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TRIFLUOROMETHYL GROUP ON QUARTERNARY CARBON; SYNTHESIS OF 16,16,16-TRIFLUORORETINAL

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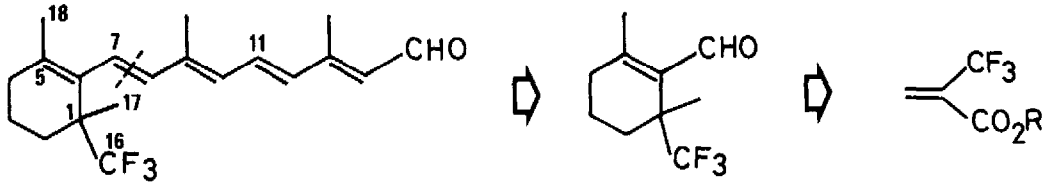
Summary: The synthesis of racemic 16,16,16-trifluororetinal through the Diels-Alder reaction of 2-(trifluoromethyl)propenoic acid with functionalized diene is discussed.

In our study on the chemistry of fluorinated retinal and its bacteriorhodopsin (bRh), it was found that the introduction of small and electronegative fluorine atom at a particular position on the retinal chromophore was very useful to understand the electronic charges in the protein's binding site.[1] For the purpose of obtaining further information on the hydrophobic binding site of the retinal , 16,16,16-trifluororetinal (1) is considered interesting chromophore. Since the introduction of fluorine atoms into C_{16} of retinal causes the quarternary carbon C_1 to become asymmetric, it is expected that the trifluoromethyl group on chiral C_1 in each enantiomer might induce the different fluorine-effect on the binding rate with apoprotein. It should also be worthwhile to study about the opsin shift[2] induced by each enantiomer of 1. Those data should give some significant informations on the protein's binding site of the β-ionone ring region.[3] In this communication, we describe the synthetic study of racemic 1 through the Diels-Alder reaction of fluorinated dienophile.



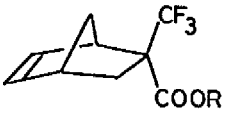
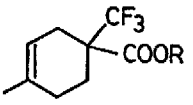
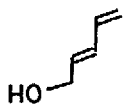
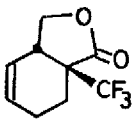
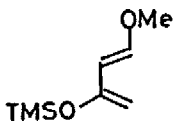
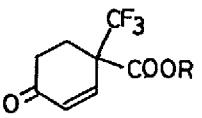
1 2 3

R= H or CH_2CF_3

Retrosynthetically, fluorinated β-cyclocitral (2), a key intermediate for the synthesis of retinal 1, can be taken back to trifluoromethylated compound (3), which is a useful compound for the forthcoming preparetion of optically active 2. To our knowledge, there has been no report on the Diels-Alder reaction of 3. Therefore, we tried the Diels-Alder reaction of 3 with some typical dienes prior to the preparation of 2. Results in table 1 show

that the reactivity of 3 as a dienophile is higher than that of methacrylic acid because of the electron withdrawing effect of the trifluoromethyl group.[4)]

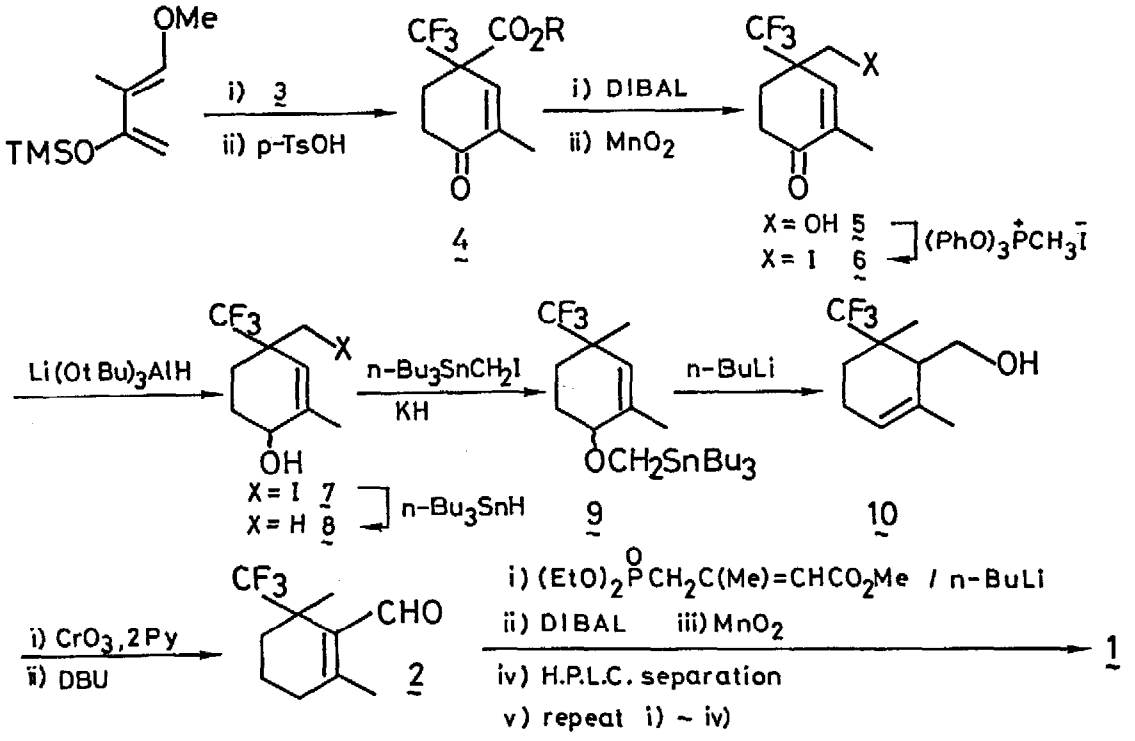
Table 1. The Diels-Alder Reaction of 3

Diene	Solv.	Temp.	Product	Yield (%)
	CH_2Cl_2	room temp.		81 R=H[a)]
	CH_2Cl_2	120°C		74 R=H[b)]
	Benzene	110°C		48 R=H
	CH_2Cl_2	room temp.		79 $R=CH_2CF_3$[c)]

a) endo-COOH/exo-COOH=2, The stereochemistry was determined by iodo-lactonization of the stereoisomers. Only the endo-COOH isomer cyclized to give the iodo-lactone.[4)] b) The ratio of the regio isomers was 10/1 (para type isomer was the major one). c) Yield refers to the acid-treated product (TsOH/MeOH).

Reaction of 3 with (E)-1-methoxy-2-methyl-3-trimethylsilyl-oxy-1,3-butadiene[5)] and subsequent treatment of the crude Diels-Alder adduct with p-toluenesulfonic acid gave the enone (4) in good yield (87%). The reduction of 4 (DIBAL-H,) and subsequent oxidation of allylic alcohol (MnO_2/CH_2Cl_2) gave the alcohol (5) in 55 % yield. Although the alcohol group of 5 could be converted to methyl group by two step-procedures [$(PhO)_3P^+CH_3I^-$ and nBu_3SnH], product was obtained in low yield due to the high volatility of the product. For easier handling, the enone carbonyl of iodide 6 was reduced [Li(t-BuO)$_3$AlH/Et_2O] to give iodo alcohol (7)[6)] (86%, from 5). Subsequent reduction of 7 with nBu_3SnH gave the methyl compound (8) in 83% yield. Formation of the tri-n-butylstannylmethyl ether (9) (n-Bu_3SnCH_2I/KH, THF) and the [2,3]-Wittig rearrangement[7)] (n-BuLi, THF, -78°C) of 9 gave the rearranged

alcohol (10) as a mixture of diastereomers in 50 % yield. The alcohol (10) was oxidized (CrO_3.2Py, celite, CH_2Cl_2) to aldehyde which was then isomerized to the β-cyclocitral derivative (2)[8] (60 %, from 10) by treatment with base (DBU, Et_2O, 0°C).[9] The racemic retinal (1)[10] was obtained by the established procedure.[11]



The preparation of optically pure 1[12] and the determination of the absolute configuration will be reported in the near future.

Refernces and Notes

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4) J. S. Meek and W. B. Trapp, J. Am. Chem. Soc., 79, 3909 (1957). It should be noted that the ratio (endo-COOH/exo-COOH = 2) of the cyclopentadiene adduct is inverted from that of the adducts obtained by the reactions of α-alkylated propenoic acids with cylopentadiene. This interesting effect of the trifluoromethyl group has also been reported in the case of 3-(trifluoromethyl)propenoic acid. J. G. Martin and R. K. Hill, Cem. Rev., 61, 537 (1961).

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6) Two separable diastereomers were obtained in a ratio of 1:2.6, the former less polar than the latter. The relative stereochemistry was not determined. The isomer derived from the more polar isomer 7 by nBu_3SnH reduction gave higher yield of the [2,3] Wittig rearrangement product than that derived from the less polar isomer 7. The following are some of the reducing reagents examined (numbers refer to the ratio of less polar/more polar): $NaBH_4$ 1/1.7, $K(O\text{-}iPr)_3BH$ 1/1.8, $Li(O\text{-}tBu)_3AlH$ 1/2.6, DIBAL 2/1, L-Selectride 1.4/1.

7) W. C. Still, A. Mitra, J. Am. Chem. Soc., 100, 1927 (1978).

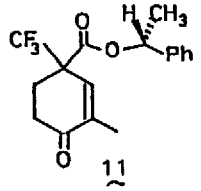
8) ^{1}H-NMR ($CDCl_3$)δ;1.51 (s, 3H, 6-Me), 1.53-1.70 (m, 3H), 1.85 (m, 1H), 2.13 (s, 3H, 2-Me), 2.20 (m, 2H, allylic), 10.06 (s, 1H, CHO). ^{19}F-NMR ($CDCl_3$)ppm; 7.3 (higher field from the external benzotrifluoride signal). IR (CCl_4) ν cm^{-1}; 1685. High resolution mass spectrum, Calcd. for $C_{10}H_{13}F_3O$ 206.0918, Found 206.0940.

9) The isomerization of the α-cyclocitral to the β-isomer under basic conditions; M. Rosenberger and G. Saucy, Ger. Offen, 2,520,186. C.A., 84, 121303u (1976).

10) ^{1}H-NMR ($CDCl_3$) δ;1.23 (s, 3H, 1-Me), 1.6 (bs, 4H), 2.0-2.15 (m, 2H), 1.76 (s, 3H, 5-Me), 2.05 (s, 3H, 9-Me), 2.33 (s, 3H, 13-Me), 5.98 (d, 1H, J=8Hz, 14-H), 6.1 (d, 1H, J=16Hz, 8-H), 6.18 (d, 1H, J=11.5Hz, 10-H), 6.24 (d, 1H, J=16Hz, 7-H), 6.37 (d, 1H, J=15Hz, 12-H), 7.12 (dd, 1H, J=11.5 and 15Hz, 11-H), 10.11 (d, 1H, J=8Hz, CHO). High resolution mass spectrum, Calcd. for $C_{20}H_{25}F_3O$ 338.1856, Found 338.1887.

11) T. Taguchi, A. Hosoda and Y. Kobayashi, Tetrahedron Lett.,26, 6209 (1985).

12) Separation of a mixture of the diastereomers (11) was achieved by preparative scale HPLC.



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