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STEREOSELECTIVE SYNTHESIS OF 11Z-9-DEMETHYL-9-BENZYL- AND 9-PHENYL-RETINALS AND THEIR INTERACTION WITH BOVINE OPSIN

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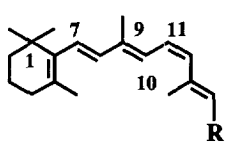
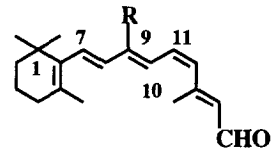
Abstract: 11Z-9-Demethyl-9-benzyl- and 9-phenyl-retinals were synthesized stereoselectively from the β-ionone analog-tricarbonyliron complexes and their interaction with bovine opsin was investigated.

Rhodopsin (Rh) **1** is the visual pigment which contains 11Z-retinal **2** as a chromophore bound to the ε–amino group of the apoprotein lysine residue through a protonated Schiff base (PSB).[1] The visual transduction process is initiated by isomerization of the 11Z-retinal chromophore in rhodopsin to all-*E*-isomer accompanying with the conformational change of apoprotein.[2] Recently, it was suggested that an interaction between the 9-methyl group of retinal and the amino acid residues of apoprotein played an important role for exhibiting the biological function.[3] In order to clarify the effect of 9-substituents in rhodopsin chromophore, we wish to describe here the stereoselective synthesis of 11Z-9-demethyl-9-benzyl- and 9-phenyl-retinals **3a, b** and their interaction with bovine opsin.



1: R=CH=N$^+$H-opsin
2: R=CHO



3a: R=CH_2Ph
b: R=Ph

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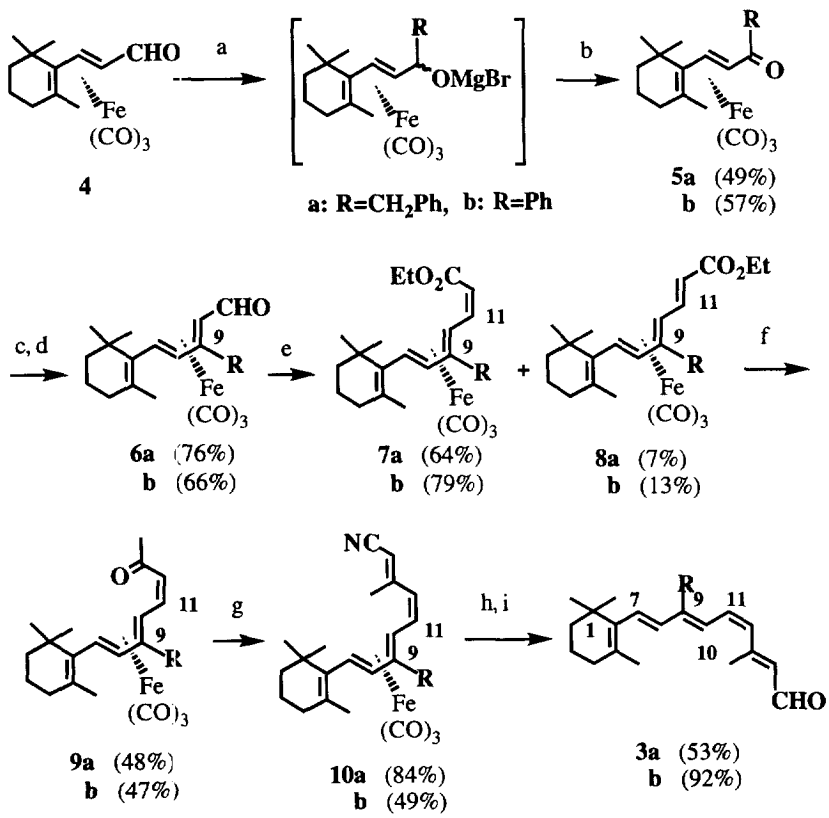
In connection with our study on the stereoselective synthesis of retinoids and carotenoids,[4, 5] we developed the stereoselective synthesis of 11*Z*-retinal by use of tricarbonyliron complex.[5] We applied this methodology to the synthesis of 11*Z*-retinal analogs. The β-ionone analogs-tricarbonyliron complexes **5a**, **b**,[6, 7] the key intermediates for the synthesis of **3**, were obtained from dienylaldehyde-tricarbonyliron complex **4** by Grignard reaction followed by oxidation using diazocarbonyldipiperidine without decomplexation. Treatment of **5** with lithium salt of acetonitrile[8] followed by DIBAL reduction gave the β-ionylideneacetaldehyde-tricarbonyliron complexes **6a**, **b**[6, 9] in excellent yields. The Peterson reaction of **6** with lithium enolate of ethyl trimethylsilylacetate in THF at -70℃ afforded the 11*Z*-isomers **7a**, **b**[6, 9] predominantly accompanied by 11*E*-isomers **8a**, **b**.[6, 9] The geometry of the newly produced double bond at the 11 position in **7a** and **7b** was determined



Reagents: a) $PhCH_2MgBr$ or PhMgBr / THF, 0°C; b) azodicarbonyldipiperidine / THF, 0°C; c) LDA, CH_3CN / THF, -50°C; d) DIBAL / CH_2Cl_2, 0°C; e) LDA, $TMSCH_2CO_2Et$ / THF, -70°C; f) Ph_3SnCH_2I, *n*-BuLi / Et_2O, 0°C; g) $(i\text{-PrO})_2P(O)CH_2CN$, NaH / THF, r.t.; h) $CuCl_2$ / EtOH, r.t.; i) DIBAL / toluene, 0°C

from the coupling constant in their NMR spectra. The 11Z-esters **7** were transformed to the C18-ketone-tricarbonyliron complexes **9**[6, 9] using triphenylstannylmethyllithium[10] in moderate yields. The Emmons-Horner reaction of **9** with diisopropyl cyanomethylphosphonate gave the nitriles **10**[6, 11] as a sole product, which were converted to the 11Z-retinals **3**[6, 11] by the sequence of decomplexation and DIBAL reduction. The stereochemistry of an 11 position of **3** was unchanged during these transformations.

Binding experiments of **3** with bovine opsin, isolated according to a previously reported method,[12] were carried out in a 3-[(3-cholamidopropyl)dimethylammonio]propane-1-sulfonate – phosphatidylcholin (CHAPS-PC) mixture. The benzyl analog afford the new artificial pigment, on the contrary, the phenyl analog did not bind with the apoprotein, and these data was summarized in the Table. These results suggests that the methylene group on 9 position in retinal is very important to bind with apoproptein.

Table. Absorption Maxima and Opsin Shifts of Rhodopsin and its Analogs.

Chromo-phores	Aldehydes[a] λ max / nm	PSB[a] λ max / nm	Pigments[b] λ max / nm	Opsin Shifts Δν / cm^{-1}
Retinal **2**	376.5	440	498	2650
Benzyl-retinal **3a**	372	440	472	1540
Phenyl-retinal **3b**	379	444	–	–

a) In methanol. b) In CHAPS-PC mixture.

In summary, we showed that the new method for the stereoselective Z-olefin synthesis using the Peterson reaction of tricarbonyliron complex is a powerful tool for the stereoselective synthesis of 11Z-9-substituted retinal analogs **3**. In order to elucidate the steric cavity around the 9-methyl group in retinal, the synthesis of various 9-substituted analogs are in progress and the results will be published in near future.

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6. Satisfactory ^{1}H-NMR, IR and MS spectral data were obtained.
7. ^{1}H-NMR data for compounds **5a** and **5b** are as follows;
For **5a** : (300 MHz, $CDCl_3$) δ 1.04 (3H, s, 1- Me), 1.40 (3H, s, 1-Me), 1.42 (3H, s, 1-Me), 1.45 -1.70 (4H, m, 2,3-H_2), 1.80-1.92 (2H, m, 4-H_2), 2.34 (1H, d, *J*=8.5, 8-H), 3.67 (2H, s, CH_2), 5.64 (1H, d, *J*=8.5, 7-H), 7.24-7.36 (5H, m, Ph); For **5b** : (300 MHz, $CDCl_3$) δ 1.36 (3H, s, 1-Me), 1.48 (3H, s, 1-Me), 1.50 (3H, s, 1-Me), 1.52 -1.70 (4H, m, 2,3-H_2), 1.94-2.20 (2H, m, 4-H_2), 3.10 (1H, d, *J*=8, 8-H), 5.96 (1H, d, *J*=8, 7-H), 7.46 (2H, t, *J*=7, Ar-H), 7.56 (1H, t, *J*=7, Ar-H), 7.95 (2H, d, *J*=7, Ar-H)
8. In the reaction of **4** with lithium salt of acetonitrile, addition, dehydration and migration of tricarbonyliron complex occuried; see, reference 4.
9. ^{1}H-NMR data for compounds **6a**, **7a**, **8a** and **9a** are as follows:
For **6a** : (300 MHz, $CDCl_3$) δ 1.05 (3H, s, 1- Me), 1.14 (1H, d, *J*=6, 10-H), 1.21 (3H, s, 1-Me), 1.36 -1.60 (4H, m, 2,3-H_2), 1.78 (3H, s, 5-Me), 1.90-2.05 (2H, m, 4-H_2), 2.52 (1H, d, *J*=11, 7-H), 4.00 (1H, d, *J*=15, CH_2), 4.35(1H, d, *J*=15, CH_2), 5.66 (1H, d, *J*=11, 8-H), 7.20-7.45 (5H, m, Ph), 9.61 (1H, d, *J*=6, CHO); For **7a** : (300 MHz, $CDCl_3$) δ 1.07 (3H, s, 1- Me), 1.22 (3H, s, 1- Me), 1.29 (3H, t, *J*=7, $CH_2\underline{CH_3}$), 1.35-1.60 (4H, m, 2,3-H_2), 1.82 (3H, s, 5-Me), 1.96-2.04 (2H, m, 4-H_2), 2.49 (1H, d, *J*=11, 10-H), 3.17 (1H, d, *J*=11.5, 7-H), 3.83 (1H, d, *J*=15, CH_2), 4.06 (1H, d, *J*=15, CH_2), 4.18 (2H, q, *J*=7, $\underline{CH_2}CH_3$), 5.57 (1H, d, *J*=11.5, 8-H), 5.68 (1H, d, *J*=11, 12-H), 6.55 (1H, t, *J*=11, 11-H), 7.21-7.40 (5H, m, Ph); For **8a** : (300 MHz, $CDCl_3$) δ 1.04 (3H, s, 1- Me), 1.19 (3H, s, 1- Me), 1.30 (3H, t, *J*=7, $CH_2\underline{CH_3}$), 1.36 -1.61 (4H, m, 2,3-H_2), 1.59 (1H, d, *J*=11, 10-H) ,1.90 (3H, s, 5-Me), 1.96-2.04 (2H, m, 4-H_2), 2.24 (1H, d, *J*=11, 7-H), 3.84 (1H, d, *J*=15, CH_2), 4.06 (1H, d, *J*=15, CH_2), 4.20 (2H, q, *J*=7, $\underline{CH_2}CH_3$), 5.58 (1H, d, *J*=11, 8-H), 5.98 (1H, d, *J*=15, 12-H), 7.25 (1H, dd, *J*=15, 11, 11-H), 7.25-7.37 (5H, m, Ph); For **9a** : (300 MHz, $CDCl_3$) δ 1.11 (3H, s, 1- Me), 1.25 (3H, s, 1- Me), 1.20-1.40 (4H, m, 2,3-H_2), 1.70-1.81 (2H, m, 4-H_2), 1.79 (6H, s, 5,13-Me), 2.73 (1H, d, *J*=11, 7-H) , 3.49 (1H, d, *J*=15, CH_2), 3.79 (1H, d, *J*=15, CH_2), 3.85 (1H, d, *J*=11, 10-H), 5.50 (1H, d, *J*=11, 8-H), 5.60 (1H, d, *J*=11, 12-H), 6.55 (1H, t, *J*=11, 11-H), 7.00-7.22 (5H, m, Ph).
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11. ^{1}H-NMR data for compounds **10a**, **3a** and **3b** are as follows,
For **10a** : (300 MHz, $CDCl_3$) δ 1.08 (3H, s, 1- Me), 1.23 (3H, s, 1-Me), 1.30-1.45 (4H, m, 2,3-H_2), 1.66 (3H, s, 5-Me), 1.70-1.80 (2H, m, 4-H_2), 1.87 (3H, s, 13-Me), 1.88 (1H, d, *J*=12, 10-H), 2.18 (1H, d, *J*=11, 7-H), 3.41 (1H, d, *J*=15, CH_2), 3.72 (1H, d, *J*=15, CH_2), 4.79 (1H, s, 14-H), 5.31 (1H, d, *J*=12, 12-H), 5.51 (1H, d, *J*=11, 8-H), 5.76 (1H, t, *J*=12, 11-H), 7.00-7.22 (5H, m, Ph); For **3a** : (300 MHz, $CDCl_3$) δ 0.90 (6H, s, 1-Me × 2), 1.20-1.55 (4H, m, 2,3-H_2), 1.62 (3H, s, 5-Me), 1.77 (3H, s, 13-Me), 1.80-1.90 (2H, m, 4-H_2), 3.67 (2H, s, CH_2), 5.58 (1H, d, *J*=12, 12-H), 6.12 (1H, d, *J*=8, 14-H), 6.18 (1H, d, *J*=16, 8-H), 6.35 (1H, d, *J*=16, 7-H), 6.39 (1H, t, *J*=12, 11-H), 6.78 (1H, d, *J*=12, 10-H), 7.00-7.20 (5H, m, Ph); 9.91 (1H, d, *J*=8, CHO); For **3b** : (300 MHz, $CDCl_3$) δ 0.96 (6H, s, 1-Me × 2), 1.32-1.56 (4H, m, 2,3-H_2), 1.68 (3H, s, 5-Me), 1.77 (3H, s, 13-Me), 1.84-1.91 (2H, m, 4-H_2), 5.41 (1H, d, *J*=12, 12-H), 6.11 (1H, d, *J*=16, 8-H), 6.13 (1H, d, *J*=8, 14-H), 6.19 (1H, t, *J*=12, 11-H), 6.45 (1H, d, *J*=16, 7-H), 6.82 (1H, d, *J*=12, 10-H), 7.11-7.22 (5H, m, Ph), 9.92 (1H, d, *J*=8, CHO).
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