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New Hindered Isomers of 3-Dehydroretinal (Vitamin A_2).†

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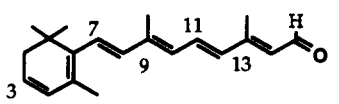
Abstract. The preparation of six new isomers (7-cis, 7,9-dicis, 7,11-dicis, 7,13-dicis, 7,9,11-tricis and 7,9,13-tricis) of 3-dehydroretinal (1, vitamin A_2), and their spectroscopic properties are reported. Because of the unexpected 1,7-H migration in photo-sensitized isomerization of the smaller building blocks in the dehydro-series, the introduction of the 7-cis geometry in the synthesis of new hindered isomers of 3-dehydroretinal required construction of this cis-double bond prior to that of the 3,4-double bond. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The method of selective triplet sensitization provided a ready entry to the hindered 7-cis geometry in lower homologs of vitamin A,[1] which eventually led to the synthesis of all 16 possible stereoisomers of retinal.[2] This photochemical procedure, however, was found not to be effective in isomerizing 3-dehydro-β-ionone (2).[3] Thus, for some time, only six isomers (all-trans, 13-cis, 11-cis, 9-cis, 11,13-dicis and 9,13-dicis) of vitamin A_2 were known,[4] which were used for identifying the chromophore in the naturally occurring visual pigment porphyropsin.[5] The only new isomer that has since appeared in the literature is the 7-cis, obtained through photoisomerization of the all-trans isomer in a polar solvent.[6] Only recently, in a preliminary report a new synthetic sequence was described, which led to the preparation of the 7-cis and 7,13-dicis isomers of 3-dehydroretinal (3-DHR, 1).[7] We now present a detailed account of this synthetic effort including the application of the procedure to preparation of other previously unknown isomers in the series.



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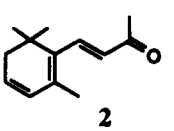

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† New isomers of Vitamin A 20. For previous paper in the series, see ref. 7.

EXPERIMENTAL

Methods. H NMR spectra were recorded on a 300 MHz spectrometer; UV-Vis spectra on a PE λ-19 spectrometer. Preparative photoisomerization was performed under deoxygenated conditions using a 200 W Hanovia medium pressure Hg lamp.

Material. 3-Hydroxy-β-ionone was prepared from β-ionone in three steps.[8] Allylic bromination of β-ionone (198 g) with NBS (214 g) followed by dehydrobromination with N,N-dimethylaniline gave 3-dehydro-β-ionone in 43% yield. Conversion of the ketone (48 g) to its ethylene ketal was accomplished by refluxing in a benzene solution with ethylene glycol (35 g), triethylorthoformate (78 g) and *p*-toluenesulfonic acid (0.2 g) in 88% yield.[9] Hydroboration of the ketal (8.0 g) was best achieved by reaction with BBN (100 ml, 0.5 M in THF) under refluxing THF (40 ml) for 6h, followed by sequential addition of 10 ml of methanol, 10 ml of a 3 M solution of NaOH and 8 ml 30% hydrogen peroxide.[8] After standard workup, and flash chromatography, 3-hydroxy-β-ionone was obtained in 54% yield. Its H NMR spectrum showed that the reaction proceeded regiospecifically, i.e., undetectable amounts of the 4-hydroxy isomer.

3-Hydroxy-β-ionylideneacetonitrile, **3a** was prepared by C2 extension with the cyanophosphonate[4b,10] giving a mixture of all-trans and 9-cis **3a** in 77% yield. Conversion to the 7-cis isomers was accomplished by photosensitized irradiation of the triene mixture in deuterated acetone in the presence of a catalytic amount of Rose Bengal with >350 nm light (Corning O-52 filter). The 7-cis and 7,9-dicis isomers of **3a** were isolated after column chromatography on a silica gel column (40% ethyl acetate/hexane). Selected H NMR data ($CDCl_3$), 7-cis: δ 6.19 (d, J = 12.7, H-7), 6.09 (d, J = 12.4 Hz, H-8), 5.31 (s, H-10), 4.01 ppm (m, H-3). 7,9-Dicis: δ 6.66 (d, J = 12.5, H-8), 6.29 (d, J = 12.5 Hz, H-7), 5.14 (s, H-10), 4.02 ppm (m, H-3).

3-Hydroxy-β-ionylideneacetaldehyde, **3b.** DIBAL-H (11 ml 1.0 M hexane solution) reduction of the 7-cis 3-hydroxy-β-ionylideneacetonitrile (1.0 g) gave 7-cis-**5** in 60% yield. H NMR ($CDCl_3$): δ 10.07 (d, J = 8.1, H-11), 6.25 (d, J = 12.1, H-7), 6.16 (d, J = 12.1, H-8), 5.99 (d, J = 8.1 Hz, H-10), 4.01 ppm (m, H-3). 7,9-dicis-**3b** was prepared in a similar manner. H NMR ($CDCl_3$): δ 10.10 (d, J = 8.1, H-11), 6.95 (d, J = 12.7, H-8), 6.32 (d, J = 12.7, H-7), 5.82 (d, J = 8.1 Hz, H-10), 4.01 ppm (m, H-3).

7-Cis-3-hydroxyretinonitrile, **4a.** NaH (0.3 g, 60% in mineral oil), after removal of the mineral oil, was suspended in 15 ml anhydrous THF at 0°C, then a 15 ml THF solution of C5 phosphonate (1.03 g, 5 mmol) was added. The mixture was warmed to rt. The supernatant was transferred to a dried round bottom flask and cooled to -78°C to which 7-cis-**3b** (0.56 g, 2.5 mmol) in 15 ml THF was added. After stirring at -78°C for 1h, the reaction mixture was warmed to rt and stirred for an additional hour. The reaction was quenched with saturated NH_4Cl solution. After extraction with ether, the organic layer was combined and dried over $MgSO_4$. Upon evaporation of solvent, the residue was separated by column chromatography on silica gel (40% ethyl acetate/hexane). Two fractions of product were obtained: 7,13-dicis-**4a** (30 mg) and 7-cis-**4a** (575 mg), yield = 85%. H NMR (CD_3CN), 7-cis: 6.86 (dd, $J_{10,11}$ = 11.5, $J_{11,12}$ = 15.0, H-11), 6.54 (d, $J_{11,12}$ = 15.0, H-12), 6.18 (d, $J_{10,11}$ = 11.5, H-10), 6.13 (d, $J_{7,8}$ = 12.6, H-8), 5.92 (d, $J_{7,8}$ = 12.6 Hz, H-7), 5.18 (1H, s, H-14), 4.02 ppm (m, H-3). 7,13-Dicis: 6.78 (d, $J_{11,12}$ = 15.0, H-12), 6.90 (dd, $J_{10,11}$ = 11.0, $J_{11,12}$ = 15.2, H-11), 6.29 (d, $J_{10,11}$ = 11.0, H-10), 6.18 (d, $J_{7,8}$ = 12.6, H-8), 5.92 (d, J = 12.6 Hz, H-7), 5.10 (s, H-14), 4.02 ppm (m, H-3).

7,9-Dicis 3-hydroxyretinonitrile, **4a** (with a small amount of the 7,9,13-tricis isomer) was prepared by a procedure similar to that of 7-cis-**4a** in 91% yield. H NMR (CD_3CN), 7,9-dicis: δ 6.96 (dd, $J_{10,11}$ = 11.3, $J_{11,12}$ = 15.1, H-11), 6.60 (d, $J_{7,8}$ = 12.5, H-8), 6.21 (d, $J_{11,12}$ = 15.2, H-12), 6.06 (d, $J_{7,8}$ = 12.4, H-7), 5.98 (d, $J_{10,11}$ = 11.5 Hz, H-10), 5.19 (s, H-14), 4.00 ppm (m, H-3). 7,9,13-Tricis: δ 6.96 (dd, $J_{10,11}$ = 11.3, $J_{11,12}$ = 15.1, H-11), 6.72 (d, $J_{11,12}$ = 15.1, H-12), 6.62 (d, $J_{7,8}$ = 12.5, H-8), 6.08 (d, J = 12.4, H-7), 5.98 (d, $J_{10,11}$ = 11.5 Hz, H-10), 5.10 (s, H-14), 4.00 ppm (m, H-3).

7,11-Dicis 3-hydroxyretinonitrile, **4a**. A solution of the fluorinated C5 phosphonate (533 mg), 18-crown-6 (1.2 g, purified by recrystallization in CH_3CN) in 30 ml of anhydrous THF was cooled to -78°C under argon and treated with 3.3 ml $KN(TMS)_2$ (0.5 M in toluene).[2] 7-Cis-**3b** (191.2 mg, 0.82 mmol) in 10 ml anhydrous THF was then added and the resulting mixture was stirred for 1h at -78°C and 30 min at rt. The reaction was quenched with saturated NH_4Cl solution, and the mixture extracted with ether. The ether extracts were dried over $MgSO_4$ and solvent evaporated. The residue was purified on a silica gel column (40% ethyl acetate/hexanes). A mixture of four isomers (7-cis, 7,13-dicis, 7,11-dicis and minor 7,11,13-tricis) were obtained with 7,11-dicis being the major (>60%) isomer. H NMR (CD_3CN): δ 6.64 (t, $J_{10,11}$ = 12.4, $J_{11,12}$ = 12.8, H-11), 6.61 (d, $J_{10,11}$ = 12.4, H-10), 6.16 (d, $J_{7,8}$ = 12.5, H-8), 5.95 (d, $J_{11,12}$ = 12.0, H-12), 5.95 (d, J = 12.4 Hz, H-7), 5.34 (s, H-14), 3.90 (m, H-3), 2.21 (s, 13-CH_3), 1.87 (s, 9-CH_3), 1.51 (s, 5-CH_3), 1.06 ppm (ss, 1-CH_3, 1'-CH_3).

7,9,11-Tricis-**4a** was prepared following a procedure similar to that of 7,11-dicis-**4a**. After column chromatography (silica gel, 40% ethyl acetate/hexane), a mixture of four isomers (450 mg), 7,9-dicis, 7,9,13-tricis, 7,9,11-tricis (major, >60%) and possibly all-cis (unable to isolate) isomers were obtained. H NMR (CD_3CN), 7,9,11-tricis: δ 6.68 (t, $J_{10,11}$ = 11.4, $J_{11,12}$ = 11.5, H-11), 6.56 (d, $J_{7,8}$ = 12.6, H-8), 6.42 (d, $J_{10,11}$ = 11.8, H-10), 6.09 (d, $J_{7,8}$ = 12.6, H-7), 5.88 (d, $J_{11,12}$ = 11.8 Hz, H-12), 5.37 (s, H-14), 3.87 ppm (m, H-3).

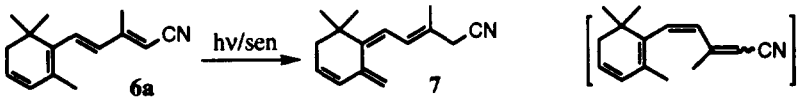
7-Cis and 7,13-dicis 3-dehydroretinonitrile, **5**. A mixture of 7-cis and 7,13-dicis-**4a** (51.6 mg), tosyl chloride (66 mg) and DMAP (64 mg) was stirred in 10 ml methylene chloride overnight. The mixture of 3-tosyl retinonitrile, **4b**, (70.1 mg), after purification by column chromatography (silica gel, 20% ethyl acetate in hexane), was reacted with an excess of KOH and 18-crown-6 in chilled methanol. After 24 h, the reaction mixture was worked up and the crude product purified by column chromatography on silica gel (20% ethyl acetate in hexane) giving an isomeric mixture of 3-dehydroretinonitrile, **5**, in 61% yield. A small amount was subjected to preparative hplc for small amounts for characterization data. H NMR ($CDCl_3$). 7-cis: δ 6.88 (dxd, $J_{10,11}$ = 11.6, $J_{11,12}$ = 15.2, H-11), 6.27 (d, $J_{11,12}$ = 15.2, H-12), 6.10 (d, $J_{10,11}$ = 11.6, H-10), 6.00 (d, $J_{7,8}$ = 13.2. H-7), 5.88 (d, $H_{7,8}$ = 5.88 Hz, H-8), 5.79 (bs, H-3, -4), 5.18 ppm (s, H-14). 7,13-dicis: 6.89 (dxd, $J_{10,11}$ = 11.9, $J_{11,12}$ = 15.1, H-11), 6.78 (d, $J_{11,12}$ = 15.1, H-11), 6.28 (d, $H_{10,11}$ = 11.9), 6.20 (d, $J_{7,8}$ = 12.2, H-8), 5.94 (d, $J_{7,8}$ = 12.2 Hz), 5.78 (s, H-3, -4), 5.08 ppm (s, H-14). HRMS for 7-cis: calcd. for $C_{20}H_{25}N$ = 279.1981, found 279.1982.

7-Cis and 7,13-dicis 3-dehydroretinal, **1**. Conversion of the isomeric mixture of the nitrile **5** to 7-cis and 7,13-dicis-**1** was accomplished in the same manner as for **3b**. The two isomers were isolated by preparative HPLC (2% ether in hexane, 10 mm 5μ DYNAMAX silica gel column). 7,9-Dicis-, 7,11-dicis-, 7,9,11-tricis- and 7,9,13-tricis-**1** were prepared following similar sequences of reactions with the appropriate 3-hydroxyretinonitrile. The order of elution of six isomers of **1** on the HPLC column was: 7,9,13-tricis, 7,13-dicis, 13-cis, 7,9-dicis, 7-cis and

all-trans. H NMR and UV-Vis data of these new isomers are listed in Table 1 below. HRMS for 7-cis: calcd. for $C_{20}H_{26}O$ = 282.1977, found 282.1991.

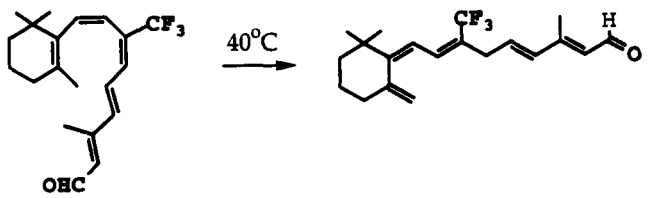
RESULTS AND DISCUSSION

The photochemical entry to the 7-cis geometry in the dehydro-series. Triplet sensitized irradiation (>350 nm) of 3-dehydro-β-ionylideneacetonitrile (**6a**) or the corresponding ethyl tetraene ester (**6b**) was attempted with a low energy sensitizer (Rose Bengal, E_T = 39.4 kcal/mole[11] or zinc porphine, 40.6 kcal/mole)[12] as well as a conventional sensitizer used for the trienes in the vitamin A series (benzanthrone, 46 kcal/mole).[13] In no cases were any new isomers containing the hindered 7-cis geometry detected. Instead prolonged irradiation led primarily to a blue-shifted product (deconjugated) which was isolated by preparative HPLC. The presence of a two-H signal at 5.11 and 5.22 ppm and the disappearance of the 5-methyl signal clearly suggested the possibility of a sigmatropic hydrogen migration product, known to take place in the vitamin A series.[14] However, retention of H7 and H8 (6.41 and 6.02 ppm, J = 10.8 Hz) showed that the product is consistent with a 1,7-H shift product, **7**.



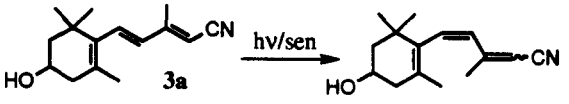
6a **7**

The fact that the rare 1,7-H migration, rather than the more commonly observed 1,5-hydrogen migration in direct irradiation of compounds in the vitamin A series,[14] has taken place suggests that the product derived from a secondary thermal process in a manner similar to that observed for rearrangement of 7,9-dicis 9-CF_3-retinal.[15] A



further circumstantial evidence for the thermal rearrangement was the observation that formation of the 1,7-shift product was temperature dependent: efficiency of product formation reduced by more than 5-fold upon lowering the irradiation temperature from rt to 0°C. Therefore, we conclude that its formation likely proceeded by way of an inefficient isomerization to the 7-cis isomer followed by a thermal 1,7-H shift reaction. This unexpected secondary process clearly precluded selective photosensitization as a suitable entry to the hindered 7-cis geometry of the missing isomers of 3-DHR.

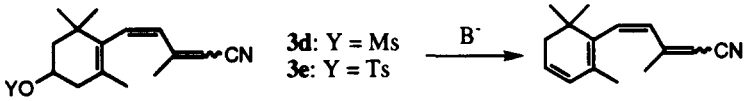
On the other hand, sensitized irradiation of 3-hydroxy-C15-nitrile (**3a**), prepared by C2-extension of 3-hydroxy-β-ionone, was found to proceed in the same manner as the C15-nitrile,[13] yielding primarily equal amounts of the 7-cis and 7,9-dicis isomers with a small residual amount of the all-trans and 9-cis isomers (~5%) in the photostationary mixture. The difference in the photochemical behavior of **3a** and **6a** is likely the combined consequence of the different shape of the excited torsional potential curves between a triene and longer polyenes (lower



versus higher in energy for the respective perpendicular species)[16] and the difference in the polyene conformation of a hindered dehydro derivative from the parent vitamin A counter part.

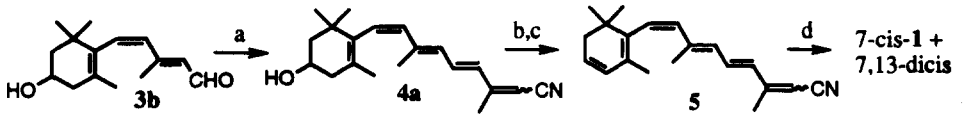
7-Cis, 7,9-dicis, 7,13-dicis and 7,9,13-tricis isomers of 3-DHR. The following synthetic sequence for the synthesis of four new hindered isomers of 3-DHR was designed in view of the photochemical observations mentioned above. By necessity, the hindered 7-cis geometry was introduced prior to the construction of the extra 3,4 double bond of the A_2 series. The 7-cis and the 7,9-dicis isomers of 3-hydroxy-β-ionylideneacetonitrile (**3a**) were separable by silica gel chromatography. For further elaboration to C20 compounds, 7-cis-**3a** was converted to the corresponding 3-hydroxy-C15-aldehyde (**3b**) by reaction with DIBAL-H. Upon C5 extension, a two-isomer mixture of 7-cis- and 7,13-dicis (19 : 1)[17] 3-hydroxyretinonitrile (**4a**) was obtained, which were readily separated by column chromatography.

The next step of introduction of the 3,4-double bond had to be accomplished under conditions with complete retention of polyene configuration as well as preservation of the thermally sensitive 7-cis geometry (either 1,5-H shift or 6e electrocyclization at temperatures above 50°C).[14] We first assessed mild E2 elimination



conditions with the model C15-nitrile (7-cis-**3a**). It was found that DBU induced elimination[18] of mesylate **3d**, proceeded at a moderate rate at 55°C, led to a substantial amount of the trans isomer. The best condition that we have found is KOH induced elimination of tosylate **3e** at rt in the presence of 18-crown-6. However, a mixture of elimination products was obtained, confirming possible rearrangement under photoisomerization (see above).

Thereafter, 7-cis and 7,13-dicis isomers of 3-hydroxyretinonitrile **4a** were converted to the corresponding tosylates **4b** which upon reaction with KOH and 18-crown-6 afforded quantitatively 3-dehydroretinonitrile (7-cis- and 7,13-dicis-**5**). Lastly, partial reduction with DIBAL-H gave the target compounds 7-cis- and 7,13-dicis-3-DHR (7-cis-**1**).



a. $(RO)_2POCH_2(CH_3)C{=}CHCN$, NaH; b. TsCl; c. NaOH, 18-crown-6; d. DIBAL-H, H^+/H_2O.

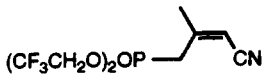
By way of similar reaction sequences, 7,9-dicis and 7,9,13-tricis isomers of 3-DHR were prepared. All isomers and their precursors were characterized by H NMR and UV-Vis spectral data (Table 1).

Table 1. Partial H NMR data[a] and UV-Vis absorption maxima[b] of isomers of 3-DHR.

Isomer	CH_3-5	H-7	H-8	H-10	H-11	H-12	$J_{7,8}$	$J_{11,12}$	λ_{max}[c]
7-cis	1.59	5.95	6.18	6.27	7.06	6.34	12.3	15.0	365 (359)
7,9-dicis	1.56	6.05	6.62	6.08	7.15	6.28	12.2	15.2	354 (351)
7,11-dicis	1.56	5.97	6.17	6.00	6.71	6.62	12.3	12.3	361 (355)
7,13-dicis	1.57	5.98	6.23	6.34	7.04	7.37	12.6	15.0	356 (357)
7,9,11-tricis	1.53	6.12	6.54	5.94	6.67	6.43	12.5	12.2	348 (345)
7,9,13-tricis	1.54	6.10	6.71	6.14	7.11	7.31	12.6	11.3	348 (346)
all-trans	1.86	6.34	6.30	6.22	7.12	6.37	15.9	15.1	385 (368)
9-cis	1.93	6.34	6.82	6.12	7.23	6.32	15.9	15.0	380 (363)
11-cis	1.87	6.35	6.28	5.94	6.70	6.57	16.0	12.2	377 (365)
13-cis	1.89	6.34	6.34	6.27	7.05	6.36		15.0	380 (363)
9,13-dicis	1.60?	6.35	6.80	6.15	7.12	7.25	15.9	15.1	375 (359)

a. In $CDCl_3$. Chemical shifts in ppm, coupling constants in Hz. b. In hexane; in nm. c. Retinal isomers in parenthesis (R. S. H. Liu in Handbook of Org. Photochem. & Photobiol., eds. Horspool & Song, CRC, 1995, p. 165).

Doubly hindered 7,11-dicis isomers. Introduction of the 11-cis geometry to the 7-cis isomers of 3-DHR was accomplished using the Still modified[19] C5 phosphonate reagent (**8**) with the C15-aldehyde, an analogous sequence previously applied to the synthesis of doubly hindered isomers of retinal.[2]



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The two-isomer photo-mixture of 3-hydroxy-C15-nitrile (**3a**) was first converted to a mixture of the C15 aldehyde (**3b**). Upon reaction of 7-cis-**3b** with the modified C5 phosphonate **8**, a mixture of 3-hydroxy-retinonitrile (**4a**) was obtained (>60% with the 11-cis geometry). The major isomer, the doubly hindered 7,11-dicis isomer, was isolated by column chromatography. Thereafter sequential tosylation, E2-elimination and partial

reduction gave 7,11-dicis-3-DHR. Under the reaction conditions, any 7,11,13-tricis 3-DHR would be expected to undergo consecutive 6e-electrocyclization to give the 7,13-dicis isomer.[2] Following a parallel sequence of reactions but starting with 7,9-dicis-**5**, 7,9,11-tricis-3-DHR (**1**) was prepared. The polyene geometry of these two new isomers was readily recognizable after comparison of their H NMR spectra with those of retinal isomers.[13]

Properties of the new hindered isomers of 3-DHR. The additional double bond in the ring in the A_2 series seems to have increased the ring-chain twist in those isomers containing the hindered 7-cis geometry. Thus, data in Table 1 show that those 3-DHR isomers containing the 7-cis geometry exhibit a much smaller red shift from the corresponding 7-cis isomer of the vitamin A series (6 nm for both the 7-cis and 7,11-dicis isomers) than the same shift for the 7-trans isomers (17 and 12 nm for respectively all-trans and 11-cis isomers). On the other hand, the barrier for interconversion of the diastereotopic methyl groups (1,1-dimethyl groups) as revealed in a dNMR study of 7-cis-3-DHR ($\Delta G^{\dagger}$ = 13.7 kcal/mole) is of the same magnitude as 7-cis-retinal (14.0 kcal/mole)[20] and 7-cis-3-dehydro-β-ionone (11.7 kcal/mole).[21] The lower coalescence temperature (250 K) for 7-cis-**1** is primarily due to the smaller chemical shift difference between the two diastereotopic methyls (δΔ 5.6 Hz vrs 9.95 Hz for 7-cis retinal[20]).

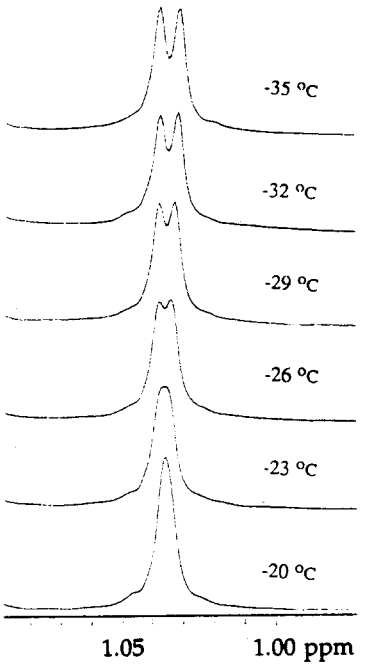

Figure 1. Temperature dependent H NMR signals (500 MHz) of the 1,1'-dimethyl groups of 7-cis-**1**, in $CDCl_3$, recorded between -35 and -20°C. The coalescence temperature was at -23°C.

Many of these isomers were found to form new isomeric visual pigment analogs (isomeric porphyropsins) when combined with bovine opsin in addition to those in the literature.[22] These new pigments have been reported separately.[23]

In conclusion, the method described above has provided a ready entry to many of the previously unknown hindered 7-cis isomers of vitamin A_2. Such isomers of 3-DHR are now equally available as those of retinal.

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