Tetrahedron Letters,Vol.26,No.24,pp 2881-2884,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

PREPARATION OF 19,19,19-TRIFLUORORETINAL(9-TRIFLUOROMETHYLRETINAL)

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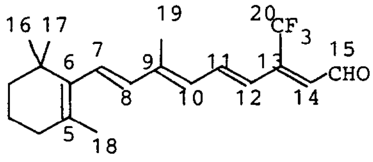
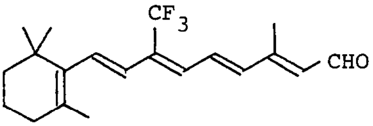
Summary: Synthetic work of all-trans-19,19,19-trifluororetinal (7E,9Z,11E,13E) is described.

In the preceding paper, we reported the syntheses and characterization of all-trans-20,20,20-trifluororetinal (7E,9E,11E,13Z) (1).[1] In this communication, we report the synthesis of 19,19,19-trifluororetinal (2) in the all-trans form (7E,9Z,11E,13E) through photolysis of the trifluoromethylated diene system previously reported.[2]



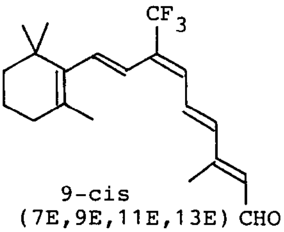
all-trans
(7E,9E,11E,13Z)

1



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

2

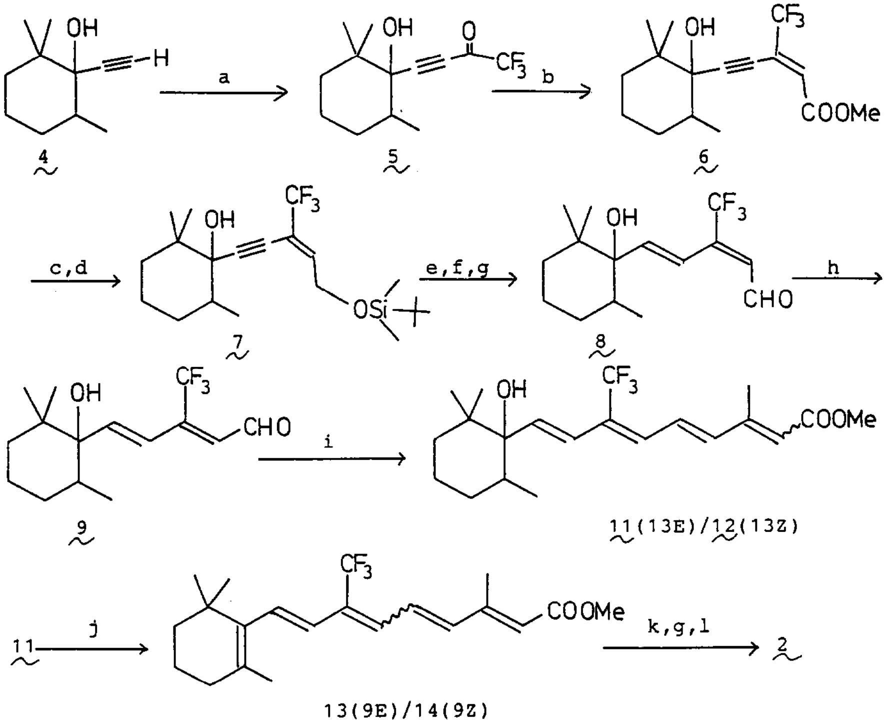


9-cis
(7E,9E,11E,13E)

3

The synthesis of 9-cis-19,19,19-trifluororetinal (7E,9E,11E,13E) (3) has been reported by Liu et al.[3] Our synthesis was initiated with 1-ethynyl-2,2,6-trimethylcyclohexanol (4).[4] The reaction of the lithium acetylide of 4 with CF_3COOEt gave hydroxy ketone (5)[5] (81%) which was treated with the Wittig reagent in Et_2O to give ester 6 as the only product.[6] Reduction of 6 with DIBAL and the subsequent protection ($tBuMe_2SiCl$/imidazole) of the primary alcohol gave 7 in 86% yield. The 9-cis aldehyde (7E,9E) (8)[7] was obtained by reduction with Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride], desilylation with nBu_4NF and oxidation with MnO_2. The yield of 8 from 7 was 42% after being purified by flash chromatography. For conversion of 8 to 9-trans aldehyde (7E,9Z) (9), a solution of 8 in acetone (Pyrex, Rayonet RPR 3000Å) was irradiated to give 9 (34%) along with recovered 8 (41%). The stereochemistry (7E,9Z) of 9 was evident from its nmr spectrum: δ 6.3 (d, J=7.5Hz, H_{10}), 6.46

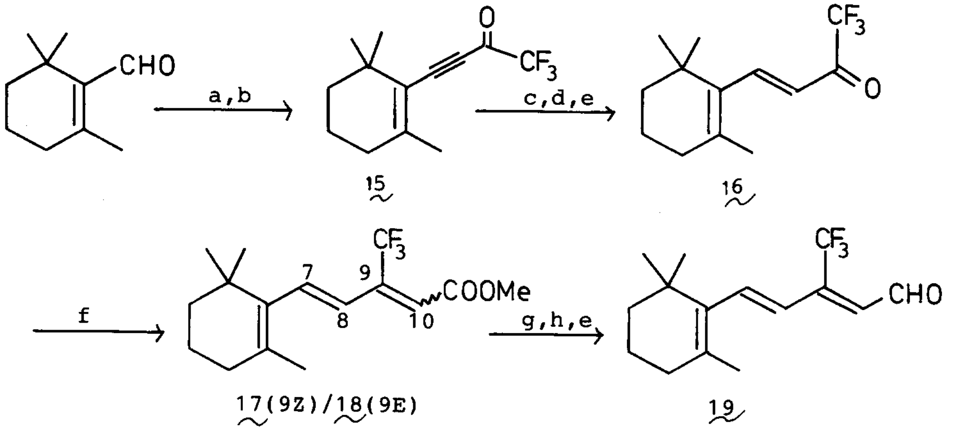
(d, J=16.5Hz, H_8), 6.8 (d, J=16.5Hz, H_7), 10.23 (dq, J=7.5, 1.5Hz, CHO). The reaction of 9 with a phosphonate reagent (10)[8] gave the all-trans ester (7E, 9Z,11E,13E) (11) (49%) and 13-cis ester (7E,9Z,11E,13Z) (12) (34%). Dehydration of 11 (p-toluenesulfonic acid/benzene, 80°C, 15 min.) gave a mixture of methyl 9-cis (E)-and 9-trans (Z)-19,19,19-trifluororetinoates (13, 14) (80%, 9E/9Z=1:3). Although these isomers could be separated with HPLC, a mixture of the esters was reduced by DIBAL and oxidized by MnO_2 to give a mixture of retinals 2 and 3, which could be separated from each other by HPLC.[9] The yield of the isolated all-trans-19,19,19-trifluororetinal (7E,9Z,11E,13E) (2)[10] was 44%. The all-trans compound (2) was stable in the dark at low temperature.



a: n-BuLi,CF_3COOEt/THF, b: $Ph_3PCHCOOMe$, c: DIBAL/Hexane,
d: $tBuMe_2SiCl$/imidazole, e: Red-Al/Et_2O, f: $n\text{-}Bu_4NF$,
g: MnO_2/CH_2Cl_2, h: hν/Me_2CO, i: $(EtO)_2\underset{O}{\overset{}{P}}\text{-}CH_2\text{-}\underset{CH_3}{C}\text{=CH-COOMe}$/NaH/THF,
j: TsOH/PhH, k: DIBAL/hexane,
l: HPLC separation. 10

It was also possible to synthesize 2 from the acetylenic ketone (15) obtained from β-cyclocytral in two steps in a 30% yield or from 4. Reduction of 15 with $NaBH_4$ followed by Red-Al reduction (80% in two steps) gave a trans allylic alcohol which was oxidized to ketone (16) (MnO_2, 65%).[11] The Peterson olefination of 16 ($TMSCH_2COOEt$/LICA)[12] gave a 1:1 mixture of esters (17,18) (98%), which could be separated by flash chromatography. The trans ester (7E,9Z) (17) was reduced by DIBAL and oxidized with MnO_2 to give aldehyde (7E,9Z) (19) (80%).[13] On treating 19 with a phosphonate reagent

(10)[8] gave the all-trans ester (14) whose spectral data were identical to those of the initially obtained compound.



$\xrightarrow{i}$ 14

a: $Ph_3P^+CH_2ClCl^-$, n-BuLi
b: 2eq. n-BuLi/CF_3COOEt, c: $NaBH_4$/EtOH,
d: Red-Al/Et_2O, e: MnO_2/CH_2Cl_2,
f: $TMSCH_2COOEt$/LICA/THF, g: separation,
h: DIBAL/Hexane, i: $(EtO)_2\underset{O}{\overset{\uparrow}{P}}CH-\underset{CH_3}{C}=CHCOOMe$/NaH 10

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) a) Y. Hanzawa, K. Kawagoe, N. Kobayashi, T. Oshima and Y. Kobayashi, preceding paper.
   b) The conventional retinal numbering system is used.
2) Y. Hanzawa, K. Kawagoe, A. Yamada and Y. Kobayashi, Tetrahedron Lett., 26, 219 (1985).
3) A. E. Asato, D. Mead, M. Denny, T. T. Bopp and R. S. H. Liu, J. Am. Chem. Soc., 104, 4979 (1982).
4) a) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, J. Chem. Soc., 1094 (1952).
   b) G. L. Olson, H. C. Cheung, K. D. Morgan, R. Borer and G. Saucy, Helv. Chim. Acta, 59, 567 (1976).
5) T. Kitazume, T. Sato and N. Ishikawa, P. 56, Abstracts of the ninth fluorine symposium in Hokkaido, Japan, 1983.
6) Although photolysis of 6 gave a mixture of the E/Z (1:1) isomers, it was convenient to carry out the photolysis of aldehyde (8) from a practical stand point.
7) ^{1}H-Nmr spectrum of 8: δ 10.29 (d, J=7.5Hz, CHO), 7.03 (d, J=16.5Hz, H_8),

6.63 (d, J=16.5Hz, H_7), 6.36 (d, J=7.5Hz, H_{10}).

8) a) G. Pattenden and B. C. L. Weedon, J. Chem. Soc. (C), 1984 (1968).
b) F. Derguini, V. Balogh-Nair and K. Nakanishi, Tetrahedron Lett., 4899 (1979).

9) The Waters Liquid Chromatograph Model 590 (μ-porasil) was used.

10) ^{1}H-Nmr spectrum of **2**: δ 10.15 (d, J=8Hz, CHO), 7.20 (dd, J=12.8, 15.5Hz, H_{11}), 6.58 (d, J=12.8Hz, H_{10}), 6.56 (d, J=16.9Hz, H_7), 6.54 (d, J=15.5Hz, H_{12}), 6.03 (d, J=8Hz, H_{14}), 6.02 (d, J=16.9Hz, H_8). ^{19}F-Nmr spectrum of **2** (in ppm down field from external benzotrifluoride): 5.5 (s). The ^{1}H-nmr spectrum of **3** was identical to that already reported.[3)]

11) This oxidation reaction (13 eq. mole of MnO_2 in CH_2Cl_2) proceeded very slowly.

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

13) ^{1}H-Nmr spectrum of **19**: δ 6.09 (d, J=16.5Hz, H_8), 6.3 (d, J=7.5Hz, H_{10}), 6.89 (d, J=16.5Hz, H_7), 10.1 (dq, J=7.5, 1.5Hz, CHO).

(Received in Japan 5 March 1985)