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7-Cis- and 7,9-Dicis-3-dehydroretinal. Hindered Isomers of Vitamin A_2 Aldehyde.†

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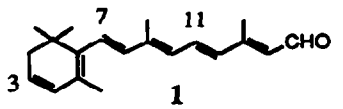
Abstract. Successful synthesis of the hindered 7-cis and 7,9-dicis isomers of 3-dehydroretinal from β-ionone is reported. The procedure, involving introduction of the hindered 7-cis geometry prior to the 3,4-double bond, should be applicable to preparation of other unknown isomers of Vitamin A_2 aldehyde.

The discovery of a photochemical method to introduce the hindered 7-cis geometry in derivatives of vitamin A[1] led to the synthesis of all sixteen possible isomers of retinal.[2] The situation, however, has been different for the closely related 3-dehydroretinal, 1 (vitamin A_2 aldehyde), which is also important in vision research because of its 11-cis isomer being the chromophore in porphyropsin pigments.[3] However, in recent years, only one new isomer has been added to the earlier known six isomers of vitamin A_2 (all-trans, 13-cis, 11-cis, 9-cis, 11,13-dicis and 9,13-dicis)[4]: the 7-cis isomer obtained from direct irradiation of the trans isomer.[5] The lack of progress toward prepa-ration of new isomers of this derivative of vitamin A is partly due to the altered photochemical properties of its lower homologs,[6] making building blocks containing the hindered 7-cis geometry relatively inaccessible. In this paper we describe a rational synthetic design to 7-cis-3-dehydroretinal. The method is potentially a general one, applicable to preparation of other unknown isomers of 3-dehydroretinal.



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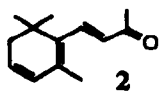

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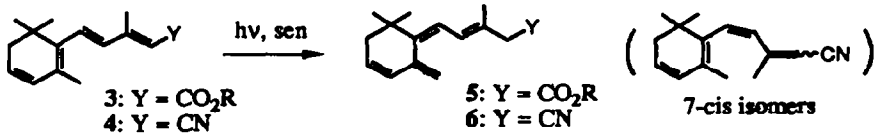
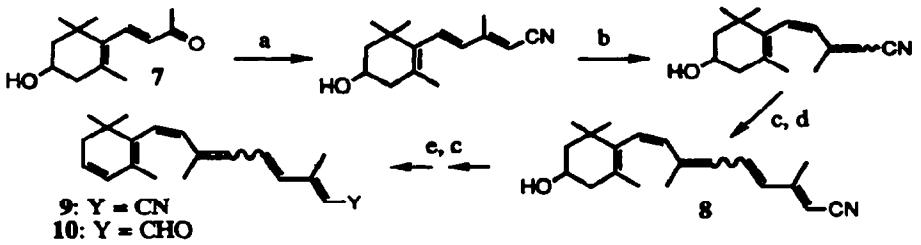
† Vitamin A isomers No. 19. For the previous paper in the series see: Y. Zhu et al. in ref. 15.

Selective triplet photosensitization was reported not to be effective for isomerizing compounds in the A_2 series, such as 3-dehydro-β-ionone (2) to its cis isomer.[6] It was suspected that deactivation of the triplet excitation energy took place exclusively via the low energy cyclohexadienyl unit. We have, therefore, prepared two C-2 extension[7] products of 2: the tetraene ester and nitrile, 3 & 4. Upon irradiation of 3 in the presence of a lower energy sensitizer (such as Rose Bengal), a new isomeric product was obtained. Its spectral data revealed that the desired 7-cis isomer was not obtained, instead they were consistent with those of the deconjugated compound 5.[8] Similarly, compound 4 yielded the related product 6. Formation of 5 and 6 can be rationalized by photoiso-merization to the 7-cis isomer which under the reaction condition underwent facile 1,7-sigmatropic hydrogen migration. Such a thermal rearrangement process, while common within the vitamin D series,[9] is rare among compounds in the vitamin A series: the only relevant examples were 1,7-shift processes of 7-cis-retinylideneacetate at ≥ 100°C[10] and 7,9-dicis-9-trifluoromethylretinal at room temperature.[11] Thus, it appears that the presence of one additional double bond in the ring is sufficient to change the polyene conformation of the 7-cis isomer to one that is more suitable for the sigmatropic process. Lowering the irradiation temperature to 0°C, while reducing efficiency of the photoreaction of 3, yielded a product mixture still containing primarily 5. Since at the C-20 stage, the 7-cis geometry is known to be stable,[4] (presumably due to the fact that a deconjugated 1,7-H migration product is not favored for a more extended polyene) we decided to follow a modified synthetic sequence in which the 3,4-double bond is introduced after assembling the C-20 skeleton in the hindered 7-cis geometry.



Standard C2-extension[7] of 3-hydroxy-β-ionone (7)[12] yielded the corresponding C-15 nitrile. Sensitized irradiation (Corning 3-70 filter, ≥ 400 nm) of an acetone solution of the trienenitrile in the presence of Rose Bengal as sensitizer resulted in selective formation (>90% conversion) of the corresponding 7-cis and 7,9-dicis isomers in approximate equal ratio.[13] Such an isomeric mixture was used for preparation of new 3-dehydoretinal isomers. Chain extension to the corresponding 3-hydroxyretinonitrile (8) was accomplished via DIBAH reduction and modified Wittig reaction with the C5-phosphonate with retention of the 7,8 and 9,10 geometry, i.e., giving mainly (> 80%) the 7-cis and 7,9-dicis isomers of 8 (7-cis and 7,9-dicis) together with small amounts of all-trans and other isomers with the 13-cis geometry.



a. C2-phosphonate, b. sensitized hv, c. DIBAH, d. C5 phosphonate, e. TsCl; KOH, 18-crown-6.

Because of the known thermal sensitivity of compounds with the 7-cis geometry to undergo 6e-electrocyclization at temperatures above 60°C,[14] conditions for the elimination reaction to 3-dehydroretinonitrile (9) isomers must be relatively mild. The two step sequence of tosylation and elimination with KOH and 18-crown-6 in methanol (12 h at room temperature) afforded the desired dehydroretinonitriles in 78% yield. No 1,7-H shift or other rearranged products were detected by ^{1}H-NMR. Subsequently, the nitrile mixture was converted to a mixture of 3-dehydroretinal (10) isomers by reaction with DIBAH. HPLC (10 mm x 25 cm Dynamax silica gel column, solvent 5% ether in hexane, flow rate 3 ml/m) retention times of the isomers paralleled those of the retinal isomers, namely the minor 13-cis isomers appearing first and closely overlapping (10-11 m), followed by the 7,9-dicis (20 m), 7-cis (24 m) and all-trans isomers (32 m). The ^{1}H-NMR spectrum of 7-cis 3-dehydroretinal was identical to that reported earlier,[4] and that of the new 7,9-dicis isomer is consistent with the expected stereochemistry: characteristic H,H coupling constants for the 7-cis,11-trans geometry, low field of H-8 for 9-cis and high field of H-12 and low field of 13-Me for 13-trans.[15]

Since preparation of other hindered isomers of retinal (including the highly twisted all-cis isomer) has been achieved via reaction sequences parallel to that described above,[2] we anticipate that the current method should be applicable to synthesis of all unknown isomers of vitamin A_2. Such an effort is underway in our laboratory. Also, to be investigated is the possible existence of porphyropsin isomers other than those from 9-cis[3] and 7-cis-10.[16]

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