Tetrahedron Letters,Vol.26,No.24,pp 2877-2880,1985 0040-4039/85 \$3.00 + .00
Printed in Great Britain

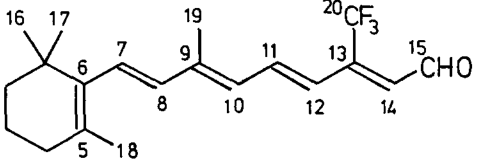
PREPARATION OF 20,20,20-TRIFLUORORETINAL(13-TRIFLUOROMETHYLRETINAL)

Yuji Hanzawa, Kei-ichi Kawagoe, Nobuo Kobayashi,
Toshihide Oshima and Yoshiro Kobayashi*

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

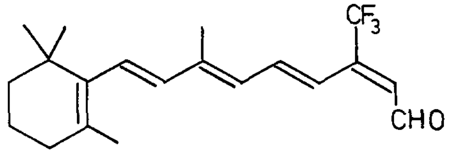
Summary: All-trans-20,20,20-trifluororetinal (1) was prepared by two ways.

In a previous study on the absorption spectra of visual pigment and bacteriorhodopsin, the external point-charge model was proposed to accout for "opsin shift".1) In order to check the validity of this model, the analogs of retinal were prepared.2) In this context, it is considered to be significant to prepare 20,20,20-trifluororetinal (1), since the fluorine substituent, characterized by strong electronegativity and small atomic size, may alter the electronic but steric properties of retinal. Although Gärtner et al.3) have reported the synthesis of 1 (all-trans=7E,9E,11E,13Z), the structure he proposed for this compound is at variance with that which Liu et al.4) determined on the basis of their experimental results. That is, they obtained the 13-cis isomer (7E,9E,11E,13E) (2) under essentially the same conditions.



all-trans (7E,9E,11E,13Z)

1

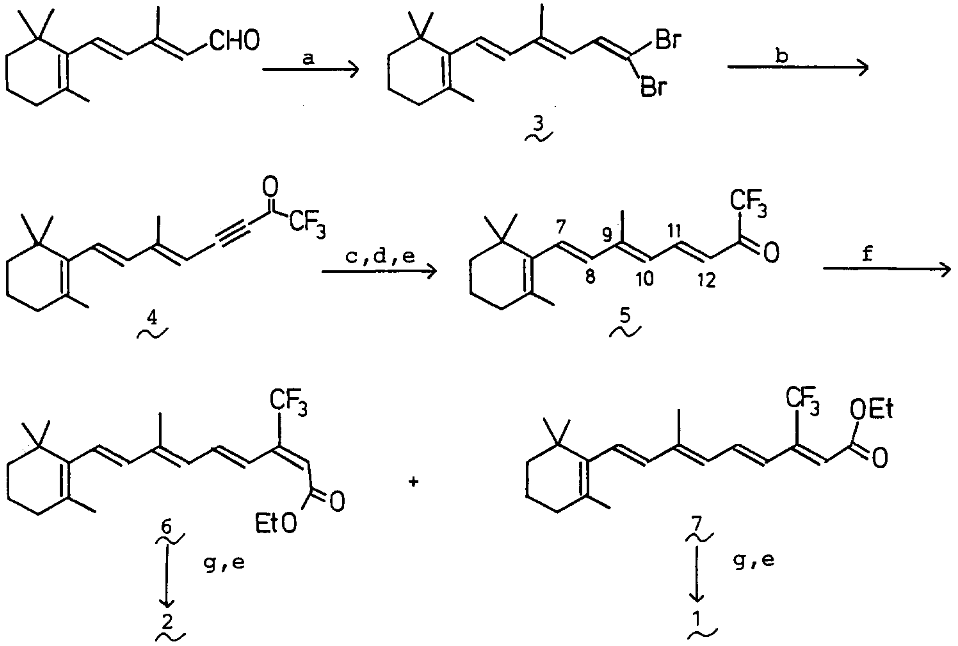


13-cis (7E,9E,11E,13E)

2

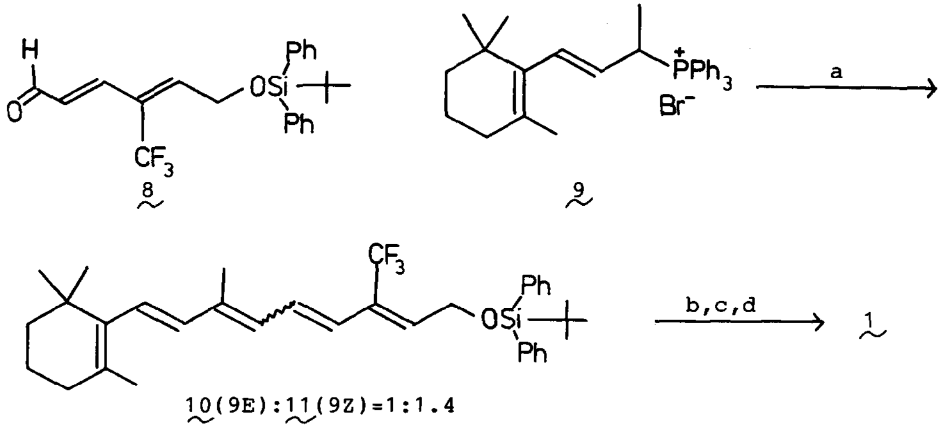
In the present paper, we report the synthesis of 1 and 2. An attempt was made to synthesize through the versatile intermediate (4) by which the preparation of 11-cis stereoisomer of 1 should be possible. Treatment of β-ionylideneacetaldehyde with CBr_4-Ph_3P gave chain-extended dibromoolefine (3)5) in more than a 90% yield, which was converted to acetylenic ketone (4)6) in a 64% yield by the reaction of n-BuLi (2 eq.) and CF_3COOEt. The triple bond was reduced with Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride] after ketone (4) was reduced with $NaBH_4$. The alcohol function was oxidized back to ketone with MnO_2 to give compound (5) (51% yield from 4). The ^1H-nmr spectrum of 5 confirmed the all-trans structure: δ 6.20 (d, J=16.5Hz, H_8), 6.27 (d, J=12Hz,

H_{10}), 6.42 (d, J=15Hz, H_{12}), 6.52 (d, J=16.5Hz, H_7), 8.04 (dd, J=15, 12Hz, H_{11}). To extend 5 by two additional carbons, we carried out the Peterson olefination of this compound. The reaction proceeded smoothly under mild conditions (-78 → -23°) ($TMSCH_2COOEt$/LICA/THF)[7] and the esters (6, 7) were obtained in a nearly 1:1 ratio (66%). These isomeric esters (6, 7) were easily separated from each other and assigned on the basis of the nmr spectrum.[8] Reduction by DIBAL and oxidation by MnO_2 of 6 and 7 gave 2 and 1,[9] respectively. The reported all-trans compound[3] was found not to be identical with our compound 1 but with compound 2 by an nmr spectra comparison.[10] No isomerization was expected to occur during the reduction and oxidation and thus, compound (1) was concluded to be all-trans-20,20,20-trifluororetinal (7E,9E,11E,13Z).



a: CBr_4-Ph_3P, b; 2eq. n-BuLi, CF_3COOEt in THF, c: $NaBH_4$/EtOH
d: Red-Al/Et_2O, e: MnO_2/CH_2Cl_2, f: $TMSCH_2COOEt$/LICA/THF, g: DIBAL/hexane

For confirmation of the structure of 1, its synthesis was carried out by a different route. During our study of trifluoromethylated diene syntheses, we prepared compound (8) by various methods.[11] The Wittig reaction of 8 with phosphonium salt (9)[12] (nBuLi/Et_2O/-20°→rt) gave a mixture of stereoisomers 10 and 11 in a 51% yield (9E/9Z=1/1.4). Deprotection (nBu_4NF) of the silyl group generated a mixture of 9E- and 9Z-20,20,20-trifluororetinols (12,13), one of which, compound 12, showed behavior identical to that observed for the retinol obtained by the reduction of 7 (all-trans) in the HPLC experiments.



a: n-BuLi/Et_2O, b: n-Bu_4NF/THF, c: HPLC separation
d: MnO_2/CH_2Cl_2

The data from the above experiments clearly indicate that the 20,20,20-trifluororetinal reported by Gärtner et al.[3] is not actually all-trans compound (1) but 13-cis compound (2) (7E,9E,11E,13E).

References and Notes

Syntheses of all-trans-19,19,19-trifluororetinal and 20,20,20-trifluororetinal were carried out independently by Liu et al. at about the same time that our research was being conducted. D. Mead, A. E. Asato and R. S. H. Liu, 10P33, " '84 International Chemical Congress of Pacific Basin Societies ", Honolulu, Hawaii, 1984.

1) M. G. Motto, M. Shever, K. Tsujimoto, V. Balogh-Nair and K. Nakanishi, J. Am. Chem. Soc., 102, 7947 (1980) and the references cited therein.
2) Trifluoromethylated analogs of retinal and retinoic acid:
   a) W. Gärtner, D. Oesterhelt, P. Towner, H. Hopf and L. Erst, J. Am. Chem. Soc., 103, 7642 (1981).
   b) S. C. Welch and J. M. Gruber, J. Org. Chem., 47, 385 (1982).
   c) A. E. Asato, D. Mead, M. Denny, T. T. Bopp and R. S. H. Liu, J. Am. Chem. Soc., 104, 4979 (1982).
3) Ref. 2a).
4) Ref. 2c).
5) E. J. Corey and P. L. Fuchs, Tetrahedron Lett., 3769 (1972).
6) Ref. 5) and T. Kitazume, T. Sato and N. Ishikawa, p. 56, Abstracts of the ninth fluorine symposium in Hokkaido, Japan, 1983.

7) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto and H. Nozaki, J. Am. Chem. Soc., 96, 1620 (1974). LICA: Lithium isopropylcyclohexylamide.

8) The ^{1}H-nmr spectrum of 6 was quite similar to that of the methyl ester. Ref. 2b) and 2c). Compound 6 was eluted first in flash chromatography (silica gel, Hexane-EtOAc).
^{1}H-Nmr spectrum of 7: δ 6.12 (d, J=15.8Hz, H_8), 6.10 (d, J=12Hz, H_{10}), 6.12 (d, J=15.8Hz, H_{12}), 6.24 (S, H_{14}) 6.32 (d, J=15.8Hz, H_7), 7.07 (dd, J=15.8, 12Hz, H_{11}).

9) The all-trans-20,20,20-trifluororetinal (1) was unstable and easily isomerized to 2 by HPLC (silica gel, Hexane-EtOAc) conditions.

10) The aldehyde proton of 1 appears at δ 10.07 (dq, J=7.7, 1.7Hz) in the dq coupling pattern due to H-H and H-F couplings. In the case of the aldehyde 2, the aldehyde proton at δ 10.14 (d, J=6.8Hz) showed no H-F coupling. This nmr coupling analysis is a very general way to determine the stereochemistry of the β-CF_3-substituted-α,β-unsaturated aldehyde system.
^{19}F-Nmr spectrum of 1 (in ppm down field from external benzotrifluoride): 6.6 (bs).

11) A part of this work has already been published: Y. Hanzawa, K. Kawagoe, A. Yamada and Y. Kobayashi, Tetrahedron Lett., 26, 219 (1985).

12) H. Pommer, Angew. Chem., 72, 811 (1960).

13) The alcohol isolated by HPLC (Waters Liquid Chromatograph Model 590, μ-porasil, 5% dioxane in Hexane) was also oxidized with MnO_2 to give 1.

(Received in Japan 5 March 1985)