Chemistry Department on silica gel columns impregnated with oxydipropionitrile[12] with uv monitoring at 254, 280, and 350 nm and using naphthalene as internal standard and crystalline, all-trans vitamin A acetate (Hoffmann-La Roche Inc.) as reference compound. The progress of reactions was generally followed by TLC

on Brinkmann silica gel GF 254 plates using uv and ceric sulfate spray followed by heating to detect spots. Products were isolated in general by extraction or dilution of the reaction mixture with the indicated solvent, washing, where appropriate, with H_2O, 20% HCl, saturated $NaHCO_3$, and brine, drying ($MgSO_4$), and solvent removal on a rotary evaporator at 30–50 °C. Column chromatography was carried out on Merck 0.05–0.2 mm silica gel or Woelm alumina, grade III. Tetrahydrofuran (THF) was dried by passage through Woelm neutral alumina, grade I. Lithium diisopropylamide (LDA) solutions were prepared from diisopropylamine (distilled from CaH_2) and *n*-butyllithium (Ventron Corp.) and were titrated[15] before use.

Preparation of *trans*-1-Arylsulfonyl-2-methyl-4-acetoxy-2-butenes (6) from 5. General Procedure. Acetoxy sulfones **6** (Table I, method A) were prepared by warming a suspension of the sodium or lithium arylsulfinate (1.2 mol) in dry dimethylformamide (DMF) at 60 °C with chloro acetate **5** (1.0 mol) for 3–6 h. Concentration of the suspension to ⅓ the original volume and dilution of the concentrate by pouring onto 10 volumes of ice water precipitated the crude product **6.** Filtration and dissolution of the filtrate in ethyl acetate, drying ($MgSO_4$), and evaporation of the solvent afforded sulfones **6** in 90–95% yield, >95% pure by NMR. Analytically pure samples were obtained by recrystallization from methanol, ether, and/or ethyl acetate.

***trans*-1-*p*-Toluenesulfonyl-2-methyl-4-acetoxy-2-butene (6b).** By the above method, sodium *p*-toluenesulfinate (273.0 g, 1.54 mol, Aldrich, 97%) and chloro acetate **5** (215.4 g, 1.33 mol) in 1100 ml of DMF at 60 °C for 4.75 h afforded 357.0 g of crude acetoxy sulfone **6b** as a waxy solid (95% yield). Recrystallization of a portion from methanol afforded an analytical sample, mp 56.5–59 °C.

Preparation of 1b from Isoprene via Chloro Sulfone 8 (Table I, Method B). By the published procedure[5a], *p*-toluenesulfonyl chloride (38.2 g, 0.2 mol) and isoprene (15.0 g, 0.22 mol) afforded a mixture of chloro sulfones **8–10** (49.4 g, 95%), mp 59– 79.5 °C. Recrystallization of a 47.1-g portion from ether (235 ml) gave colorless crystals of the mixture of **8** and **10** (34.74 g, 74%), mp 68–83 °C, in a 4:1 ratio. In a similar experiment, slow crystallization from ethanol of 20.7 g of crude product afforded pure **8** (6.95 g, mp 86–88 °C): NMR δ 7.29 and 7.68 (AA′XX′, 4, J = 8.5 Hz, aromatic), 5.30 (t, 1, J = 8 Hz, HC=C), 3.96 (d, 2, J = 8 Hz, CH_2Cl), 3.70 (s, 2, CH_2SO_2), 2.40 (s, 3, CH_3Ar), and 1.82 ppm (s, 3, CH_3C=C); ir 1320 (SO_2) and 1175–1138 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{15}SO_2Cl$: C, 55.70; H, 5.84; Cl, 13.70; S 12.39. Found: C, 55.77; H, 5.87; Cl, 13.68; S, 12.22.

Chromatography of the mother liquor from the ether crystallization afforded cis isomer **9** (85% pure) as an oil: NMR δ 7.78 and 7.32 (AA′-XX′, 4, J = 8 Hz, aromatic), 5.76 (t, 1, J = 8 Hz, HC=C), 3.85 (s, 2, CH_2SO_2), 3.77 (d, 2, J = 8 Hz, CH_2Cl), 2.45 (s, 3, CH_3Ar), and 1.85 ppm (s, 3, CH_3C=C).

To a mixture of chloro sulfones **8** and **10** (25.59 g, 0.1 mol) was added sodium acetate (51.2 g, 0.62 mol) and glacial acetic acid (360 ml). The mixture was refluxed for 5.25 h, poured into water, and neutralized. The crude acetate (26.35 g, 94%) was filtered off and a 20-g portion was warmed in methanol, filtered to remove insoluble material, and saponified (60 ml of methanol, 60 ml of water, 20.0 g of sodium carbonate; 3 h, 0–5 °C). Isolation with ethyl acetate gave crude hydroxy sulfone **1b** (15.45 g, 94%). Crystallization of a 15.22-g portion from ether gave pure **1b** (10.82 g, 43% based on *p*-toluenesulfonyl chloride).

Reaction of **9** (0.101 g, 0.39 mmol) with sodium acetate (0.214 g, 2.6 mmol) in acetic acid (1.5 ml) at reflux for 28 h afforded cis acetoxy sulfone **13** (0.105 g, 95% crude): NMR δ 7.79 and 7.35 (AA′XX′, 4, J = 8 Hz, aromatic), 5.65 (t, 1, J = 7 Hz, HC=C), 4.20 (d, 2, J = 7 Hz, CH_2OAc), 3.93 (s, 2, CH_2SO_2), 2.47 (s, 3, CH_3Ar), 2.00 (s, 3, CH_3CO), and 1.87 ppm (s, 3, CH_3C=C).

Preparation of Cis Acetoxy Sulfone 13 from 12.[2] To a solution of diisobutylaluminum hydride (1.24 ml of a 25% toluene solution, 2.2 mmol) at 0 °C was added the ester **12** (0.209 g, 0.73 mmol, 1:1 cis/trans mixture) in toluene (1.8 ml). After 30 min at 0–5 °C the mixture was quenched with saturated NH_4Cl and the products isolated with ethyl acetate to give 0.145 g (82%) of a colorless solid from which the trans hydroxy sulfone **1b** crystallized. To a solution of the mother liquors from a similar crystallization (80% cis isomer, 0.156 g) in pyridine (1.5 ml) was added acetic anhydride (0.36 ml). The solution was warmed to 45 °C for 3 h and poured onto ice and the acetoxy sulfones (0.167 g, 92%, 3:2 mixture of **6b** and **13**) were isolated using ethyl acetate. The NMR peaks not assignable to **6b** were identical with the resonances observed in the product **13** of acetolysis of the cis chloro sulfone **9.**

Preparation of *trans*-1-*p*-Toluenesulfonyl-3-methyl-4-chloro-2-butene (10). Compound **10** was prepared[6] from sodium *p*-toluenesulfinate and 1,4-dichloro-2-methyl-2-butene: NMR δ 7.77 and 7.35 (AA′XX′, 4, J = 8 Hz, aromatic), 5.60 (t, 1, J = 7 Hz, HC=C), 3.98 (s, 2, CH_2Cl), 3.83 (d, 2, J = 7 Hz, CH_2SO_2), 2.48 (s, 3, CH_3Ar), and 1.48 ppm (s, 3, CH_3C=C).

Preparation of *trans*-1-Arylsulfonyl-2-methyl-4-hydroxy-2-butenes (1) from 6. General Procedure, $LiAlH_4$ Reduction. Hydroxy sulfones **1** (Table II, method B) were prepared by addition of a THF solution of the crude acetoxy sulfones **6** (1 mol) to a −20 °C suspension of lithium aluminum hydride (0.5 mol) in THF. After 0.5 h at −20 °C excess hydride and aluminates were decomposed with saturated Na_2SO_4 or $MgSO_4$ and the supernatant solutions were filtered, dried ($MgSO_4$), and concentrated to give the crude hydroxy sulfones in the yields given in Table II.

Saponification of Acetoxy Sulfones 6 to Hydroxy Sulfones 1 with Sodium Carbonate. General Procedure. Hydroxy sulfones **1** (Table II, method A) were prepared by adding a 25% aqueous solution of sodium carbonate in portions to a cold (0–5 °C) solution of the crude acetoxy sulfones **6** in methanol such that the resulting solution was 20% water and 80% methanol. After stirring for 3–5 h the mixture was filtered, concentrated to ⅓ volume, and poured onto 3–4 volumes of H_2O. Isolation with ethyl acetate gave crude hydroxy sulfones **1** which were purified by crystallization from ether–ethyl acetate mixtures to afford **1** in the yields given in Table II.

***trans*-1-*p*-Toluenesulfonyl-2-methyl-4-hydroxy-2-butene (1b).** By the above method a solution of crude acetoxy sulfone **6b** (346.8 g, 1.22 mol) in methanol (2.2 l.) was cooled to 5 °C and a solution of sodium carbonate (194 g, 1.83 mol) in water (555 ml) was added with stirring in four portions, maintaining a temperature of 0–5 °C during the addition and for an additional 4.25 h. The mixture was filtered to remove sodium acetate and the filter cake was washed with ethyl acetate (100 ml). The filtrate was concentrated to a 600-ml volume, diluted with water (2 l.), and extracted with ethyl acetate (3 × 700 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 288 g (97%) of crude **1b** as a white solid (80% pure by NMR). The crude **1b** was recrystallized from ether (1800 ml) containing ethyl acetate (50 ml) to give 198.8 g (69% yield) of **1b,** mp 59–64 °C. Recrystallization of a small portion from ether afforded analytically pure **1b,** mp 62.5–65 °C.

Preparation of 1b by Silver Carbonate Solvolysis of 8. A mixture of chloro sulfone **8** (0.1 g, 3.86 mmol), silver carbonate (0.1 g), water (1.0 ml), and acetone (3 ml) was warmed to 60 °C for 5 h. The mixture was cooled, filtered, and concentrated. The resulting oil was dissolved in ethyl acetate and the solution was washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave hydroxy sulfone **1b** as a white solid (0.09 g, 97%, >90% pure by NMR).

Preparation of 1-Bromo-3-methyl-5-(2,6,6-trimethylcyclohexen-1-yl)penta-2,4-diene (2b). To a −70 °C cooled solution of vinyl-β-ionol (**14**, 26.75 g, assay 92.2%, 0.112 mol as 100%) in anhydrous ether (275 ml) was added over 1.5 min an ethereal solution of hydrogen bromide (32 ml of 4.12 M solution, 0.132 mol, prepared by bubbling HBr into ether at 0 °C until approximately 4 M and then titrating). The solution became pink and warmed to −60 °C during the addition and a red liquid was deposited on the walls of the flask (H_2O + HBr). After 15 min at −70 to −75 °C, the cooling bath was removed and the solution was warmed to −15 °C over 15 min with a warm air blower. After 3 min at −15 °C, the reaction was quenched by the addition of water (100 ml) whereupon the temperature rose to 5 °C. The mixture was transferred to a separatory funnel and the aqueous layer was drawn off. The pale yellow ether solution was washed with saturated sodium bicarbonate (75 ml) and was dried over $MgSO_4$ to which K_2CO_3 (1 g) had been added. The solution was filtered into a 1-l. flask and the solvent was removed on a rotary evaporator with the bath kept below 30 °C until a volume of ca. 60 ml was reached. The weight of the solution was 63 g.

In another experiment, an aliquot of the ether solution was replaced by CCl_4 by successive dilutions and evaporations in an N_2 stream: NMR δ 1.00 (s, 6, *gem*-CH_3's), 1.65 (s, 3, ring CH_3), 1.86 (s, 3, vinyl CH_3), 4.03 (d, 2, J = 8 Hz, CH_2Br), 5.63 (t, 1, J = 8 Hz, H_2), and 6.00 ppm (s, 2, H_3 and H_4).

1-Chloro-3-methyl-5-(2,6,6,-trimethylcyclohexen-1-yl)penta-2,4-diene (2a). The chloride was prepared in the same manner as the bromide **2b** except ethereal HCl was used intead of HBr: NMR δ 1.00 (s, 6, *gem*-CH_3's), 1.65 (s, 3, ring CH_3) 1.86 (s, 3, vinyl CH_3), 4.07 (d, 2, J = 8 Hz, CH_2Cl), 5.53 (t, 1, J = 8 Hz, H_2), 6.00 ppm (s, 2, H_3 and H_4).

Preparation of 1-Hydroxy-3,7-dimethyl-4-arylsulfonyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,6,8-trienes (3). General Procedure for Butyllithium Alkylation with Chloride 2a. A solution of butyllithium in hexane was added over 30–45 min to a stirred, −70 °C solution of the C_5 hydroxy sulfones **1** dissolved in THF. After an additional 30–40 min, a solution of the C_{15} chloride **2a** was added

in THF at −70 °C and the reaction mixture was stirred at −70 °C for ca. 1 h. The product was isolated by allowing the reaction mixture to warm to 0 °C over 15 min, pouring onto dilute HCl, and extracting with ethyl acetate or ether. After washing with bicarbonate and brine and drying ($MgSO_4$), the solvent was evaporated to give the crude product which was chromatographed on alumina (III) or silica gel to give the pure C_{20} hydroxy sulfones **3** in the yields and with the properties given in Table III.

Alkylation with Other Bases (Table IV). The sulfone **1b** and freshly prepared C_{15} halide **2a** or **2b** were stirred in THF at −70 °C during the addition of a freshly prepared solution of base over 15–60 min, or in the indicated experiments, the base was added at −70 °C to a THF solution of the hydroxy sulfone and the resulting solution was stirred for 15–45 min prior to addition of the freshly prepared C_{15} halide. Crude products were isolated by chromatography as described in the butyllithium procedure above. Yields of C_{20} sulfone **3b** are given in Table IV.

Elimination Reactions (Table V). To a suspension of sodamide (4–10 mol) in liquid NH_3 at reflux was added *tert*-butyl alcohol followed by an ether solution of the C_{20} hydroxy sulfones **3** (1 mol) (Table V). After 1–1.5 h, NH_4Cl was added and the NH_3 was evaporated. Water was added to the residue and the mixture was extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude vitamin A alcohol. The crude alcohol was dissolved in pyridine and was treated at −20 °C with acetyl chloride in dichloromethane and stirred at −15 to −20 °C for 20 min. The mixture was poured onto ice water and was extracted with ether. The extracts were washed with bicarbonate, saturated cupric sulfate, and brine and dried ($MgSO_4$). A crystal of BHT and a drop of pyridine were added and the solvent was removed to give crude vitamin A acetate which was assayed[12,13] by uv and HPLC (Table V).

Preparation of Vitamin A Acetate through Process via Bromide 2b and *p*-Tolyl Sulfone 1b. To a solution of hydroxy sulfone **1b** (25.0 g, 0.104 mol, mp 59–64 °C) prepared as described above in dry THF (125 ml) at −70 °C was added the crude bromide solution (**2b** plus ether, 63 g) from 0.112 mol of vinyl-β-ionol (**14**). The solution was stirred in a dry ice–acetone bath and a THF solution of lithium diisopropylamide (1.33 M, 0.226 mol) was added with vigorous stirring over 5 min. After 25 min at −75 °C the cooling bath was removed and the reaction mixture (at ca. −60 °C) was poured into a separatory funnel containing 1 l. of ice and H_2O. The mixture was extracted with ether (2 × 750 ml) and the combined extracts were washed with HCl (2.4%, 1 l.) and brine (2 × 500 ml) and were dried ($MgSO_4$). Pyridine (1.0 ml) was added, and the mixture was filtered and concentrated in vacuo to give a crude orange oil (50.71 g). To the crude oil was added hexane (50 ml) and the two-phase mixture was stirred and cooled to −20 °C for 2 h. The mixture was briefly cooled in a −70 °C bath to solidify the crude sulfone and the hexane was decanted. The trituration was repeated (50 ml of hexane) and the residual crude sulfone (48.2 g) was dissolved in ether (225 ml).

The solution was added over 15 min to a rapidly stirred suspension of powdered sodamide (21.65 g, 0.555 mol, Ventron) in 450 ml of liquid NH_3 to which *tert*-butyl alcohol (96 ml) had been added. The mixture was stirred at reflux (−33 °C) for 70 min. Ammonium chloride (18.5 g) was added followed by ether (250 ml) and the NH_3 was evaporated (adding ether as needed to replenish that lost by evaporation) until the mixture came to 0 °C. The mixture was poured into a separatory funnel containing ice water (500 ml). The organic layer was separated and the aqueous layer extracted with ether (300 ml). The combined organic solutions were washed with brine (600, 300 ml) and were dried ($MgSO_4$). Evaporation of the ether at aspirator pressure and the *tert*-butyl alcohol at 0.1 mm afforded crude vitamin A alcohol (35.62 g).

The crude material was dissolved in hexane (106 ml) and the solution was degassed (Ar) and triethylamine (21.61 ml) was added. Acetic anhydride (19.35 ml) was added to the solution over 15 min and the solution was degassed again and was stirred at room temperature overnight in the dark. The solution was then cooled to 0–10 °C during the addition (10 min) of 10% sodium carbonate solution (106 ml). After stirring for 30 min at room temperature, additional 10% sodium carbonate (30 ml) was added to bring the pH of the aqueous layer to 7.5. The layers were separated and the hexane layer was washed with H_2O (2 × 35 ml). The aqueous washes were extracted with hexane (30 ml) and the combined hexane solutions were dried ($MgSO_4$). After filtration, pyridine (0.3 ml) and a few crystals of BHT were added and the hexane was removed on a rotary evaporator under subdued light at <30 °C to afford crude vitamin A acetate as a dark orange oil (36.34 g). The crude acetate was dissolved in methanol (35 ml) and the solution was stirred mechanically at 2–3 °C and after 1 h was seeded with a crystal of all-trans vitamin A acetate whereupon crystallization

	Yield, %			Isomer ratio (HPLC), all-trans: 9-cis/ 9,13-di-cis
	Based on **1b**	Based on **16**	Purity (uv), %	
Crude oil	106		73.4	98.5:1.5
Crystals	70.3	65.3	91.4	98.8:1.2

commenced. After 18 h at 2–3 °C and 4 h at −20 °C the slurry was filtered and the crystals were washed with cold (−20 °C) methanol (35 ml). The solid was dried in vacuo to afford 24.01 g of light yellow, crystalline vitamin A acetate, mp 53–58 °C (lit.[14] 57–58 °C).

Recrystallization of a 10-g sample of the mp 53–58 °C acetate from 85:15 methanol–pentane at 0 °C overnight afforded a first crop of 6.10 g of crystals, mp 56.5–60 °C, uv assay 99%.

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Registry No.—**1a,** 59830-37-4; **1b,** 59830-38-5; **1c,** 59830-39-6; **1d,** 59830-40-9; **1e,** 59830-41-0; **1f,** 59830-42-1; **2a** (X = Cl), 55732-70-2; **2b** (X = Br), 38987-92-7; **3a,** 59830-43-2; **3b,** 59830-44-3; **3c,** 59830-45-4; **3d,** 59839-81-5; **3e,** 59830-46-5; **4** (R = H), 68-26-8; **4** (R = Ac), 127-47-9; 9-*cis*-**4** (R = Ac), 29584-22-3; 9,13-di-*cis*-**4** (R = Ac), 29444-27-7; **5,** 24529-80-4; **6a,** 59830-31-8; **6b,** 59830-32-9; **6c,** 59830-33-0; **6d,** 59830-34-1; **6e,** 59830-35-2; **6f,** 59830-36-3; **8,** 59830-48-7; **9,** 59830-47-6; **10,** 59830-49-8; *trans*-**11,** 3621-52-1; *cis*-**11,** 3927-06-8; *trans*-**12,** 59830-50-1; *cis*-**12,** 59830-51-2; **13,** 59830-52-3; **14,** 31821-03-1; sodium *p*-toluenesulfinate, 824-79-3; *p*-toluenesulfonyl chloride, 98-59-9; isoprene, 78-79-5; 1,4-dichloro-2-methyl-2-butene, 29843-58-1.

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