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Synthesis of (+)-(4*S*)- and (-)-(4*R*)-11*Z*-4-Hydroxyretinals and Determination of the Absolute Stereochemistry of a Visual Pigment Chromophore in the Bioluminescent Squid, *Watasenia scintillans*

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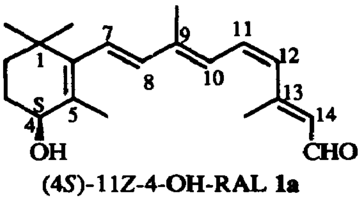
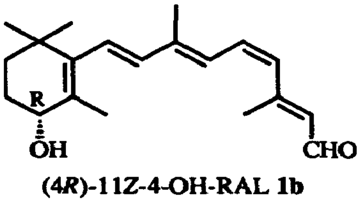
Key Words: (4S)- and (4R)-11Z-4-hydroxyretinal; visual pigment; absolute configuration; circular dichroism (CD); exciton chirality method

***Abstract:** Synthesis of (+)-(4S)- and (-)-(4R)-11Z-4-hydroxyretinals (4-OH-RALs) **1a** and **1b** was accomplished from (4S)- and (4R)-4-hydroxy-β-ionones, respectively, to determine the absolute configuration of a visual pigment chromophore in Watasenia scintillans. The CD spectra of the native chromophore and its anti-oxime agreed with those of synthetic (4R)-compounds. The CD exciton chirality method as applied to the p-dimethylaminocinnamate of (4R)-4-OH-RAL also establishes the absolute configuration of the native chromophore as **1b**.*

The bioluminescent squid, *Watasenia scintillans* has three visual pigments,[1] whose chromophores were isolated by Kito et al.[2] The major pigment based on retinal (λ_{max}=484 nm) is distributed over the whole retina, while the second pigment based on 3-dehydroretinal (λ_{max}≈500 nm), and the third pigment (λ_{max}≈470 nm) are localized in a specific area of the ventral retina. This fact indicates that the squid may discriminate different wavelength lights. A new retinal analog, 11Z-4-OH-RAL was identified as the chromophore of the third visual pigment of the squid.[2] Both the chromophore, 11Z-4-OH-RAL[3] of the third pigment and its *anti*-oxime[2] show negative Cotton effects in their CD spectra; however, the absolute configuration at C-4 remained to be determined.

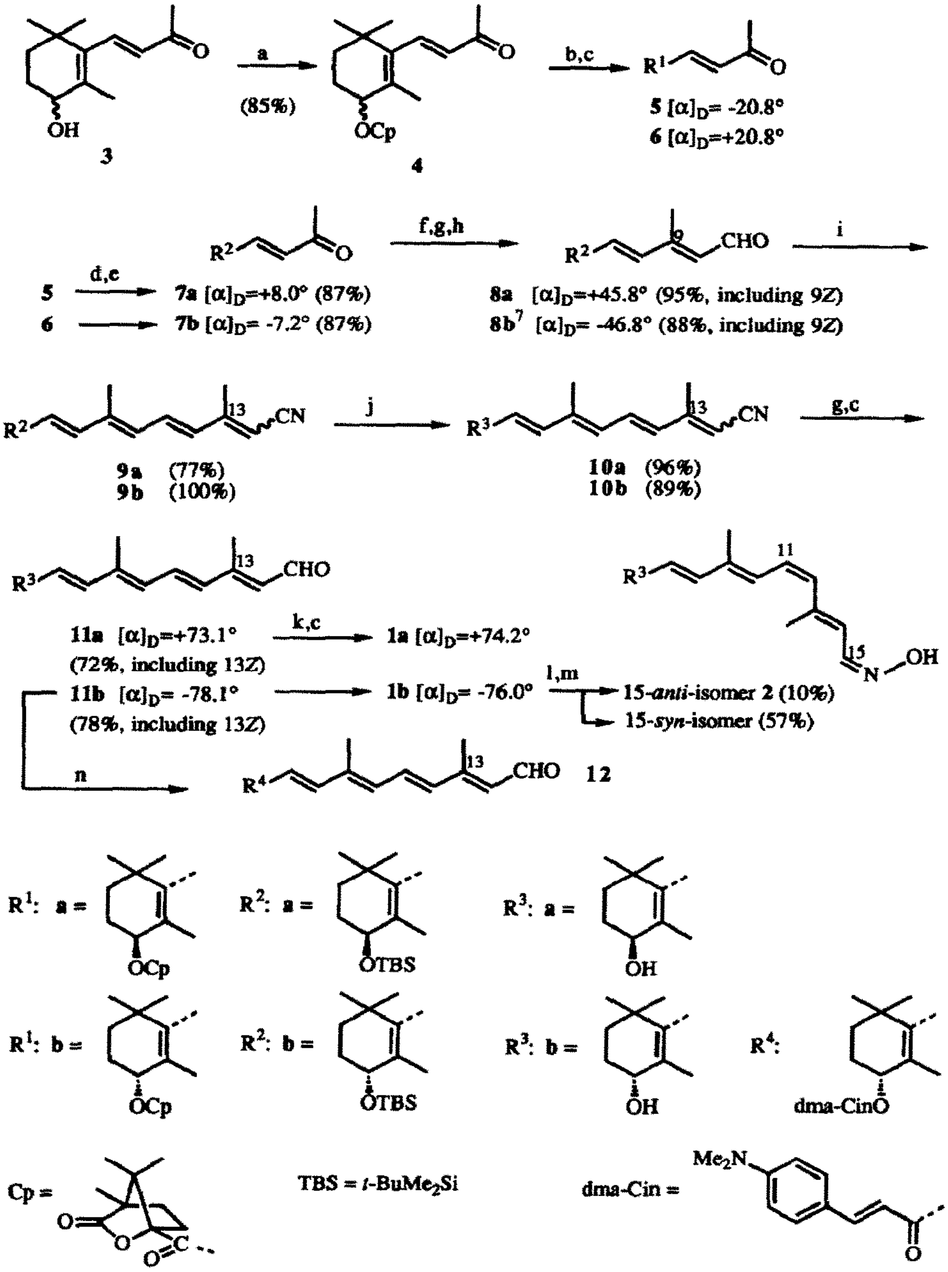


(4*S*)-11Z-4-OH-RAL **1a**



(4*R*)-11Z-4-OH-RAL **1b**

Here we report the synthesis of (4*S*)- and (4*R*)-11Z-4-OH-RALs, **1a** and **1b**, and determination of the absolute configuration at C-4 in the native chromophore. Similarly the chirality of the *anti*-oxime extracted from *Watasenia scintillans* by the oxime method[4] was also determined by use of synthetic *anti* 11Z-4-OH-RAL oxime **2**.



a) (1*S*)-(-)-camphanic acid chloride / pyridine, r.t., b) recrystallization, c) pHPLC, d) KOH / MeOH, r.t., e) TBSCl, Et_3N, 4-dimethylaminopyridine / CH_2Cl_2, r.t., f) NaH, $(i\text{-}PrO)_2P(O)CH_2CN$ / THF, r.t., g) DIBAH / *n*-hexane or Et_2O, -60°C~-40°C, then SiO_2-H_2O, h) SiO_2-low pressure column chromatography, i) NaH, $(EtO)_2P(O)CH_2C(CH_3){:}CHCN$ / THF, r.t., j) $(n\text{-}Bu)_4NF$ / THF, 0°C~r.t., k) hν / MeOH, 0°C, l) NH_2OH, $NaHCO_3$ / MeOH, r.t., m) flash chromatography, n) *p*-dimethylaminocinnamoyl triazole, DBU /CH_2Cl_2, r.t.

Scheme

Optically active 4-OH-RALs were prepared as shown in the Scheme. (4*S*)-Camphanate **5** and (4*R*)-one **6** were derived from racemic 4-hydroxy-β-ionone **3** according to the Haag's procedure.[5] All spectral data including their chiroptical properties of **5** and **6** were in fair agreement with those in the literature,[5] leading to the identification of the chirality for C-4 of **5** and **6**.

After hydrolysis of the camphanate group in **5**, the resulting hydroxyl group was protected by TBS (*tert*-butyldimethylsilyl) group. Condensation of **7a** with diisopropyl cyanomethylphosphonate using NaH and succesive DIBAH (diisobutylaluminum hydride) reduction of the resulting nitrile group gave aldehyde **8a** and its 9Z-isomer. The Emmons-Horner reaction of **8a** with C_5-phosphonate was carried out in the presence of NaH to provide nitrile **9a** as a mixture of 13Z- and all-*E* isomers in a ratio of 1:5. After deprotection of the silyl group in **9a**, the 4-hydroxyretinonitrile **10a** was converted to 4-OH-RAL as a mixture of 13Z- and all-*E*-isomers **11a** in a ratio of 1:2, which were isolated in pure form, respectively, by preparative HPLC in the dark.

The isomer **11b** was also prepared from **6** according to the same route as that for **11a**. The *p*-dimethylaminocinnamate **12** derived from **11b** employing the established method[6] showed typical exciton split CD Cotton effects (Fig. 1). Negative first and positive second Cotton effects should be expected since the α-*p*-dimethylaminocinnnamoyl group and the pentaenal chromophore constitute a counter-clockwise screw, thus confirming the absolute configuration of (4*R*)-4-OH-RAL **1b**.

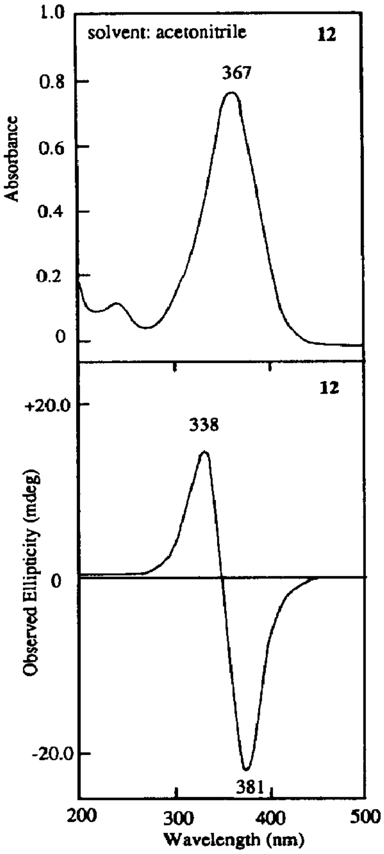


Fig. 1

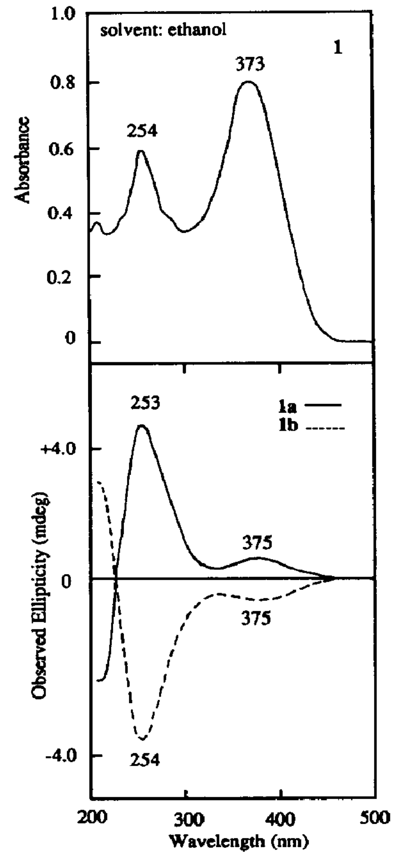


Fig. 2

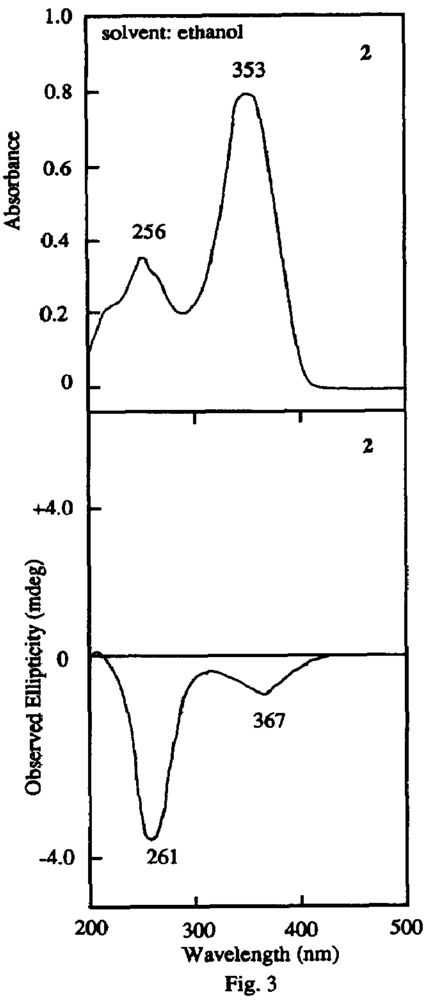


Fig. 3

The (4*S*)-11*Z*-isomer **1a** was obtained from the photoisomerization[8] mixture of **11a** which included 11Z,13Z-, 13Z-, all-*E*-, 11Z- and 9Z-isomers; (4*R*)-11Z-4-OH-RAL **1b** was prepared similarly. All isolated isomers were characterized by ^{1}H-NMR data. These are the first synthesis of optically active 4-OH-RALs.

The UV/CD data (Fig. 2) of **1b** agreed with those of native chromophore[3] extracted from *Watasenia scintillans*. This establishes the C-4 chirality of the third visual pigment chromophore as being 4*R*. In addition, the negative CD spectrum (Fig. 3) of the *anti*-isomer of (4*R*)-11*Z*-4-OH-RAL oxime **2**, prepared from **1b**, agreed with that of *anti*-isomer of native 11Z-4-OH-RAL oxime[2] isolated from *Watasenia scintillans*. The data presented here establishes the absolute stereochemistry of native 11Z-4-OH-RAL as 4*R* or **1b**.

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9. Satisfactory ^{1}H-NMR, UV-VIS, IR and MS spectral data of all compounds were obtained. Characteristic data for compounds **11b**, **1b**, **2** and **12** are as follows,
   11b: UV-VIS λ_{max} nm (EtOH): 377; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.01 and 1.04 (each 3H, each s, gem-Me), 1.83 (3H, s, 5-Me), 2.01 (3H, s, 9-Me), 2.32 (3H, s, 13-Me), 4.00 (1H, m, 4-H), 5.97 (1H, d, *J* 8, 14-H), 6.16 (1H, d, *J* 16, 8-H), 6.19 (1H, d, *J* 11.5, 10-H), 6.29 (1H, d, *J* 16, 7-H), 6.38 (1H, d, *J* 15, 12-H), 7.12 (1H, dd, *J* 15, 11.5, 11-H) and 10.11 (1H, d, *J* 8, CHO); **1b**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.00 and 1.03 (each 3H, each s, gem-Me), 1.82 (3H, s, 5-Me), 1.97 (3H, s, 9-Me), 2.34 (3H, s, 13-Me), 4.00 (1H, m, 4-H), 5.95 (1H, d, *J* 11, 10-H), 6.07 (1H, d, *J* 8, 14-H), 6.14 (1H, d, *J* 16, 8-H), 6.28 (1H, d, *J* 16, 7-H), 6.53 (1H, d, *J* 12, 12-H), 6.67 (1H, t-like, *J* 12, 11-H) and 10.08 (1H, d, *J* 8, CHO); **2**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.00 and 1.03 (each 3H, each s, gem-Me), 1.82 (3H, s, 5-Me), 1.94 (3H, s, 9-Me), 2.09 (3H, s, 13-Me), 4.00 (1H, t-like, *J* 4.5, 4-H), 5.99 (1H, d, *J* 11, 10-H), 6.13 (1H, d, *J* 16, 8-H), 6.21 (1H, d, *J* 16, 7-H), 6.50 (1H, t, *J* 11, 11-H), 6.62 (1H, d, *J* 11, 12-H), 6.74 (1H, d, *J* 9.5, 14-H), and 7.47 (1H, d, *J* 9.5, 15-H); **12**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.04 and 1.09 (each 3H, each s, gem-Me), 1.73 (3H, s, 5-Me), 2.03 (3H, s, 9-Me), 2.32 (3H, d, *J* 1, 13-Me), 3.01 (6H, s, NMe_2), 5.37 (1H, t, *J* 4.5, 4-H), 5.97 (1H, br d, *J* 8, 14-H), 6.21 (1H, d, *J* 11.5, 10-H), 6.22 (1H, d, *J* 16.5, 8-H), 6.25 (1H, d, *J* 16, ArCH=C$\underline{H}$-), 6.31 (1H, br d, *J* 16.5, 7-H), 6.38 (1H, d, *J* 15, 12-H), 6.66 (2H, d-like, *J* 9, Ar-H×2), 7.12 (1H, dd, *J* 15, 11.5, 11-H), 7.42 (2H, d-like, *J* 9, Ar-H×2), 7.63 (1H, d, *J* 16, ArC$\underline{H}$=CH-) and 10.10 (1H, d, *J* 8, CHO).

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