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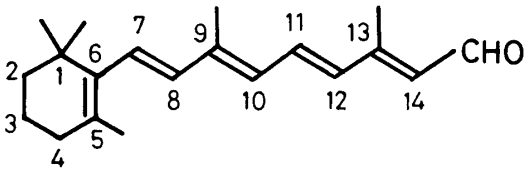
A SHORT PATH SYNTHESIS OF RETINALS. SYNTHESIS OF ^{13}C- OR ^{2}H-LABELED RETINALS

Hiroyuki Akita[1)]
Department of Chemistry, Columbia University
New York, New York, 10027, USA

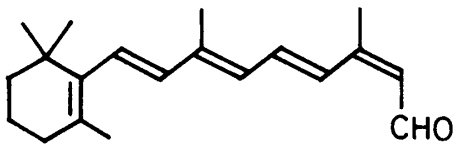
Trimethylsilylated acetaldehyde t-butylimine 4 was found to be an effective two carbon-homologenation reagent in the synthesis of retinals and its congeners. A short path synthesis of retinals (1 and 2) by using 4 and its application to the synthesis of ^{13}C-labeled retinal 12 and octadeuterium retinal 27 is described.

KEYWORDS——retinal; retinoid; vitamin A aldehyde; visual pigment; α,β-unsaturated aldehyde synthesis; silylated imine

During the course of our studies on visual pigments[2)] and bacteriorhodopsin,[3)] we were interested in efficient syntheses of retinals (1 and 2) in order to prepare their ^{13}C- or ^{2}H-labeled analogs.



"all trans" 1



"13-cis" 2

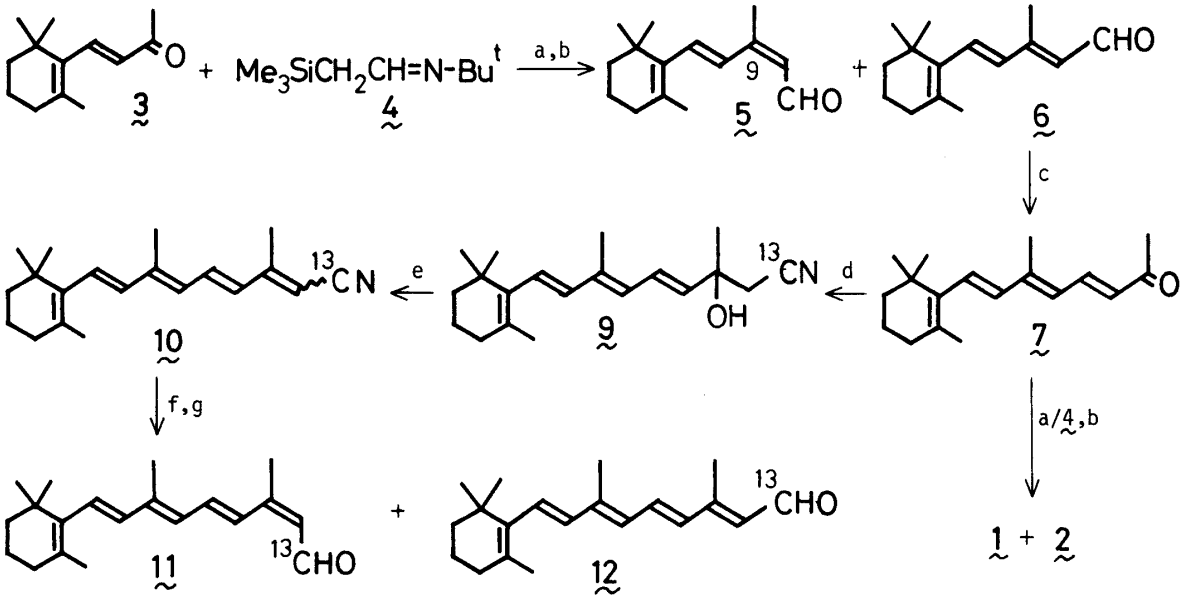
One of the most frequently used methods in retinals synthesis is the Wittig-Horner reaction involving the phosphonate carbanion. However, this method has certain limitations with such carbonyl compounds as highly-hindered or polyconjugated ketone. On the other hand, it was reported that the known trimethylsilylated acetaldehyde t-butylimine 4 reacted with simple ketones to give α,β-unsaturated aldehydes.[4)] Herein, we report the effectiveness of this reagent 4 in the three-step synthesis of retinals 1 and 2 and its application in the synthesis of ^{13}C- and ^{2}H-labeled retinals.

Reaction of β-ionone 3 with the anion of 4 gave a mixture of the β-ionylideneacetaldehyde (C_{15}-aldehyde 5 and 6), which could be separated by silica-gel chromatography (flash[5)]) into "9-cis" 5 (30%) and "all trans" 6 (58%), whose NMR spectra were identical with those of authentic samples reported by Heathcock et al.[6)] Aldol condensation of 6 with acetone in the presence of 1N-NaOH gave the known "C_{18}-ketone" 7[7)] in 72% yield. The "C_{18}-ketone" 7 yielded a mixture of 13-cis retinal 2 (17%) and all trans retinal 1 (37%) when reacted with the anion of 4.

The synthesis of ^{13}C-labeled retinals 11 and 12 was next carried out. The "C_{18}-ketone" 7 was reacted with acetonitrile-1-^{13}C 8 (90% atom % ^{13}C) in the presence of n-BuLi to give hydroxy

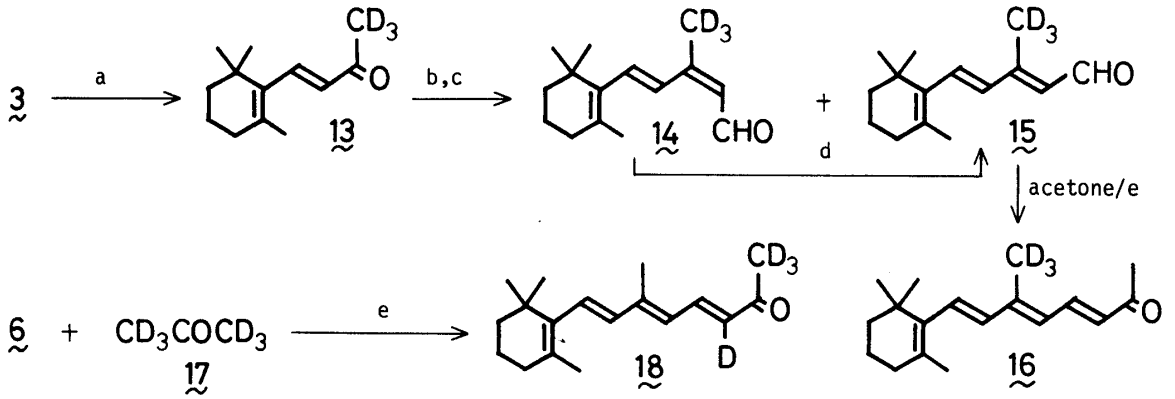
cyanide 9 (33%), which was treated with iodine in benzene to afford the cyano-retinal 10 (36%). DIBAL-H reduction of 10 gave the 13-cis ^{13}C-labeled retinal 11 (14%) and the all trans ^{13}C-labeled retinal 12 (33%). NMR spectra[8] of 11 and 12 were identical with those of the reported[9] non-labeled retinal (1 and 2) except for signals due to the aldehyde proton 11 δ 10.20, $J_{15,^{13}C}$=169.6 Hz, 12 δ 10.11, $J_{15,^{13}C}$=169.7 Hz and their molecular weights, 11 and 12, M^++1=286 (CI-MS).

Chart 1



a; LDA/THF, -78°C b; $(COOH)_2$ c; acetone/1N-NaOH d; $Me^{13}CN$(8)/n-BuLi
e; I_2/PhH f; $HAl(i\text{-}Bu)_2$/n-Hexane, -78°C g; KOOC-COONa

Chart 2

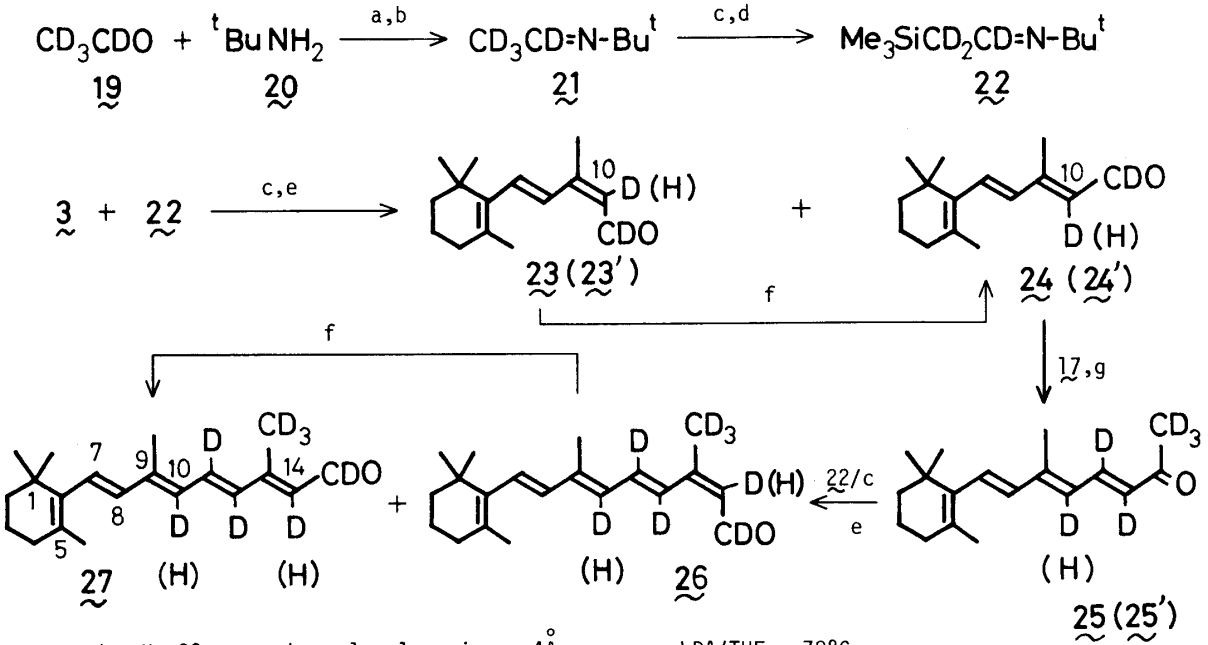


a; $NaOD/D_2O$ in dioxane b; 4/LDA/THF, -78°C c; $(COOH)_2$
d; I_2/PhH e; $Al(O\text{-}^tBu)_3/^tBuOH$ in PhH

The synthesis of poly deuterium (^2H)-labeled retinal was carried out as follows. Care must be taken in the preparation of deuterium compound to avoid conversion of deuterium into hydrogen. Some preliminary experiment were carried out in order to examine deuterium exchange reaction in the condensation process as shown in Chart 2. The reaction of β-ionone-d_3 13, prepared by treatment of 3 with sodium deutroxide in D_2O, and the anion of 4 afforded the "9-cis" C_{15}-aldehyde-d_3 14 (M^++1=222, 24%) and the "all trans" C_{15}-aldehyde-d_3 15 (M^++1=222, 47%). The "cis"

aldehyde 14 was converted into the "all trans" aldehyde 15 in 55% yield by treatment with iodine in benzene. The latter aldehyde 15 was treated with acetone in the presence of $Al(O\text{-}t\text{-}Bu)_3$/t-BuOH in dry benzene and subsequent silica-gel chromatography without working up a reaction mixture to provide the "C_{18}-ketone-d_3" 16 (M^++1=262, 41%). Another aldol condensation of 6 and acetone-d_6 by the same reagent as in the previous case gave the "C_{18}-ketone-d_4" 18 (M^++1=263, 30%). ^{1}H-NMR showed that no deuterium exchange reaction occurs during the course of these reactions.

Chart 3



a; dry Na_2SO_4 b; molecular sieves 4Å c; LDA/THF, -78°C

d; Me_3SiCl e; $(COOH)_2$ f; I_2/PhH g; $Al(O\text{-}^tBu)_3/^tBuOH$ in PhH

Finally, octadeuterium retinal 27 was prepared by a combination of the first mentioned three-step synthesis of retinals (1 and 2) and a model experiment as shown in Chart 3. Commercially available acetaldehyde-d_4 19 was condensed with t-butylamine in the presence of anhydrous Na_2SO_4 and subsequently dried over molecular sieves 4 Å to afford the acetaldehyde-d_4 t-butylimine 21 (bp 60-75°C, 95%). Treatment of 21 with LDA and subsequent quenching with trimethylsilyl chloride provided the trimethylsilylated acetaldehyde-d_3 t-butylimine 22 (bp 28-55°C/14 mmHg, 52%). No deuterium exchange reaction occurred in the preparation of 22 from 19. The reaction of 3 and 22 in the presence of LDA gave the "9-cis" β-ionylideneacetaldehyde-d_2 23[10] (18%) and the "all trans" β-ionylideneacetaldehyde-d_2 24[10] (36%). The NMR spectra of both aldehydes 23 and 24 were identical with non-deuterated aldehydes 5[6] and 6[6] except for the signal due to 10-hydrogen and aldehyde-hydrogen. In this process, deuterium at C(10)-position were partially exchanged by hydrogen atom as shown by NMR spectra (23'; δ 5.83 br s, 24'; δ 5.90 br s). The conversion of 23 to 24 was accomplished by isomerization with iodine in 66% yield. Aldol condensation of 24 with acetone-d_6 17 in the presence of $Al(O\text{-}t\text{-}Bu)_3$/t-BuOH and the subsequent purification provided the "C_{18}-ketone-d_6" 25[11] (45%). The ratio of d_6(25)/d_5(25') was 83/17 on the basis of a comparison of the NMR signals due to 7-H and 8-H. Two carbon-homologenation reaction of 25 with the anion of 22 was carried out, and careful purification of a reaction mixture by silica-gel chromatography provided the 13-cis retinal-d_8 26 (19%) and the all trans retinal-d_8 27 (38%).

The desired 27 was also obtained by the isomerization of 26 by treatment of iodine in dry benzene in 31% yield. It was found by NMR analysis that final all trans deuterium retinal[12] contained at least 62% D_8 compound 27. The CI-MS spectra of these deuterated compounds were consistent with the ^2H-content: 23; M^++1=221, 24; M^++1=221, 25; M^++1=265, and 27; M^++1=293.

In conclusion, a short path synthesis of retinals using trimethylsilylated acetaldehyde t-butylimine 4 was developed, and this method has been effectively applied for the synthesis of ^{13}C- or ^2H-labeled retinals 11, 12, and 27. The above mentioned 4 is an effective two-carbon homologenation reagent for relatively unreactive ketones such as polyconjugated ketones. In the retinal field the t-butylimine reagent 4 was first used in the synthesis of a retinal containing a seven-membered ring in the side chain.[2a]

Bioorganic and spectroscopic studies of bacteriorhodopsin using these isotopically-labeled retinals, 12, 27, etc., are in progress.

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8) 11; ^1H NMR($CDCl_3$) δ 1.04 (s, 1-Me_2), 1.72 (s, 5-Me), 2.02 (s, 9-Me), 2.14 (s, 13-Me), 5.85 (d, J=8 Hz, 14-H), 6.13 (d, J=16 Hz, 8-H), 6.22 (d, J=10 Hz, 10-H), 6.38 (d, J=16 Hz, 7-H), 7.01 (dd, J=15 Hz, J=10 Hz, 11-H), 7.31 (d, J=15 Hz, 12-H), 10.20 (dd, J=8 Hz, J=169.6 Hz, 15-H). 12; ^1H NMR($CDCl_3$) δ 1.04 (s, 1-Me_2), 1.71 (s, 5-Me), 2.02 (s, 9-Me), 2.32 (s, 13-Me), 5.97 (d, J=8 Hz, 14-H), 6.22 (s, 7-H, 8-H), 6.18 (d, J=11.4 Hz, 10-H), 6.35 (d, J=15 Hz, 12-H), 7.15 (dd, J=15 Hz, J=11.4 Hz, 11-H), 10.11 (dd, J=8 Hz, J=169.7 Hz, 15-H).

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10) 23; ^1H NMR($CDCl_3$) δ 1.08 (s, 1-Me_2), 1.77 (s, 5-Me), 2.13 (s, 9-Me), 6.57, 7.12 (each d, J=16 Hz, 7-H, 8-H). 24; ^1H NMR($CDCl_3$) δ 1.05 (s, 1-Me_2), 1.72 (s, 5-Me), 2.30 (s, 9-Me), 6.14, 6.72 (each d, J=16 Hz, 7-H, 8-H).

11) 25; ^1H NMR($CDCl_3$) δ 1.03 (s, 1-Me_2), 1.68 (s, 5-Me), 2.03 (s, 9-Me), 6.10 (d, J=16 Hz, 8-H), 6.40 (d, J=16 Hz, 7-H). 25' ^1H NMR($CDCl_3$) δ 6.11 (br s, 10-H).

12) ^1H NMR($CDCl_3$) δ 1.04 (s, 1-Me_2), 1.72 (s, 5-Me), 2.02 (s, 9-Me), 6.38 (d, J=16 Hz, 7-H), 6.14 (d, J=16 Hz, 8-H). Chemical shifts due to deuterium exchange product; δ 5.98 (s, 14-H), 6.20 (br s, 10-H).

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