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THE HIGHLY STEREOSELECTIVE SYNTHESIS OF ALL-TRANS AND 13-CIS VITAMIN A VIA DOUBLE ELIMINATION REACTION[1)]

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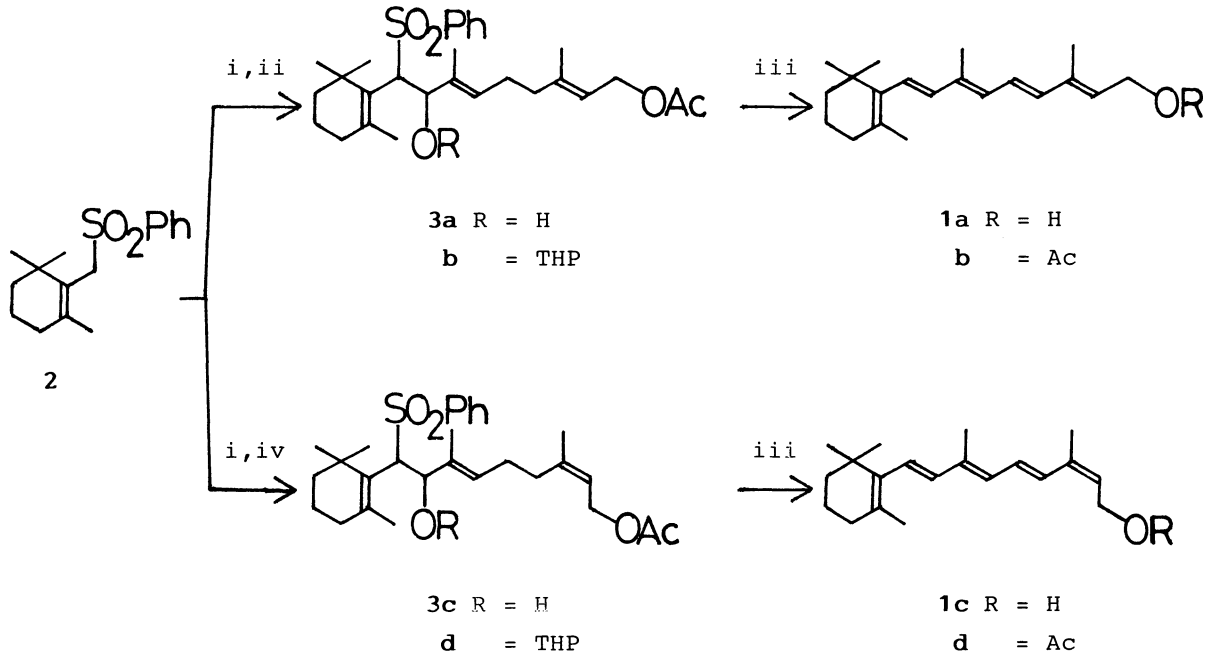
Stereocontrolled convergent synthesis of vitamin A was achieved by the double elimination method employing the C_{10} sulfone and the C_{10} aldehydes as starting materials. Thus the all-trans and 13-cis isomers were obtained with the stereochemical purity of 95% and 90%, respectively.

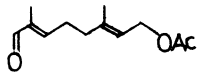
Stereocontrol of trisubstituted double bonds is one of the most significant problems in the synthesis of vitamin A derivatives.[2)] Although there have appeared various reports on vitamin A synthesis, the stereochemical purity is not always satisfactory. It is crucial to increase the content of the all-trans 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).

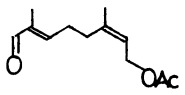
As shown in Scheme 1, the first step is coupling of the C_{10} sulfone with the C_{10} aldehyde. β-Cyclogeranyl sulfone (**2**)[4)] (1.67 g, 6 mmol) and n-BuLi (3.3 mmol) was stirred in THF (20 mmol) at -78 °C for 2 h. To the resultant anion was added the C_{10} aldehyde **4**[5)] (630 mg, 3 mmol) prepared 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 C_{10} sulfone **2** (750 mg, 84%).[6)] Then, **3a** was converted to the



i) BuLi, THF, -78 °C, 2 h or EtMgBr, THF, room temp , 2 h

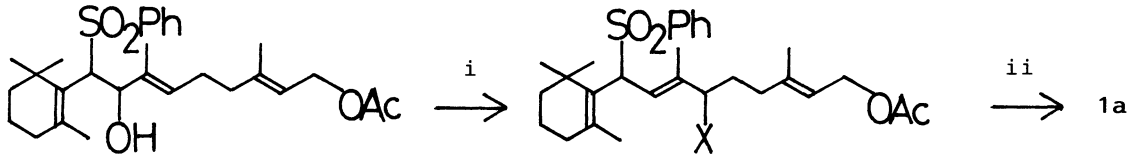
ii)  (**4**), THF, -78 °C, 3 h

iii) MeOK, cyclohexane, 38 °C, 2 h

iv)  (**5**), THF, -78 °C, 3 h

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 NH_4Cl. The organic layer was dried ($MgSO_4$) and evaporated, giving crude vitamin A (**1a**), which was treated with Ac_2O (0.68 ml)/Et_3N (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.



3a **6a** X = Cl
b = Br

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-dicis[7] = 90:2:2:6) was obtained in 76% yield based on **3d**.

Next, we have found that the double elimination reation 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 monoterpenoid 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 (≲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 °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).

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