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Isomers of 10-fluoro-20-^{13}C-retinal and the corresponding rhodopsin analogs

Jiahong Ni, Jin Liu, Leticia U. Colmenares and Robert S. H. Liu*

Department of Chemistry, University of Hawaii, Honolulu, HI 96822, USA

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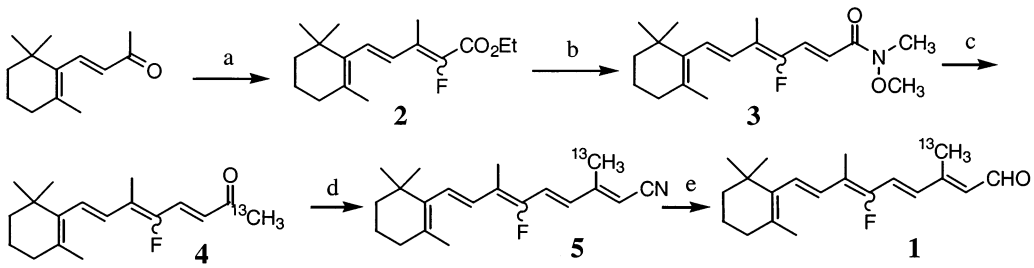
Abstract—The doubly-labeled 10-fluoro-20-^{13}C-retinal has been prepared. Five isomers have been isolated and two isomeric rhodopsin analogs prepared. The latter are intended for REDOR distance measurements.

The visual pigment rhodopsin is an integral membrane protein in the disk membrane of vertebrate rod cells. It contains the hindered 11-*cis* retinal isomer as a chromophore, bound to Lys_{296} through a protonated Schiff base linkage.[1] The exact twisted conformation of the polyene chromophore has been of concern to many research groups. This is due to its effect on the following properties of the visual pigment, e.g. the absorption maxima,[2] its chirality as a result of the helical twist,[3] and the enhanced photoreactivity.[4]

Solid-state NMR, using singly or doubly ^{13}C-enriched samples, has provided a wealth of structural information about the retinal chromophore and its interaction with the opsin binding site.[5] More recently, the development of new pulse sequences in rotational echo double-resonance (REDOR) methods allow measurement of heteronuclear dipole couplings, which in turn yields information concerning distances between the nuclei of concern.[5,6] The coupling between ^{19}F and ^{13}C is of particular interest because it is recognized that their nuclear parameters are likely to allow larger distances (up to 11 Å) to be measured.[5] In this paper, we report the successful combination of the synthetic techniques developed for the preparation of fluorinated[7] and ^{13}C isotopically-labeled[8] retinals for the synthesis of the first ^{19}F,^{13}C doubly-labeled retinal, i.e. the title compound, 10-fluoro-20-^{13}C-retinal.

A modification of the established 13+2+3+2 strategy in vitamin A synthesis[9] is shown in Scheme 1. The steps for introducing the labels are the following. The 10-F substituent was introduced following the established procedure of reaction of β-ionone with ethyl diethylphosphonofluoroacetate in the presence of NaH.[7] The ^{13}C label was introduced in the manner established by Lugtenburg et al.,[8] i.e. via the intermediacy of C-17-methoxymethylamide **3** reacting with a labeled methyl Grignard. The two isomers (9-*cis* to all-*trans* ~4:1) of amide **3** are readily separated by column chromatography. Therefore, subsequent chain-extension reactions were carried out with the separated



Scheme 1. (a) $(EtO)_2POCFHCO_2Et$+NaH; (b) DIBAL-H, MnO_2, $(EtO)_2POCH_2CO_2Et$+NaH, HN(OMe)Me+*n*-BuLi; (c) $^{13}CH_3MgI$; (d) $(EtO)_2POCH_2CN$+*n*-BuLi; (e) DIBAL-H.

* Corresponding author. Tel.: 808-956-5723; fax: 808-956-5908; e-mail: rliu@gold.chem.hawaii.edu

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isomers, yielding two sets of readily-separable isomers of retinal (9-*cis* and 9,13-di-*cis*; 13-*cis* and all-*trans*).[7] The data from the NMR spectra of all these isomers are listed[10] and they were found to be identical to those reported for 10-fluororetinal,[7] with the only exception being the large ^{13}C–H coupling constant ($\sim$128 Hz) for 13-Me. Additionally, the 11-*cis* isomer, characterized by its UV spectrum,[7] was also obtained from irradiation of the synthetic mixture in acetonitrile.[9]

We have also prepared the rhodopsin pigment analogs in good yields (>50%) from the 11-*cis* and 9-*cis* isomers of **1**. Expectedly, their absorption maxima (502 and 486 nm, respectively) are identical to those reported earlier[7] for the singly-labeled isomers.

In summary, a convenient method has been devised for the synthesis of a doubly-labeled retinal, which led to the isolation of four isomers of 10-fluoro-20-^{13}C-retinal. The resultant rhodopsin analogs now await detailed REDOR NMR analyses. The 11-*cis* pigment will be an independent test for the helical twist obtained recently with doubly-labeled ^{13}C samples,[11] and the 9-*cis* isomer, with a longer distance between the C,F nuclei, will offer a meaningful independent test for the method.

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10. Partial ^1H and ^{19}F NMR data for four isomers of **1**. **All-*trans***: ^1H NMR (300 MHz, $CDCl_3$): δ 10.14 (d, 1H, $J=8.1$ Hz, H-15), 6.88 (dd, 1H, $J=26.6$ and 15.4, H-11), 6.69 (d, 1H, $J=16.4$, H-7), 6.65 (dd, 1H, $J=15.4$ and 4.9, H-12), 6.33 (d, 1H, $J=16.4$, H-8), 6.06 (t, 1H, $J=8.1$, H-14), 2.32 ppm (d, 3H, $J=127.9$ Hz, $^{13}CH_3$-13); ^{19}F NMR (376.4 MHz, $CDCl_3$): −124.5 ppm (d, $J=26.8$ Hz). **13-*cis***: ^1H NMR: δ 10.27 (d, 1H, $J=8.3$ Hz, H-15), 7.54 (dd, 1H, $J=15.1$ and 5.4, H-12), 6.80 (dd, 1H, $J=26.9$ and 15.1, H-11), 6.73 (d, 1H, $J=16.2$, H-7), 6.36 (d, 1H, $J=7.2$, H-14), 2.16 (d, 3H, $J=127.7$ Hz, $^{13}CH_3$-13); ^{19}F NMR: −124.66 ppm (d, $J=26.8$). **9-*cis***: ^1H NMR: δ 10.14 (d, 1H, $J=8.0$ Hz, H-15), 6.98 (dd, 1H, $J=26.9$ and 15.3, H-11), 6.63 (dd, 1H, $J=15.3$ and 4.6, H-12), 6.39 (d, 1H, $J=15$, H-7), 6.31 (d, 1H, $J=15.1$, H-8), 6.09 (t, 1H, $J=7.8$, H-14), 2.34 (d, 3H, $J=127.9$ Hz, $^{13}CH_3$-13); ^{19}F NMR: −119.8 ppm (d, $J=26.7$). **9,13-di-*cis***: ^1H NMR: δ 10.27 (d, 1H, $J=8.0$ Hz, H-15), 7.51 (dd, 1H, $J=15.1$ and 5.4, H-12), 6.87 (dd, 1H, $J=26.9$ and 15.1, H-11), 6.38 (d, 1H, $J=15.4$, H-7), 6.31 (d, 1H, $J=15.4$, H-8), 5.94 (t, 1H, $J=7.4$, H-14), 2.16 (d, 3H, $J=127.7$ Hz, $^{13}CH_3$-13); ^{19}F NMR: −120.1 ppm (d, $J=26.7$).
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