Stereocontrolled Synthesis of Vitamin A through a Double Elimination Reaction. A Novel Convergent C_{10} + C_{10} Route

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The first convergent C_{10} + C_{10} route for vitamin A has been developed. The double elimination reaction of β-alkoxy or δ-halo sulfones proceeds with excellent stereocontrol to afford the all-trans and 13-cis isomers of 90–95% purity. The double elimination reaction of β-alkoxy sulfones is initiated by deprotonation of an allylic hydrogen in **9**, while the reaction of δ-halo sulfones proceeds through the Michael addition of potassium methoxide. Nevertheless, formation of the reactive intermediate **10** under mild conditions is crucial to achieve a smooth double elimination reaction in both cases.

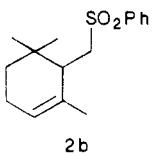
Despite its long history, there still remains an extensive need for an effective synthetic method for vitamin A (**1a**).[2] Since **1a** is unstable thermally and photolytically as well as in oxidative and acidic conditions, various approaches via retinoic acid or retinal have been reported. However, these are not actually practical and thus it is crucial to realize mild reaction conditions for the direct synthesis of **1a**. Another significant problem is how to control the stereochemistry. In particular, contamination by the 9-cis isomer reduces the biological activity drastically. Whereas the stereochemistry had been determined mainly on the basis of UV spectra, recent development of the HPLC technique has provided us with a more convenient and reliable method for the stereochemical elucidation.[2] According to this new method, the highest content for the all-trans isomer attained among previous works has been reported to be at most 85%.[3g-i]

There have been appeared various convergent approaches to assemble the C_{20} skelton involving the C_{15} + C_5 route,[3] the C_{14} + C_6 route,[4] and the C_{13} + C_7 route.[5] Another possible one, the C_{10} + C_{10} route, if realized, would be of both synthetic and practical interest because of the availability of raw materials from monoterpenoid compounds. Although this strategy has been applied to the relatively stable methyl retinoate,[6] no successful results have been obtained for **1a**.

It is also important to choose an appropriate reaction to combine each component. The base-catalyzed condensation of aldehydes was the first choice,[3a,c] and the Grignard[4] and Wittig[3d] reactions were employed later. Organolithium compounds[3e] and silyl enol ether[3f] have also been applied. More recently, the desulfonylation method that had been developed initially for methyl retinoate by Julia et al.[7] has received much attention.[3g-j,5,6]

We have communicated a convenient C_{10} + C_{10} route to methyl retinoate through a double elimination reaction via β-alkoxy sulfone intermediates.[8] Notable features of this method are twofold: (i) the one-pot generation of two double bonds from a β-alkoxy sulfone precursor makes the process highly simple and (ii) the stereochemistry of the C_9 and C_{11} double bond is exclusively *E*. Accordingly, this process seemed to us promising for a stereoselective synthesis of **1a**. This is indeed the case. The modification of this process has enabled us to realize a simple convergent synthesis of **1a**, giving rise to the all-trans content up to 95%. Furthermore, the highly stereoselective synthesis of the 13-cis isomer has been achieved as well for the first time.[9]

Synthesis. Scheme I illustrates one of the procedures established in this study (method A). The first step is the coupling of the β-cyclogeranyl sulfone **2a** with the C_{10} aldehyde **3** that can be prepared by oxidation of geranyl acetate. The sulfone **2a** was treated with *n*-BuLi in THF at −78 °C or EtMgBr in toluene at 40–45 °C, and the aldehyde **3** was added into this solution at −78 °C or −40 to −30 °C, respectively. The mixture was stirred at these temperatures for 2 h. The reaction should be quenched at the same temperature in order to suppress the retroaldol reaction. The best result was obtained when **2**, *n*-BuLi, and **3** were employed in 2.0:1.1:1.0 ratio. The employment of the cyclogeranyl sulfone in excess is noteworthy. Preparation of **2a** by acid-promoted cyclization of a geranyl sulfone inevitably results in contamination by the α-isomer **2b** (<25%).[10] However, the separation of **2a** from **2b** is unnecessary since the metalation takes place



2b

on the allylic sulfone **2a** exclusively under the present reaction conditions. Column chromatography of the reaction products afforded **4** (diastereomeric ratio 98:2)[11] in 93% yield together with the recovered cyclogeranyl sulfones (84%). The employment of EtMgBr in place of *n*-BuLi afforded quite similar yields of **4** (91%) and the

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(11) The assignment of the threo and erythro isomers has not been made yet.

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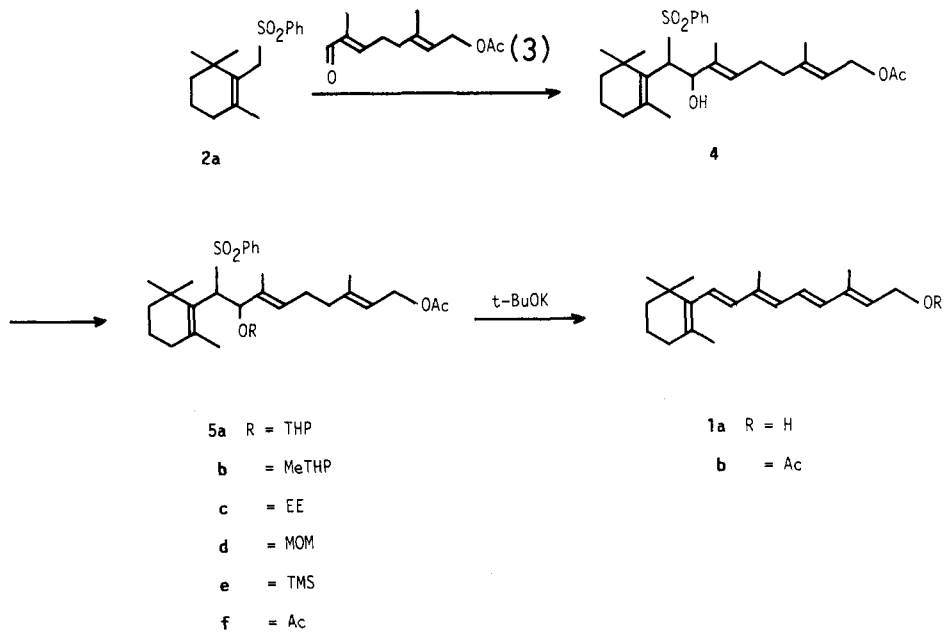
Scheme I



recovered cyclogeranyl sulfones (88%). The diastereomeric ratio in this case was found to be 75:25. As described later, however, the diastereomeric purity exerts no influence on the next reactions. The coupling product **4** was then converted to the corresponding ethers or acetate. The tetrahydropyranyl (THP) **5a**, 4-methyltetrahydropyran-2-yl (MeTHP) **5b**, and 1-ethoxyethyl (EE) **5c** ethers were obtained by the reaction with respective vinyl ethers in the presence of a catalytic amount of *p*-toluenesulfonic acid or PPTS. Treatment of **4** with dimethoxymethane in the presence of P_2O_5 or with trimethylchlorosilane in the presence of Et_3N/4-(dimethylamino)pyridine afforded the methoxymethyl (MOM) **5d** and trimethylsilyl (TMS) **5e** ethers, respectively. The acetate **5f** was prepared in a usual manner (Ac_2O/pyridine). Attempts to prepare simple alkyl ethers by the Williamson synthesis failed on account of predominance of the retro-aldol reaction.

Finally, **5** was subjected to the potassium alkoxide promoted double elimination reaction. The reaction conditions were investigated in detail for **5a** (Table I). The reaction should be conducted below 40 °C, otherwise significant decomposition of **1a** took place. Potassium methoxide (MeOK) gave rise to slightly better results than potassium *tert*-butoxide (*t*-BuOK) with respect to yields as well as the stereochemical outcome. In general, hydrocarbons proved to be a suitable solvent. The analogous solvent effect has been reported in the previous desulfonylation method.[3h] While employment of THF enhances the conversion of **5a**, the decomposition of **1a** also was accelerated in this solvent. No reaction occurred in methanol.

Having established optimum conditions, we applied the double elimination reaction to other β-alkoxy sulfones **5**. Satisfactory results were obtained for α-alkoxy ethers (acetals) **5b–d** (entry 6–8 in Table I). It should be noted that the diastereomeric ratio in **5a–d** had no influence on the elimination. The stereochemistry of vitamin A (**1a**) thus obtained was determined on the basis of HPLC (Figure 1a) and their yields were determined as vitamin A acetate (**1b**) after column chromatographic isolation. There was observed no essential effect of the α-alkoxy group on both yields and the stereoselectivity.

On treatment with *t*-BuOK, the β-hydroxy sulfone **4** yielded the sulfone **2** on account of the retro-aldol reaction.

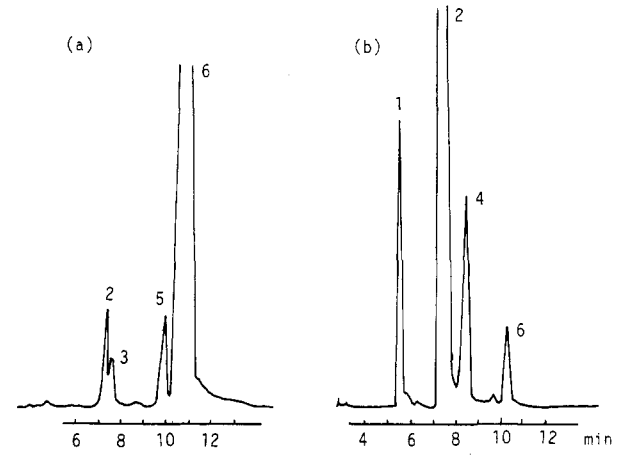
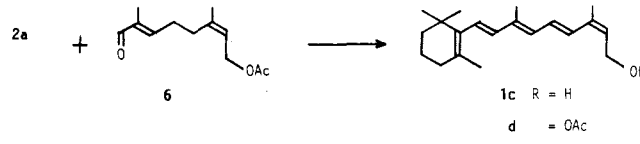


Figure 1. HPLC of **1a** (left) and **1c** (right): (1) 11,13-di-cis; (2) 13-cis; (3) 11-cis; (4) 9,13-di-cis; (5) 9-cis; (6) all-trans.

Scheme II



Similar results were obtained for the silyl ether **5e** and the acetate **5f**. In these cases, a nucleophilic attack of an alkoxide anion on the TMS or acetoxy group predominates over the elimination. While it seemed of great interest to investigate whether or not the α-alkoxy ether plays a crucial role for the elimination, we were unable to prepare simple alkyl ethers.

Another notable feature of the present method is exemplified by the reaction with the aldehyde **6** prepared from neryl acetate (Scheme II). The 13-cis isomer **1d** was formed in good yield (76%). The excellent stereoselectivity of **1c** is evident from Figure 1b (13-cis:all-trans:9,13-di-cis:11,13-di-cis[12] = 90:2:2:6). This is the first example of the highly stereoselective direct synthesis of the 13-cis

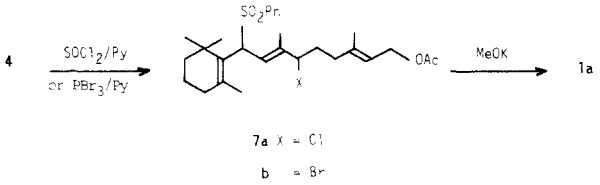
(12) The assignments of stereoisomers were made by comparison with authentic samples except for the 11,13-di-cis isomer which could not be obtained. Accordingly, this isomer was tentatively assigned.

Table I. Synthesis of Vitamin A from 5

entry	sulfone 5	base	solvent[a]	reaction temp, °C	reaction time, h	vitamin A yield,[b] %	vitamin A all-trans:9-cis: 13-cis:11-cis[c]
1	5a	*t*-BuOK	T(20)/B(1)	40	2.5	67	90:2:5:3
2		*t*-BuOK	T	20	3.5	63	92:2:4:2
3		*t*-BuOK	C	20	4.0	69	92:1:4:3
4		MeOK	M	35	1.0		
5		MeOK	C	38	2.0	77	95:2:2:1
6	5b	MeOK	C	38	2.0	72	94:2:3:1
7	5c	MeOK	C	38	2.0	83	95:2:2:1
8	5d	MeOK	C	38	2.0	78	93:3:3:1

[a] T, toluene; B, *tert*-butyl alcohol; C, cyclohexane; M, methanol. [b] Isolated yields after column chromatography. [c] Determined as **1a** by means of HPLC.

Scheme III

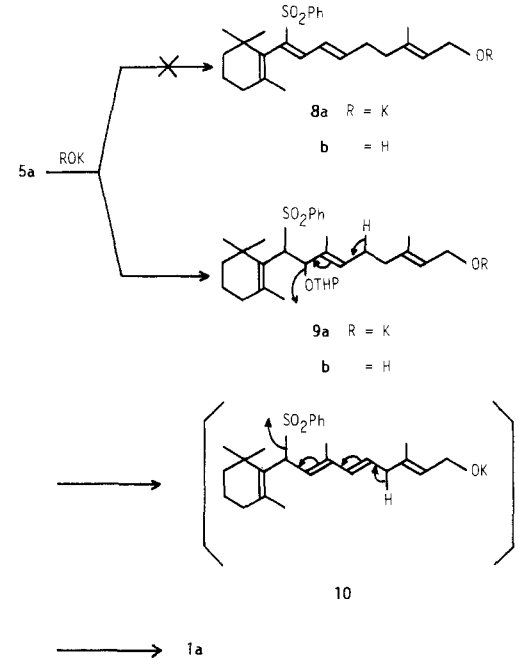


isomer.[13] Apparently, the stereochemical outcome in this reaction is completely dependent on the aldehydes employed. It is concluded, therefore, that the isomerization of the double bond at the 13- or 9-position is kinetically controlled.

In our continuing study, we have found that halo sulfones undergo a facile double elimination reaction as well. This reaction was applied to the vitamin A synthesis (method B) as shown in Scheme III. Treatment of the β-hydroxy sulfone **4** with thionyl chloride or phosphous tribromide in the presence of pyridine afforded the chloride **7a** or the bromide **7b**. Subjection of these compounds to the *t*-BuOK-promoted elimination gave no successful results. Interestingly, however, the reaction with MeOK proceeded smoothly with satisfactory yield (70%) and the stereochemical outcome (all-trans:9-cis:13-cis:11-cis = 93:4:2:1) for both halides.

Mechanistic Aspects of the Double Elimination Reaction. We first investigated the double elimination according to method A employing **5a** as a representative example. By analogy with the mechanistic consideration of the double elimination reaction of β-alkoxy sulfones,[14] we supposed that the initial step is the 1,2-elimination of the THPO group to give **8** (Scheme IV). This is not the case, however. Treatment of **5a** with 2 equiv of *t*-BuOK at room temperature resulted in hydrolysis of the terminal acetate group to give **9b**, but no 1,2-elimination occurred at all. MeOK gave the same results. Under similar conditions, in general, β-alkoxy sulfones easily undergo the 1,2-elimintion. Apparently, the α-hydrogen of the sulfonyl group in **5a** which is sterically congested by bulky trimethylcyclohexenyl and THPO groups resists the attack of an alkoxide anion. TLC monitoring of the reaction with a large excess (4–10 equiv) of potassium alkoxides indicated that **5a** was initially converted into **9a** at room temperature. Then, **9a** was gradually consumed to give **1a** at elevated temperature (35–40 °C). No sign of intermediacy of the polyenyl sulfone **8a** was detected. These observations can be explained in terms of deprotonation of an allylic hydrogen at the 11-position in **9a** followed by the 1,4-elimination of the THPO group to give **10**. This is

Scheme IV



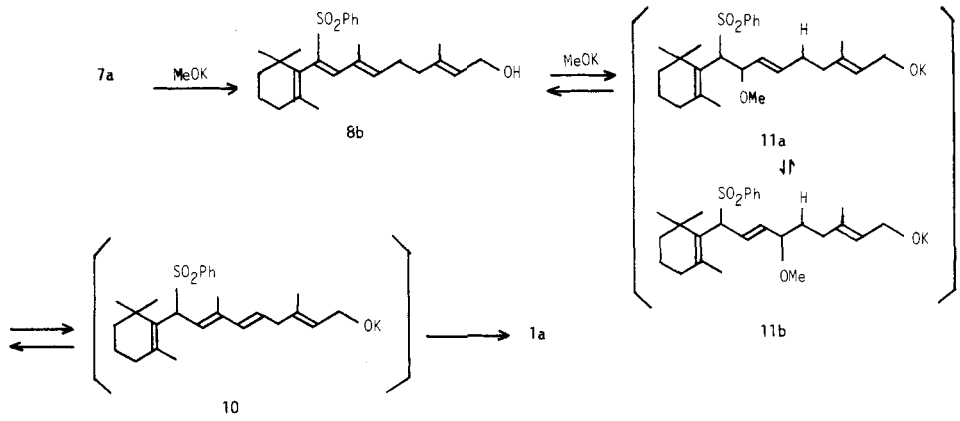
consistent with the following two facts. (1) The diastereomeric ratio has no influence on the elimination since the 1,2-elimination, if operative, should be somewhat dependent on the diastereomeric ratio. (2) In contrast to a facile 1,2-elimination of usual β-alkoxy sulfones at room temperature, the transformation of **9** to **10** failed to occur below 35 °C. More energy is required for deprotonation of an allylic hydrogen than the acidic α-hydrogen of the phenylsulfonyl group. Once **10** is formed, the 1,6-elimination of sulfinic acid takes place immediately since the hydrogen at the 12-position in **10** is highly reactive due to a double allylic character. As a result, it is reasonably assumed that conversion of **10** into **1a** is much faster than that of **9a** into **10**. Consequently, no intermediates could be detected during the transformation of **9a** into **1a**.

We next discuss method B which has turned out to be mechanistically different from the former method. Treatment of the α-chloro sulfone **7a** with 2 equiv of MeOK afforded the polyenyl sulfone **8b** (Scheme V). On the other hand, no reaction occurred with *t*-BuOK. Probably, a bulky *tert*-butoxy anion is not allowed to approach the α-hydrogen of a phenylsulfonyl group. Of further interest is that MeOK effected desulfonylation of **8b** smoothly to give **1a** while *t*-BuOK induced no reaction at all under similar conditions. Under forcing conditions, complex unidentifiable products were obtained in the latter case. Possibly, the isomerization of **8b** to **10** was effected by the Michael addition of MeOK. The addition could

(13) The synthesis of the 13-cis isomer from the corresponding retinoic acid has been reported.[2c]

(14) Otera, J.; Misawa, H.; Sugimoto, K. *J. Org. Chem.*, preceding paper in this issue.

Scheme V



proceed in two ways, via **11a** or **11b**. Although this reaction might be reversed by the retro-Michael addition, an alternative elimination of methanol can afford the highly reactive intermediate **10**. In this respect, **11a** rather than **11b** can be viewed as the intermediate responsible for the elimination since abstraction of an allylic proton is much easier.

Potassium *tert*-butoxide does not undergo the Michael addition due to its less nucleophilic character. The isomerization of **8b** to **10** through abstraction of the allylic proton at the 11-position in **8b** might have taken place to some extent under forcing conditions. However, decomposition of **1a** was more rapid in this case so that complex reaction products were obtained.

In conclusion, the first convergent $C_{10} + C_{10}$ route for **1a** has been realized in a highly stereoselective manner by the two double elimination methods. It seems of synthetic interest and practical significance that either of isomers can be produced merely by changing the aldehyde component. To the best of our knowledge, the stereochemical purity of the all-trans isomer attained in this study is much superior to those of previous works. The product can be served for the practical use without further purification. From a mechanistic point of view, the present methods are different from a simple double elimination which consists of a sequence of vinyl sulfone formation, isomerization to allylic sulfone, and elimination of phenyl sulfinic acid.[14] Nevertheless, the formation of allylic sulfone **10** under mild conditions is suggested to be pivotal to every double elimination reaction in common.

Experimental Section

All reactions were carried out under a nitrogen or argon atmosphere. Potassium alkoxides were sublimed before use. Solvents were purified by standard methods. Column chromatography was performed on silica gel (Wako gel C-200) or alumina (Merk 1097). ^{1}H NMR spectra were recorded with Hitachi R-24B (60 MHz), JEOLCO JNM FX-100 (100 MHz), and JEOLCO JNM GX-500 (500 MHz) spectrometers. Mass spectra were measured with a JEOLCO JMS D-300 spectrometer. The HPLC analyses were run on a Waters solvent delivery system Model 6000A on a μ-Porasil column (3.9 mm × 150 mm). The stereochemistry of vitamin A was determined on the HPLC by flowing a mixture of hexane–1-pentanol (200:1) as an eluent (2.0 mL/min). Melting points were uncorrected. Cyclogeranyl sulfones were prepared according to the reported method.[10]

8-Acetoxy-2,6-dimethylocta-2(*E*),6(*E*)-dienal (3) and -2-(*E*),6(*Z*)-dienal (6). To a stirred solution of SeO_2 (23.8 mg, 0.21 mmol) and salicylic acid (148 mg, 1.07 mmol) in dichloromethane (20 mL) was added dropwise *tert*-butyl hydroperoxide (70% solution, 3.85 mL) and geranyl acetate (1.95 g, 10.7 mmol).[15] After being stirred for 27 h at room temperature, the mixture was poured into ice water and extracted with dichloromethane. The organic layer was washed with $Na_2S_2O_3$ and $NaHCO_3$ solutions, dried ($MgSO_4$), and evaporated to give a crude mixture (2.01 g) of **3** and the corresponding allyl alcohol. The crude products were converted to the allyl alcohol by treating $NaBH_4$ in methanol–ether at 0 °C. The allyl alcohol thus obtained (575 mg, 2.9 mmol) and PDC (1.61 g, 4.28 mmol) were stirred in dichloromethane (20 mL) at room temperature in the dark for 10 h. The reaction mixture was diluted with ether and filtered. The filtrate was evaporated and the residual oil was chromatographed (5:1 hexane–ether) to give pure **3** (523 mg, 92%).[16] Employment of neryl acetate in place of geranyl acetate gave **6** analogously in 90% yield.

1-Acetoxy-8-hydroxy-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-9-(phenylsulfonyl)-2(*E*),6(*E*)-nonadiene (4). To a THF solution (60 mL) of **2a** (5.0 g, 18 mmol) contaminated by ca. 10% of **2b** was added *n*-BuLi (1.5 N, 6.6 mL, 9.9 mmol) at −78 °C, and the solution was stirred at this temperature for 2 h. To this solution was added **3** (1.89 g, 9 mmol) in THF (15 mL) at −78 °C. After being stirred for 3 h, the mixture was quenched with water at −78 °C and extracted with benzene. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residual oil was subjected to column chromatography to give a mixture of **2a** and **2b** (2.25 g, 15:1 hexane–ethyl acetate) and **4** (4.01 g, 93%, 5:1 hexane–ethyl acetate): ^{1}H NMR (500 MHz) (CCl_4) δ 0.72 (s, 3 H), 0.82 (s, 3 H), 1.38–1.77 (m, 4 H), 1.56 (s, 3 H), 1.70 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 1.95–2.02 (m, 6 H), 3.47 (br s, 1 H), 4.04 (d, 1 H, J = 8 Hz), 4.58 (d, 2 H, J = 6 Hz), 5.04 (d, 1 H, J = 8 Hz), 5.30–5.40 (m, 2 H), 7.48–7.57 (m, 2 H), 7.57–7.63 (m, 1 H), 8.00–8.05 (m, 2 H); IR (film) 3500, 1735, 1140 cm^{-1}. Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.81; H, 8.25. Found: C, 68.66; H, 8.39.

Metalation of **2a** also was effected with EtMgBr. To a toluene solution (100 mL) of **2a** (10.8 g, 38.8 mmol) was added EtMgBr (1.06 N ether solution, 24.2 mL, 25.6 mmol) at 20 °C. After being stirred for 3 h at 40–45 °C, the solution was cooled to −40 °C. A toluene solution (10 mL) of **3** (4.02 g, 19.1 mmol) was added dropwise to this solution. The mixture was stirred at −40 to −30 °C for 2 h and, then, quenched with 10% HCl solution. Workup gave **4** (8.46 g, 91%) and a mixture of **2a** and **2b** (5.39 g).

Synthesis of 5a–c. To a dichloromethane solution (15 mL) of **4** (1.36 g, 2.80 mmol) and a catalytic amount of *p*-toluenesulfonic acid was added dihydropyran (0.72 g, 8.4 mmol) at 0 °C. The solution was stirred for 3 h at room temperature and extracted with dichloromethane–$NaHCO_3$ solution. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. Column chromatography (5:1 hexane–ethyl acetate) of the residue furnished **5a** (1.59 g, 99%): ^{1}H NMR (60 MHz) (CCl_4) δ 0.57–1.08 (m, 6 H), 1.33 (s, 3 H), 1.57 (s, 3 H), 1.87 (s, 3 H), 1.92 (s, 3 H), 1.13–2.57 (m, 16 H), 3.00–5.47 (m, 7 H), 4.33 (d, 2 H, J = 6 Hz), 7.13–7.50 (m, 3 H), 7.67–8.07 (m, 2 H); IR (film) 1745, 1150 cm^{-1}; MS, m/e 573 ($M^+ + 1$), 572 (M^+).

An analogous procedure employing 4-methyldihydropyran catalyzed by *p*-toluenesulfonic acid and ethyl vinyl ether catalyzed by PPTS gave **5b** and **5c** in 99% and 94% yields, respectively.

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(16) Mori, K.; Ohki, M.; Matsui, M. *Tetrahedron* **1974**, *30*, 715.

Synthesis of 5d. To a mixture of **4** (2.67 g, 5.5 mmol) and dimethoxymethane (9.65 mL, 110 mmol) was added P_2O_5 (0.22 g, 1.54 mmol). The mixture was stirred at room temperature. After 2 and 5 h, additional portions of P_2O_5 (0.21 g) were added to this mixture. After being stirred for 24 h, the mixture was extracted with toluene and $NaHCO_3$ solution. The organic layer was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was chromatographed (5:1 hexane–ethyl acetate) to give **5d** (2.68 g, 92%): ^1H NMR (100 MHz) ($CDCl_3$) δ 0.69–1.99 (m, 28 H), 3.16, 3.35 (s, 3 H), 3.96–5.60 (m, 8 H), 7.38–8.01 (m, 5 H); MS, m/e 532 (M^+).

Synthesis of 5e. To a mixture of **4** (3.89 g, 8.0 mmol), 4-(dimethylamino)pyridine (0.10 g, 0.8 mmol), triethylamine (1.74 g, 16 mmol), and dichloromethane (20 mL) was added trimethylchlorosilane (1.38 g, 12 mmol). The mixture was stirred at room temperature for 2.5 h and then poured into hexane (300 mL). The resultant suspension was washed with cold $NaHCO_3$ solution twice, dried ($MgSO_4$), and evaporated. The residue was chromatographed (5:1 hexane–ethyl acetate) to give **5e** (4.25 g, 95%): ^1H NMR (100 MHz) ($CDCl_3$) δ 0.05 (s, 9 H), 0.64 (s, 3 H), 0.92 (s, 3 H), 1.20–2.07 (m, 22 H), 4.02 (d, 1 H, J = 10 Hz), 4.47 (d, 2 H, J = 7 Hz), 4.94 (d, 1 H, J = 10 Hz), 5.23 (m, 2 H), 7.33–7.50 (m, 3 H), 7.83–8.00 (m, 2 H); MS, m/e 560 (M^+).

Synthesis of 5f. A mixture of **4** (200 mg, 0.41 mmol), acetic anhydride (5 mL), pyridine (5 mL), and a catalytic amount of 4-(dimethylamino)pyridine was stirred at room temperature for 10 h. The mixture was extracted with benzene and 1 N HCl. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. Column chromatography of the residue (15:1 hexane–ethyl acetate) afforded **5f** (206 mg, 95%): ^1H NMR (500 MHz) (CCl_4) δ 0.72 (s, 3 H), 1.06 (s, 3 H), 1.43 (s, 3 H), 1.56 (s, 3 H), 1.28–1.63 (m, 4 H), 1.85 (s, 3 H), 1.95 (s, 3 H), 2.01 (s, 3 H), 1.76–2.15 (m, 6 H), 4.13 (d, 1 H, J = 8 Hz), 4.47 (d, 2 H, J = 6 Hz), 5.16–5.30 (m, 2 H), 5.90 (d, 1 H, J = 8 Hz), 7.42–7.51 (m, 2 H), 7.51–7.58 (m, 1 H), 7.82–7.89 (m, 2 H).

Synthesis of All-Trans Vitamin A (1a) from 5. Typical Procedure. A mixture of **5a** (571 mg, 1.0 mmol) and MeOK (700 mg, 9.9 mmol) in cyclohexane (15 mL) was stirred in the dark at 38 °C for 2 h. The reaction mixture was extracted with diisopropyl ether–saturated NH_4Cl solution. The organic layer was separated, dried ($MgSO_4$), and evaporated, giving crude vitamin A, which was found to be a mixture of all-trans, 9-cis, 13-cis, and 11-cis isomers (95:2:2:1) on the basis of HPLC analysis. The crude vitamin A was treated with acetic anhydride (0.6 mL)/Et_3N (1.1 mL) in hexane (4 mL). The reaction mixture was washed with hexane–H_2O–methanol. The organic layer was dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography on neutral alumina (95:5 hexane–diisopropyl ether) to give **1a** (254 mg, 77%) which was identified by comparison with an authentic specimen.

Synthesis of 13-Cis Vitamin A (1c). A similar procedure to that of **1a** employing **6** in place of **3** furnished **1c** in 76% yield (13-cis:all-trans:9,13-di-cis:11,13-di-cis = 90:2:2:6).

1-Acetoxy-6-chloro-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-9-(phenylsulfonyl)-2,7-nonadiene (7a). A benzene solution (60 mL) containing **4** (7.38 g, 15 mmol), thionyl chloride (2.13 g, 18 mmol), and pyridine (11.9 g, 150 mmol) was stirred at room temperature for 16 h. The reaction mixture was extracted with ether–0.1 N H_2SO_4. The organic layer was washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated. Column chromatography of the residue (5:1 hexane–ethyl acetate) yielded **7a** (7.18 g, 94%): ^1H NMR (500 MHz) (CCl_4) δ 0.76 (s, 3 H), 0.87 (s, 3 H), 1.59 (s, 3 H), 1.82 (s, 3 H) 1.96 (s, 3 H), 2.02 (s, 3 H), 1.28–2.15 (m, 10 H), 4.25 (t, 1 H, J = 6 Hz), 4.40 (d, 1 H, J = 8 Hz), 4.41–4.53 (d, 2 H, J = 6 Hz), 5.20 (t, 1 H, J = 6 Hz), 5.88 (d, 1 H, J = 8 Hz), 7.39–7.51 (m, 2 H), 7.51–7.59 (m, 1 H), 7.73–7.85 (m, 2 H); IR (film) 1745, 1150, 685 cm^{-1}. Anal. Calcd for $C_{28}H_{39}ClO_4S$: C, 66.32; H, 7.75. Found: C, 66.07; H, 7.86.

1-Acetoxy-6-bromo-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-9-(phenylsulfonyl)-2,7-nonadiene (7b). To a dichloromethane solution (20 mL) of **2a** (2.44 g, 5.0 mmol) and pyridine (0.12 g, 1.51 mmol) was added PBr_3 (0.89 g, 3.3 mmol) at 0 °C. The mixture was stirred at this temperature for 1.5 h and extracted with ether–saturated $NaHCO_3$ solution. The organic layer was washed with saturated brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (5:1 hexane–ethyl acetate) to give **7b** (2.3 g, 85%): ^1H NMR (100 MHz) ($CDCl_3$) δ 1.71–2.03 (m, 28 H), 4.32–4.75 (m, 4 H), 5.24 (m, 1 H), 5.90 (m, 1 H), 7.43–7.90 (m, 5 H); IR (film) 1730, 1135, 670 cm^{-1}; mass spectrum, m/e 550 (M^+), 470 (M^+ – HBr), 409 (M^+ – $C_6H_5SO_2$).

Synthesis of 1a from 7. Typical Procedure. A cyclohexane solution (15 mL) of **7a** (495 mg, 0.98 mmol) and MeOK (700 mg, 10 mmol) was stirred at 38 °C for 2 h. Workup as described above afforded **1b** (225 mg, 70%, all-trans:9-cis:13-cis:11-cis = 93:3:3:1).

Empolyment of **7b** in place of **7a** afforded quite similar results with respect to yield (70%) and the stereochemical outcome (all-trans:9-cis:13-cis:11-cis = 93:3:3:1).

Reaction of 5a with 2 equiv of *t*-BuOK. A toluene solution (15 mL) of **5a** (572 mg, 1 mmol) and *t*-BuOK (224 mg, 2 mmol) was stirred at room temperature for 2 h. The reaction mixture was extracted with hexane–water. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give **9b** (470 mg, 89%): ^1H NMR (60 Hz) (CCl_4) δ 0.57–1.07 (m, 6 H), 1.27 (s, 3 H), 1.47 (s, 3 H), 1.87 (s, 3 H), 1.10–2.30 (m, 16 H), 3.00–5.30 (m, 8 H), 3.76 (d, 2 H, J = 6 Hz), 7.03–7.40 (m, 3 H), 7.50–7.90 (m, 2 H).

Reaction of 7a with 2 equiv of MeOK. A toluene solution (15 mL) of **7a** (300 mg, 0.59 mmol) and MeOK (83 mg, 1.19 mmol) was stirred at room temperature for 2 h. Usual workup and column chromatography (2:1 hexane–ethyl acetate) furnished **8b** (230 mg, 91%): ^1H NMR (60 MHz) (CCl_4) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.16 (s, 3 H), 1.58 (br s, 6 H), 2.23 (s, 1 H), 0.83–2.30 (m, 10 H), 3.87 (d, 2 H, J = 6 Hz), 4.93–5.87 (m, 2 H), 6.87 (s, 1 H), 7.10–7.80 (m, 5 H). Anal. Calcd for $C_{26}H_{36}O_3S$: C, 72.86; H, 8.47. Found: C, 72.62; H, 8.40.

Synthesis of 1a from 8b. A cyclohexane solution (15 mL) of **8b** (450 mg, 1.05 mmol) and MeOK (700 mg, 10 mmol) was stirred at 38 °C for 2 h. Usual workup followed by acetylation affored **1b** (329 mg, 77%); all-trans:9-cis:13-cis:11-cis = 93:3:3:1.

Registry No. **1a**, 68-26-8; **1b**, 127-47-9; **1c**, 2052-63-3; **2a**, 56691-74-8; **3**, 37905-02-5; **3** alcohol, 38290-51-6; **4**, 103905-01-7; **5a**, 103905-07-3; **5b**, 103905-02-8; **5c**, 103905-03-9; **5d**, 103905-04-0; **5e**, 103905-05-1; **5f**, 103905-06-2; **6**, 94853-00-6; **7a**, 103905-08-4; **7b**, 103905-09-5; **8b**, 103905-11-9; **9b**, 103905-10-8; EtOCH=CH_2, 109-92-2; 4-methyldihydropyran, 2270-61-3; salicylic acid, 69-72-7; geranyl acetate, 105-87-3; neryl acetate, 141-12-8.