

THE HIGHLY STEREOSELECTIVE SYNTHESIS OF ALL-TRANS AND 13-CIS VITAMIN A
VIA DOUBLE ELIMINATION REACTION¹⁾Junzo OTERA,* Hiromitsu MISAWA, Tadakatsu MANDAI, Takashi ONISHI,[†]
Shigeaki SUZUKI,[†] and Yoshiji FUJITA[†]

Okayama University of Science, Ridai-cho, Okayama 700

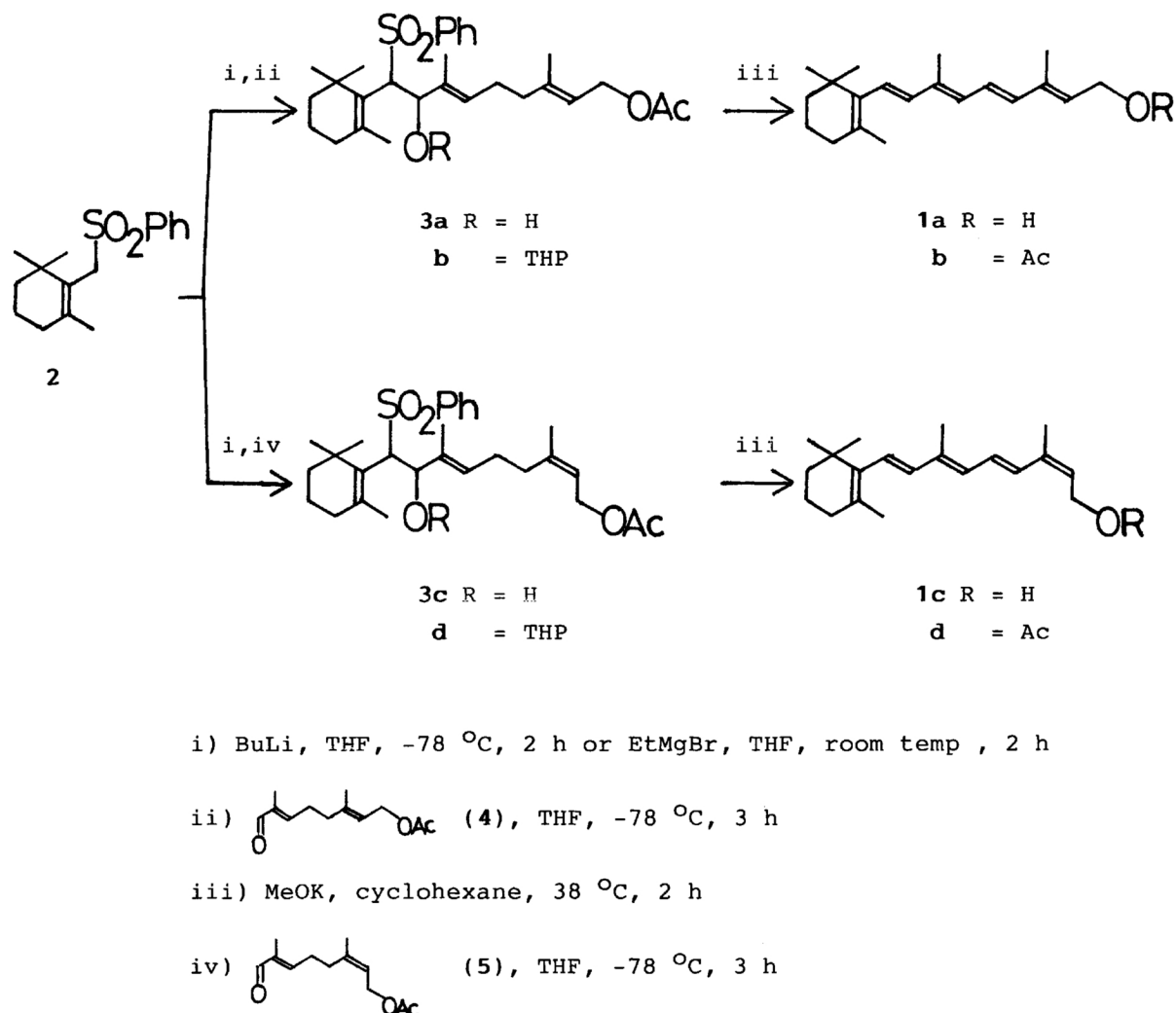
[†]Central Research Laboratories, Kuraray Co. Ltd., Sakazu,
Kurashiki, Okayama 710

Stereocontrolled convergent synthesis of vitamin A was achieved by the double elimination method employing the C₁₀ sulfone and the C₁₀ aldehydes as starting materials. Thus the all-trans and 13-cis isomers were obtained with the stereochemical purity of 95% and 90%, respectively.

Stereocontrol of trisubstituted double bonds is one of the most significant problems in the synthesis of vitamin A derivatives.²⁾ Although there have appeared various reports on vitamin A synthesis, the stereochemical purity is not always satisfactory. It is crucial to increase the content of the all-trans isomer for obtaining a high biological activity. Here we wish to describe a highly stereoselective synthesis of vitamin A, which affords the all-trans isomer (**1a**) of 95% purity. Moreover, the present procedure proved to provide the 13-cis isomer (**1c**) in a highly stereoselective manner (≈90%) for the first time.

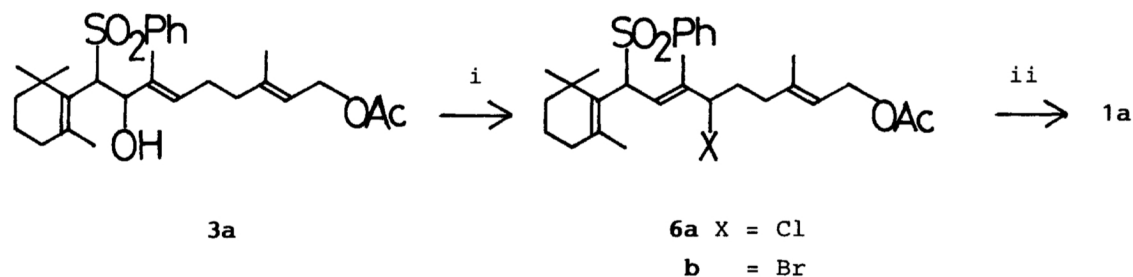
Our strategy is based on the double elimination method of β-alkoxy sulfones which was developed previously in our laboratory.³⁾ It was found that the procedure employed successfully for retinoic acid cannot be applied to vitamin A on account of its instability. However, the difficulty was bypassed by employing a hydrocarbon solvent such as cyclohexane or toluene instead of polar solvents previously used. Furthermore, potassium methoxide (MeOK) proved to give better yields and stereochemical outcome than potassium t-butoxide (t-BuOK).

As shown in Scheme 1, the first step is coupling of the C₁₀ sulfone with the C₁₀ aldehyde. β-Cyclogeranyl sulfone (**2**)⁴⁾ (1.67 g, 6 mmol) and n-BuLi (3.3 mmol) was stirred in THF (20 mmol) at -78 °C for 2 h. To the resultant anion was added the C₁₀ aldehyde **4**⁵⁾ (630 mg, 3 mmol) prepared from geranyl acetate in THF (5 ml) at -78 °C and the mixture was stirred at this temperature for 3 h. Usual workup and column chromatography on silica gel (5:1 hexane-ethyl acetate) afforded β-hydroxy sulfone **3a** (1.36 g, 93%) and the excessively employed C₁₀ sulfone **2** (750 mg, 84%).⁶⁾ Then, **3a** was converted to the



Scheme 1.

tetrahydropyranyl ether **3b** quantitatively on treatment with dihydropyrane in the presence of a catalytic amount of p-toluenesulfonic acid in dichloromethane. The double elimination reaction proceeded well with either t-BuOK or MeOK. However, the latter proved to give somewhat better results with respect to yields as well as the stereochemical outcome. For instance, the mixture of **3b** (571 mg, 0.999 mmol) and MeOK (700 mg, 7.7 mmol) in cyclohexane (15 ml) was stirred at 38 °C for 2 h. The reaction mixture was extracted with diisopropyl ether-aqueous NH₄Cl. The organic layer was dried (MgSO₄) and evaporated, giving crude vitamin A (**1a**), which was treated with Ac₂O (0.68 ml)/Et₃N (1.1 ml) in hexane (4 ml). Usual workup of the reaction mixture afforded a red orange oil (343 mg) containing vitamin A acetate (**1b**) (254 mg, 77% based on **3b** assayed by HPLC). HPLC analysis indicated that **1a** thus obtained consisted of all-trans (95%), 13-cis + 11-cis (3%), and 9-cis (2%) isomers.



- i) SOCl_2 , pyridine, benzene, rt, 2 h or PBr_3 , pyridine, dichloromethane, 2 h
 ii) MeOK, cyclohexane, 38°C , 2 h

Scheme 2.

From the above findings, the double elimination process proved to have an excellent preference for trans geometry at the 9- and 11-position. Accordingly, an effective method for the 13-cis isomer should be achieved by use of neryl acetate. This is indeed the case. When the aldehyde **5**⁵⁾ was employed in place of **4**, the 13-cis isomer **1d** (13-cis: all-trans:9-cis + 9,13-dicis: 11,13-dicis⁷⁾ = 90:2:2:6) was obtained in 76% yield based on **3d**.

Next, we have found that the double elimination reaction occurs in the case of δ -halo sulfones as well. As a result, another effective route to **1a** has been established as shown in Scheme 2. A benzene solution (20 ml) containing **3a** (2.44 g, 5 mmol), thionyl chloride (0.71 g, 6 mmol), and pyridine (3.95 g, 50 mmol) was stirred at room temperature for 2 h. Usual workup and column chromatography on silica gel afforded the chloride **6a** (2.37 g, 94%) as white crystals. Treatment of **3a** with PBr_3 in dichloromethane in the presence of pyridine afforded the bromide **6b** in 85% yield. The mixture of **6a** (495 mg, 0.98 mmol) and MeOK (700 mg, 10 mmol) in cyclohexane (15 ml) was stirred at 38°C for 2 h. Usual workup and subsequent acetylation of the crude product gave vitamin A acetate **1b** (224 mg, 70% based on **6a**, all-trans:9-cis:13-cis = 93:3:4 assayed by HPLC). The quite similar results (70% yield, all-trans:9-cis:13-cis = 93:3:4) were obtained employing the bromide **6b** in place of **6a**. It should be added to note that *t*-BuOK failed to induce the double elimination reaction of δ -halo sulfones **6**. In this case, the terminal acetate group was hydrolyzed but no elimination reaction occurred at all. Prolonged reaction gave rise to complex decomposition products.

In conclusion, the present method provides a novel synthetic method for vitamin A through the first $C_{10} + C_{10}$ coupling mode. The method is of practical importance since the starting materials are readily available from mono-terpenoid compounds. The one-pot generation of two double bonds from β - or δ -substituted sulfones makes the process highly simple. Of further significance is that the stereochemical outcome is conveniently controlled by the aldehydes employed. It should be noted that the all-trans isomer obtained from **3b** is stereochemically pure enough for the practical use without further purification. To the best of our knowledge, the isomeric purity is much superior to those previously reported ($\leq 85\%$) for the all-trans isomer.⁸⁾ Moreover, this is the first example for the highly stereoselective direct synthesis of the 13-cis isomer.⁹⁾

References

- 1) The nomenclature of vitamin A isomers is in accordance with the conventional method.²⁾
- 2) R. S. Liu and A. E. Asato, *Tetrahedron*, **40**, 1931 (1984).
- 3) T. Mandai, T. Yanagi, K. Araki, Y. Morisaki, M. Kawada, and J. Otera, *J. Am. Chem. Soc.*, **106**, 3670 (1984).
- 4) S. Torii, K. Uneyama, and M. Ishihara, *Chem. Lett.*, **1975**, 479.
- 5) Aldehydes **4** and **5** were prepared by the Sharpless oxidation (t -BuOOH- SeO_2) of geranyl or neryl acetate: M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526, 1977.
- 6) Employment of $EtMgBr$ in place of $BuLi$ gave similar results. $EtMgBr$ in THF was added into a THF solution of **2** at room temperature and the mixture was stirred for 2 h at this temperature. After being cooled at $-78^\circ C$, the mixture was treated with the aldehyde **4** affording **3a** in 87% yield together with recovered **2** (89%).
- 7) The HPLC peaks were definitely assigned on the basis of comparison with those of authentic samples except one peak which was tentatively attributed to 11,13-dicis.
- 8) P. S. Manchand, M. Rosenberger, G. Saucy, P. A. Wehrli, H. Wong, L. Chambers, M. P. Ferro, and W. Jackson, *Helv. Chim. Acta.*, **59**, 387 (1976). P. Chabardes, J. P. Decor, J. Vartagnat, *Tetrahedron*, **33**, 2799 (1977).
- 9) The synthesis of the 13-cis isomer from the corresponding retinoic acid has been reported: M. Matsui, S. Okano, K. Yamashita, M. Miyano, S. Kitamura, A. Kobayashi, T. Sato, and R. Mikami, *J. Vitaminol.* **4**, 178 (1958).

(Received September 20, 1985)