Tetrahedron Letters,Vol.26,No.50,pp 6209-6212,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

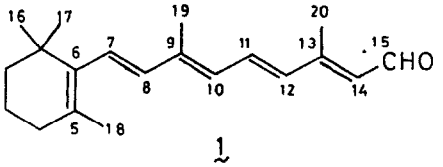
SYNTHESIS OF(7E,9E,11E,13E)-18,18,18-TRIFLUORORETINAL (ALL-TRANS 5-TRIFLUOROMETHYLRETINAL)

Takeo Taguchi, Akihiko Hosoda, and Yoshiro Kobayashi*

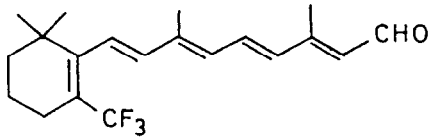
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: All-trans-18,18,18-trifluororetinal (2) was synthesized through trifluorocyclocitral (3) as a key intermediate.

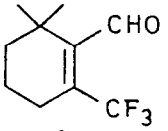
All-trans retinal (1) is recognized as the chromophore of bacteriorhodopsin (bR) in purple membrane of Halobacterium halobium, which transports protons unidiretionally across the membrane by using light energy absorbed by its chromophore.[1] To account for the variance in the absorpsion maxima of various visual pigments and the purple color of bR, the external point-charge model has recently been proposed by Nakanishi.[2] Substitution of hydrogen(s) of 1 with fluorine should cause a change in its electronic nature, but not appreciablly so in its steric environment.[3] Moreover, the presence of fluorine in 1 would be expected to be utilized as a label for probing structural information and mechanistic detail of bR and its associated processes.[4]



1



2



3

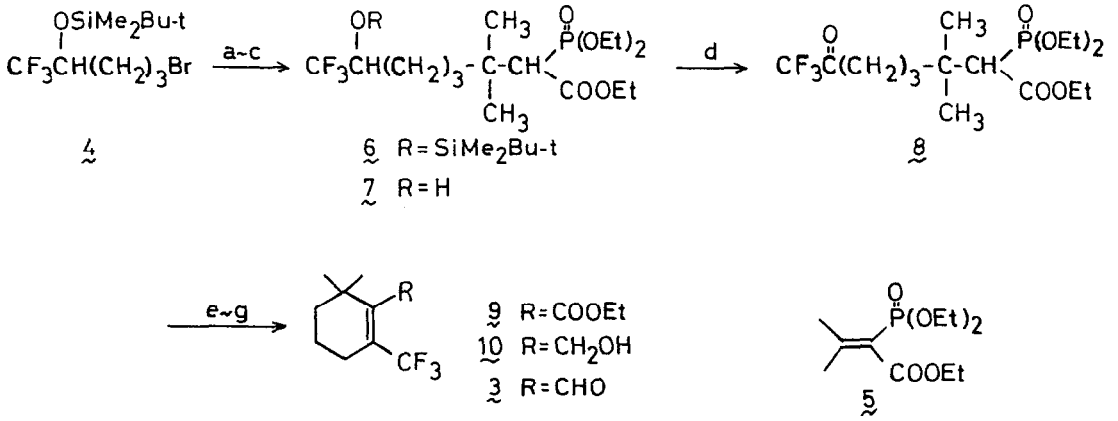
For this purpose, retinals with fluorine(s) on the side chain were synthesized and their binding study was investigated.[5,6,7]

In this paper we wish to report the first synthesis of (7E,9E,11E,13E)-18,18,18-trifluororetinal (all-trans-5-trifluoromethylretinal)(2).

For the synthesis of 18,18,18-trifluororetinal including all-trans isomer (2), trifluorocyclocitral (3) is considered an important key intermediate.

The conjugate addition of the Grignard reagent formed from the silyloxybromide (4)[8] to the phosphonate (5)[9] in the presence of the copper complex[10] gave the adduct (6, 86%), which in turn desilylated (n-Bu_4NF, THF) and oxidized ($Na_2Cr_2O_7 \cdot 2H_2O$, AcOH-c-H_2SO_4, r.t.) to the ketone (8, 89%). Cyclization of 8 proceeded effectively, but somewhat slowly by treatment with LiH in a mixture of THF and HMPA (3:1) under reflux for 48h to give the ester (9, 78%). Conversion of the ester (9) to trifluorocyclocitral (3) was achieved by the reduction of the ester group (DIBAL-H, n-hexane, -78°C, 24h, 10, 73%) followed by oxidation (MnO_2, CH_2Cl_2, r.t., 3h, 3, 94%)[11] (Scheme I).

Scheme I

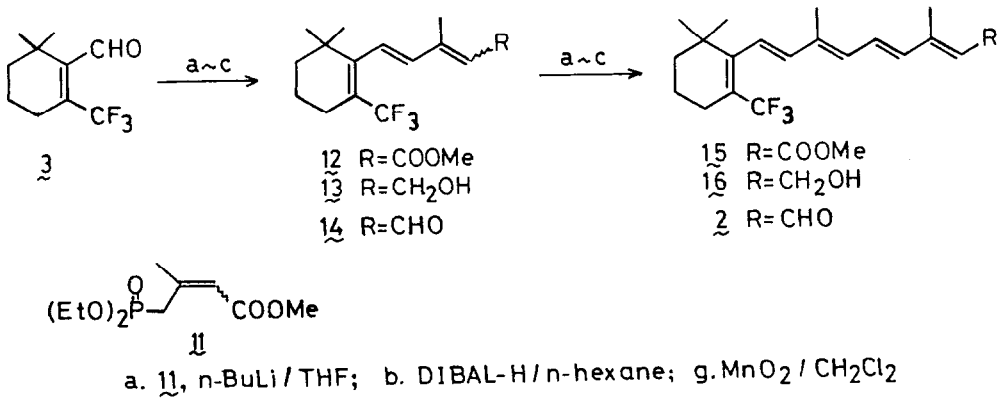


The repeated C_5-elongation methodology for the synthesis of retinal from cyclocitral was applied to the trifluorocyclocitral (3) under modified reaction conditions.[13]

Thus, the treatment of the C_5-phosphonate (11, E:Z=1:3, 3.5 equiv.) with n-BuLi (3.0 equiv.) at -78° in THF followed by the reaction with 3 at room temperature for 10h gave the triene-ester (12, 64%; E,E/Z,E=ca 6:1),[14] which was converted to the aldehyde 14 without separation of the stereoisomer.

DIBAL-H reduction (n-hexane, -78°C, 1h, 13, 94%) followed by oxidation (MnO_2, CH_2Cl_2, r.t., 3h) gave after the purification by column chromatography (SiO_2) the desired (E,E)-dienal [14, 60%, ^{1}H-NMR($CDCl_3$)δ: 5.98(1H, d, J=8 Hz, H-10), 6.14 (1H, d, J=16.2 Hz, H-8), 6.69 (1H, dq, J=16.2 and 2.5 Hz, H-7), 10.13 (1H, d, J=8 Hz, H-11); ^{19}F-NMR($CDCl_3$)δ: 5.58] and the (E,Z)-isomer [10%, ^{1}H-NMR($CDCl_3$)δ: 5.90 (1H, d, J=8 Hz, H-10), 6.60 (1H, dq, J=16 and 2.5 Hz, H-7), 6.99 (1H, d, J=16 Hz, H-8), 10.14 (1H, d, J=8.1 Hz, H-11); ^{19}F-NMR ($CDCl_3$)δ: 5.56]. A similar reaction of 14 with the phosphonate (11, E:Z=1.9:1) gave the trifluororetinoate (15, 78%), which, in turn, was reduced with DIBAL-H (16, quant.), oxidized with MnO_2 and purified by column chromatography to the desired all-trans trifluororetinal [2, 69%, ^{1}H-NMR($CDCl_3$)δ: 5.98 (1H, d, J=8 Hz, H-14), 6.12 (1H, d, J=16.2 Hz, H-8), 6.21 (1H, d, J=11.4 Hz, H-10), 6.31 (1H, dq, J=16.2 and 2.5 Hz, H-7), 6.39 (1H, d, J=15.2 Hz, H-12), 7.1 (1H, dd, J=15.1 and 11.4 Hz, H-11), 10.11 (1H, d, J=8.1 Hz, H-15); ^{19}F-NMR($CDCl_3$)δ: 5.56] (Scheme II).

Scheme II



As shown in this paper, trifluorocyclocitral (3) is a useful intermediate for the synthesis of 18,18,18-trifluororetinal and other isomers such as 11-cis eg., which are currently being synthesized. The binding study of 2 is now being carried out and the results will be published elsewhere.

References and Notes

1) W. Stoeckenius and R. A. Bogomolni, Annu. Rev. Bioche., 52, 587 (1981).
2) M. G. Motto, M. Sheves, K. Tsujimoto, V. Baloph-Nair, and K. Nakanishi, J. Am. Chem. Soc., 102, 7947 (1980) and the references cited therein.
3) R. Filler, in "Biomedicinal Aspects of Fluorine Chemistry" ed. by R. Filler and Y. Kobayashi, Elsevier Biomedical Press and Kodansha Ltd., 1982, pp 1-32.

4) J. T. Gerig, in "Biochemical Magnetic Resonance" ed. by L. J. Berliner and J. Ruebins, Plenum Press, New York, 1978, pp 139-203.
5) R. S. H. Liu and A. E. Asato, Tetrahedron, 40, 1931 (1984).
6) a) D. Mead, R. Loh, A. E. Asato and R. S. H. Liu, Tetrahedron Lett., 26, 2873 (1985); b) Y. Hanzawa, K. Kawagoe, N. Kobayashi, T. Oshima and Y. Kobayashi, ibid., 26, 2877 (1985); c) Y. Hanzawa, A. Yamada and Y. Kobayashi, ibid., 26, 2881 (1985) and references cited in ref. 6b).
7) A. B. Barua and J. A. Olson, J. Lipid. Res., 25, 304 (1984).
8) 4 was prepared from propargyl alcohol THP ether according to the following scheme.
$HC\equiv C\text{-}CH_2OTHP \xrightarrow{a\text{-}f} 4$
a) n-BuLi, THF then CF_3COOEt, 83.0%[6b] b) $NaBH_4$, EtOH, 90.3%
c) H_2/PtO_2, MeOH, quant. d) $Me_2(tBu)SiOTf$, 2,6-lutidine, CH_2Cl_2, quant.
e) p-TsOH, MeOH, 85% f) MsCl, Et_3N, CH_2Cl_2, then LiBr, acetone, 90%.
9) 5 was prepared in 98% yield by phenylselenylation of ethyl α-diethyl-phosphonoisobutylate (NaH, THF then PhSeCl, -78°C) followed by the oxidation (30%-H_2O_2, CH_2Cl_2, 0°C).
10) K. E. Bernady, J. F. Poletto, J. Nocera, P. Mirando, R. E. Schaub, and M. J. Weiss, J. Org. Chem. 45, 4702 (1980).
11) 3: ^{1}H-NMR($CDCl_3$)δ 1.13 (6H, s), 1.30-1.82 (4H, m), 2.21 (2H, t, J=6 Hz), 9.98 (1H, q, J=4.2 Hz). ^{19}F-NMR($CDCl_3$)δ: 6.4.[12]
12) In ^{19}F-NMR spectrum chemical shift is shown in ppm down from external benzotrifluoride.
13) M. I. Dawson, P. D. Hobbs, R. L-S. Chan and Wan-Ru Chao, J. Med. Chem., 24, 1214 (1981).
14) When either NaH or LDA was used instead of n-BuLi, isomerization of the double bond of 3 to the α-trifluorocyclocitral and the condensation reaction with this proceeded as its side reaction.

(Received in Japan 1 October 1985)