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Synthesis of 8,18-Ethanoretinal and Its Interaction with Apo-Retinochrome

Akimori Wada,[a] Miho Sakai,[a] Tomoya Kinumi,[b] Kazuo Tsujimoto,[b] and Masayoshi Ito[a,*]

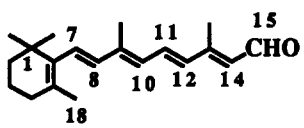
[a]Kobe Women's College of Pharmacy, 4-19-1, Motoyamakita-machi, Higashinada, Kobe 658, Japan

[b]Department of Applied Physics and Chemistry, The University of Electro-Communications, 1-5-1, Chofugaoka, Chofu, Tokyo 182, Japan

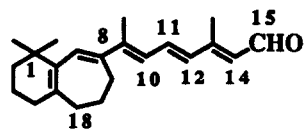
Key Words: 8,18-ethanoretinal; retinal analog; apo-retinochrome; retinochrome;opsin shift

Abstract: *All-(E)-8,18-ethanoretinal was synthesized from 2,2-dimethylcyclohexanone, and its binding experiment with apo-retinochrome afforded the new retinochrome analog, whose opsin shift exhibited fairly similar to that of the natural retinochrome.*

It is well known that a retinal molecule is a chromophore of protein pigments such as rhodopsin, bacteriorhodopsin, and retinochrome.[1] Recently, a number of reports have appeared on dealing with the synthesis of retinal analogs for bioorganic studies.[2] We also have synthesized some retinal analogs[3] to clarify the photobleaching process of rhodopsin.[4] At this time, in order to investigate the conformation aroud the cyclohexene ring in the retinochrome chromophore, we describe here the synthesis of all-(*E*)-8,18-ethanoretinal **2**, in which C8 and C18 positions in **1** are connected by an ethylene group, and its interaction with apo-retinochrome.



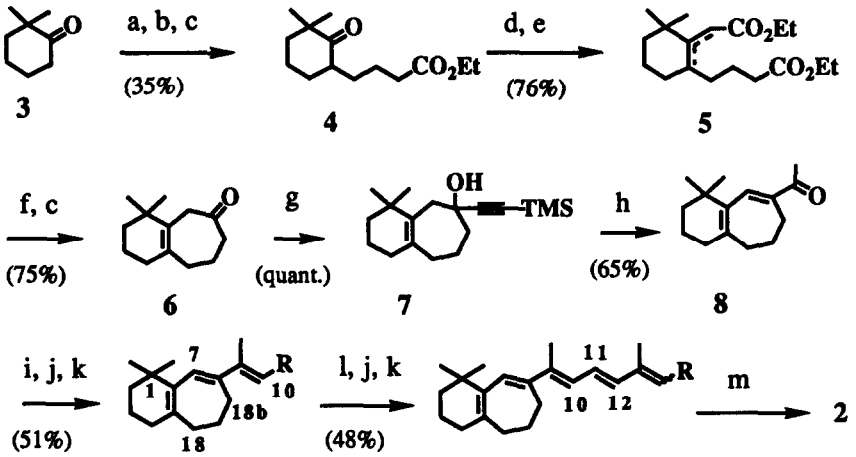
1 All-(*E*)-retinal



2 All-(*E*)-8,18-ethanoretinal

The introduction of ethoxycarbonylpropyl chain into the β-keto ester enolate derived from 2,2-dimethylcyclohexanone **3** followed by demethoxycarbonylation gave the keto ester **4**, which was treated with ethyl acetate in the presence of lithium diisopropylamide (LDA), followed by dehydration using thionyl

chloride to afford the diester **5** as an isomeric mixture of double bond [endo:exo=2.4:1 by gas chromatography]. Fortunately, a Dieckmann condensation of **5** by the high dilution method using potassium *t*-butoxide and subsequent deethoxycarbonylation employing magnesium chloride gave the bicyclic ketone **6**[5,6] as a single isomer. Trimethylsilylethynylation of **6** with trimethylsilylethynylcerium (III) reagent,[7] prepared from trimethysilylethynyllithium and cerium (III) chloride in THF, afforded the alcohol **7** in quantitatively. Treatment of the adduct **7** with formic acid[8] caused dehydration, desilylation, hydration and keto-enol isomerization at the same time to give the bicyclo ketone **8**,[5,9] which has the same chromophore as β-ionone. The condensation of **8** with triethyl phosphonoacetate using NaH provided the ester **9**.[5,9] The geometry of newly produced double bond was decided as (*E*) from the strong NOESY correlation between



a) NaH, $(MeO)_2CO$ / C_6H_6, reflux, b) NaH, $Br(CH_2)_3CO_2Et$ / 10% DMF-THF, reflux, c) $MgCl_2 \cdot 6H_2O$ / DMSO, 150°C, d) LDA, AcOEt / THF, -78°C, e) $SOCl_2$ / pyridine, 0°C, f) *t*-BuOK / xylene, reflux, g) TMS-≡-$CeCl_2$ / THF, -78°C, h) 85% HCO_2H, reflux, i) NaH, $(EtO)_2P(O)CH_2CO_2Et$ / 10% DMF-THF, reflux, j) $LiAlH_4$ / Et_2O, r.t., k) MnO_2 /CH_2Cl_2, r.t., l) *n*-BuLi, $(EtO)_2P(O)CH_2(CH_3)C{=}CHCO_2Me$ / THF, -78°-0°C, m) prep. HPLC

10-H and 18b-H in its NMR spectra. The conversion of **9** to the aldehyde **10** was achieved by $LiAlH_4$ reduction and subsequent MnO_2 oxidation. The Emmons-Horner reaction of **10** with C5-phosphonate was carried out using *n*-BuLi to give the ester **11**,[5,9] in which the geometry of the 11,12 double bond was determined as (*E*) from the coupling constant of 11-H signal in its NMR. It is noteworthy that although we used C5-phosphonate as a mixture of double bond [ca. 1:1] in the condensation, the ratio of all-(*E*) isomer in the products increased dramatically [all-(*E*):(13*Z*)=*ca.* 7:1]. This result indicated that the (13*Z*) isomer initially formed isomerized easily to the all-(*E*) isomer under the reaction conditions. The final transformation of **11** to the corresponding aldehyde **12** was established according to the usual method by $LiAlH_4$ reduction and MnO_2 oxidation and the all-(*E*) isomer **2**[5,9] was isolated in pure form by repeating the preparative HPLC in the dark. This strategy provides a flexible new route to the synthesis of bicyclic retinals.

Subsequently, the binding experiment of 2 with apo-retinochrome isolated from a squid eye according to the reported method previously[10] was carried out in a 2% digitonin solution to afford the new artificial retinochrome having the absorption maximum at 498 nm. The protonated Schiff base (PSB) of 2 with *n*-butylamine was formed by the usual method. The absorption maxima and opsin shifts of artificial pigment and natural retinochrome are shown in Table. All the values of the new retinochrome analog are very close to those of natural retinochrome. These results suggest that the conformations of both chromophores are almost same in the protein.

Table. Absorption Maxima and Opsin Shifts of Retinochromes.

Chromophores	Aldehydes[a] λ max / nm	PSB[a] λ max / nm	Retinochromes[b] λ max / nm	Opsin Shifts $\Delta\nu$ / cm^{-1}
All-(*E*)-8,18-ethanoretinal (2)	382	449	498	2200
All-(*E*)-retinal (1)	381	443	496	2400

a) in methanol. b) in ethanol.

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5. Satisfactory ^{1}H-NMR, IR, and MS spectral data were obtained.
6. ^{1}H-NMR data for compound **6** are as follows: (200 MHz, $CDCl_3$) δ 0.96 (6H, s), 1.4-1.6 (4H, m), 1.87 (2H, t, J = 6.5 Hz), 1.98 (2H, brt, J = 7 Hz), 2.1-2.3 (2H, m), 2.49 (2H, t, J = 7 Hz), 3.12 (2H, brs).
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9. ^{1}H-NMR data for compounds **8**, **9**, **11**, and **2** are as follows,
   For **8** : ^{1}H-NMR (200 MHz $CDCl_3$) δ 1.05 (3H, s), 1.4-1.8 (4H, m), 1.89 (2H, t, J = 6.5 Hz), 2.02 (2H, quin, J =6.5 Hz), 2.1-2.4 (4H, m), 2.39 (3H, s), 7.21 (1H, s); For **9** : (500 MHz, $CDCl_3$) δ 1.01 (6H, s), 1.30 (3H, t, J = 7.5 Hz), 1.46-1.50 (2H, m), 1.64-1.70 (2H, m), 1.87 (2H, t, J = 7.5 Hz), 2.10 (2H, quin. J = 7.5 Hz), 2.17 (2H, td, J = 7.5, 1.5 Hz), 2.21 (2H, t, J = 7.5 Hz), 2.38 (3H, d, J = 1 Hz), 4.18 (2H, q, J = 7.5 Hz), 5.92 (1H, d, J =1 Hz), 6.48 (1H, t, J = 1.5 Hz); For all-(*E*)-**11** : (200 MHz $CDCl_3$) δ 0.95 (6H, s), 1.4-1.7 (4H, m), 1.82 (2H, t, J = 7 Hz), 1.9-2.3 (6H, m), 2.03 (3H, s), 2.34 (3H, s), 3.69 (3H, s), 5.74 (1H, s), 6.28 (1H, d, J = 15 Hz), 6.31 (1H, s), 6.34 (1H, d, J = 12 Hz), 7.01 (1H, dd, J = 12,15 Hz); For **2**: (500 MHz, $CDCl_3$) δ 1.02 (6H, s), 1.46-1.52 (2H, m), 1.64-1.70 (2H, m), 1.87 (2H, t, J = 6 Hz), 2.10 (3H, s), 2.06-2.14 (2H, m), 2.19 (2H, t, J = 6 Hz), 2.28 (2H, t, J = 7 Hz), 2.34 (3H, s), 5.97(1H, d, J = 8 Hz), 6.39 (1H, s), 6.40 (1H, d, J = 11 Hz), 6.41 (1H, d, J = 15 Hz), 7.18 (1H, dd, J = 15,11 Hz), 10.11 (1H, d, J = 8 Hz).
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