Synthesis of Fluorinated Retinal: A C₆–C₇ *s-trans* Fixed Retinal Containing a Trifluoromethyl Group at the Terminal Position of the Conjugated System

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For the study of retinal-binding proteins by using fluorine-modified retinals, the all-*trans* bicyclic trifluororetinal (1), whose C₆–C₇ bond is fixed in the *s-trans* form by an ethano bridge, was synthesized. Introduction of a trifluoromethyl group was carried out in 70% yield by photochemical trifluoromethylation of the dienol ether compound (2) with trifluoromethyl iodide. From a comparison of the absorption maximum of 1 with that of the bicyclic retinal (12), it is clear that the electron-withdrawing trifluoromethyl group induces a notable hypsochromic shift (18 nm) of 1.

Keywords trifluoromethyl iodide; bicyclic trifluororetinal; photochemical trifluoromethylation; *s-trans* conformation; hypsochromic shift

The photo-activation process and the structure of retinal-binding proteins—bacteriorhodopsin (bR) and rhodopsin (Rh)—have been studied extensively by many research groups using retinal analogs.¹⁾ Recently, we have reported the synthesis of trifluoro analogs of retinal and an unusual effect of trifluororetinal-binding bR.²⁾ For further study of the structure and behavior of retinal-binding proteins (bR, Rh), we required a new fluorinated retinal (1), which has a fixed *s-trans* C₆–C₇³⁾ bond. The importance of the *s-trans* C₆–C₇ conformation of the retinal chromophore in native bR has been pointed out by Lugtenburg *et al.* and demonstrated spectroscopically.⁴⁾ The retinal analog 1 should be a good analog for studies on the binding site of bR and the unusual effect of the trifluororetinal-binding

bR which we have reported.²⁾ This note describes the synthesis of 1 and the effect of the electronegative trifluoromethyl group in a conjugated system.

Irradiation of a pyridine solution of 2 and trifluoromethyl iodide in a quartz vessel with a 100 W high-pressure mercury lamp gave the desired trifluoromethylated compound (3) in 70% yield along with a trace amount of an iodine-containing compound.⁵⁾ Acid treatment (CF₃COOH, yield 60%) of 3 and the subsequent reaction of the enone (4) with lithium trimethylsilylacetylide gave a mixture of diastereomers, which was desilylated (*n*-Bu₄NF, yield 61%) directly to give a diastereomeric mixture of the acetylenic alcohols (5). Dehydration (Nafion-H/CCl₄) of the alcohol function of 5 gave a mixture of isomeric products (6a and 6b, yield 28%, ratio 3.8/1) and the ketone (7) (10%).⁶⁾ The hydration of the triple bond of 6a (Hg₂O/H₂SO₄) was carried out to give 7 in 51% yield. Horner–Emmons reaction of 7 with diethyl cyanomethylphosphonate afforded a mixture of stereoisomeric cyano compounds (8) (53%), which was directly treated with diisobutylaluminum hydride (DIBAL-H) to give the aldehyde as a mixture of stereoisomers (9a and 9b, yield 78%, ratio 4.6/1). After separation of the 9*E*-aldehyde

Chart 3

(9a) from the 9Z-isomer (9b),³⁾ the reaction of 9a with methyl 4-diethylphosphono-3-methyl-2-butenate (10)⁷⁾ gave the all-*trans* ester (11) in 98% yield. All-*trans* retinal (1) was obtained in 66% yield by reduction (DIBAL-H) of 11 followed by oxidation (MnO₂).

The conformation of 1 is considered to be almost the same as that of the bicyclic retinal (12) because the trifluoromethyl group is too far away to affect sterically the rotatable C₈—C₁₅ side chain³⁾ of 1. Therefore, the molecular flattening of the conjugated system should be very similar in the two bicyclic analogs (1 and 12). This assumption is also supported by space-filling molecular models and by ¹³C-nuclear magnetic resonance (¹³C-NMR) spectral comparison of 1 and 12. In the ¹³C-NMR spectrum of 1 (see Experimental), chemical shifts of the side chain carbons (C₈—C₁₅, C₁₉ and C₂₀)³⁾ are essentially the same as those of 12 reported by Lugtenburg *et al.*⁴⁾ Evaluation of the electronic effect of the trifluoromethyl group in the conjugated system of retinal was done by comparing the absorption maxima of 1 and 12 and a clear hypsochromic shift of 1 was demonstrated. A possible explanation of the notable hypsochromic shift (18 nm) in 1 compared to 12 is the destabilization of the excited state of 1 caused by the electron-withdrawing nature of the trifluoromethyl group. In summary, we could estimate the electronic effect of the trifluoromethyl group at the terminal position of the conjugated system of retinal by preparing 1. By knowing the electronic effect of trifluoromethyl group, it is significant to study bR using trifluoro analog of retinal. The binding study with the apoprotein will be reported in a separate paper.

Experimental

¹H-Nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Bruker AM 400 or a Varian EM-390L spectrometer in CDCl₃. ¹⁹F-Nuclear magnetic resonance (¹⁹F-NMR) were recorded at 56.4 MHz on a Varian EM-360L spectrometer in CDCl₃, and chemical shifts are reported in ppm relative to benzotrifluoride as an external standard (higher field was assigned as negative). ¹³C-NMR were recorded at 100.6 MHz on a Bruker AM 400 spectrometer. Infrared (IR) spectra were recorded on a Jasco A302 infrared spectrophotometer. Absorption spectra (ultraviolet (UV)) were recorded on a Hitachi MPF-4 spectrophotometer. The electron impact (EI)- and chemical ionization (CI)-mass spectra (MS) were recorded on a Hitachi M-80. In CI-MS, isobutane was used as the reagent gas. Anhydrous tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone under an argon atmosphere just before use. Anhydrous hexane and *N,N*-dimethylformamide (DMF) were distilled from CaH₂ under an argon atmosphere. Medium pressure column chromatography (MPLC) was performed with a silica gel prepacked column (Kusano, HS-101-1), with detection at 320 or 360 nm.

1,2,6,7,8,8a-Hexahydro-3-methoxy-8a-methyl-5-trifluoromethylnaphthalene (3) CF₃I (10 ml) was added to a pyridine solution (10 ml) of 2-methoxy-3,4,4a,5,6,7-hexahydro-4a-methylnaphthalene (2) (6.1 g, 34.2 mmol) in a 300 ml quartz tube by using vacuum line and the vessel was sealed with a grease-free stopcock. The resulting solution was irradiated with a 100 W high pressure Hg lamp for 33 h at room temperature. The cooled reaction mixture was diluted with ether and washed with saturated

NaHSO₃. The separated organic phase was washed with H₂O, 1 N HCl, saturated NaHCO₃ and brine successively before drying (MgSO₄). The filtrate was concentrated to give a crude oil. Purification by column chromatography on silica gel (hexane—EtOAc=20:1) gave 3 (6.6 g, 78%). ¹H-NMR δ : 1.06 (3H, s), 1.2—1.8 (6H, m), 2.1—2.5 (4H, m), 3.64 (3H, s), 5.63 (1H, brs). ¹⁹F-NMR ppm: 5.83 (s). CI-MS m/z : 247 (M+1).

4,4a,5,6,7,8-Hexahydro-4a-methyl-8-trifluoromethyl-2(3H)-naphthalenone (4) A solution of 3 (6.5 g, 27 mmol) was treated with 80% CF₃COOH (30 ml) at 0 °C and the mixture was stirred at room temperature for 5 h. The mixture was poured into ice-H₂O and extracted with ether. The organic phase was washed with H₂O, saturated NaHCO₃ and brine before being dried (MgSO₄). The filtrate was concentrated to give a crude oil, which was purified by flash column chromatography on silica gel (hexane—EtOAc=4:1) and subsequent distillation (bp 112 °C/2 mmHg) to give pure 4 (3.75 g, 61%). IR (neat): 1680 cm⁻¹. ¹H-NMR δ : 1.25 (3H, s), 1.45—1.95 (6H, m), 2.1—2.5 (4H, m), 6.0 (1H, s). ¹⁹F-NMR ppm: -3.83 (d, J =9 Hz). EI-MS m/z : 232. High-resolution MS m/z : Calcd for C₁₂H₁₅F₃O: 232.1074. Found: 232.1089.

4,4a,5,6,7,8-Hexahydro-2-ethynyl-4a-methyl-8-trifluoromethyl-2(3H)-naphthalenol (5) A hexane solution of *n*-BuLi (16 mmol) was added to a solution of trimethylsilylacetylene (1.6 g, 16 mmol) in THF (15 ml) at -78 °C and the mixture was stirred at room temperature for 1 h. The ketone 4 (3.5 g, 15 mmol) in THF (5 ml) was added to the above solution at -78 °C and the mixture was stirred for 3 h at 0 °C. After addition of saturated NH₄Cl, the mixture was extracted with ether. The combined ether layer was washed with saturated NaHCO₃ and brine before being dried (MgSO₄). Concentration of the filtrate gave a crude product, which was directly treated with a 1 M solution of *n*-Bu₄NF (12 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with ether and the solution was washed with H₂O and brine before being dried (MgSO₄). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (hexane—EtOAc=10:1) to give 5 (2.62 g, 61%). IR (neat): 3300 cm⁻¹. ¹H-NMR δ : 1.1 (3H, s), 1.5—2.1 (10H, m), 2.5 (1H, s), 5.6 (1H, brs). ¹⁹F-NMR ppm: -3.83 (d, J =9 Hz). CI-MS m/z : 259 (M+1).

1,2,6,7,8,8a-Hexahydro-3-ethynyl-8a-methyl-5-trifluoromethylnaphthalene (6a) **1,5,6,7,8,8a-Hexahydro-3-ethynyl-8a-methyl-5-trifluoromethylnaphthalene (6b)** and **1,2,6,7,8,8a-Hexahydro-3-acetyl-8a-methyl-5-trifluoromethylnaphthalene (7)** Nafion-H (810 mg) was added to a solution of 5 (2.6 g, 10 mmol) in CCl₄ (5 ml), and the mixture was stirred at room temperature for 17 h. The filtrate was concentrated to give a crude residue, which was purified by column chromatography on silica gel (hexane→hexane—EtOAc=10:1). Less polar oil 6a (370 mg, 15%). IR (neat): 3310 cm⁻¹. ¹H-NMR δ : 1.10 (3H, s), 1.4—1.8 (6H, m), 2.25 (4H, brs), 3.0 (1H, s), 6.85 (1H, brs). ¹⁹F-NMR ppm: 6.00 (s). CI-MS m/z : 241 (M+1). More polar oil 6b (100 mg, 10%). IR (neat): 3310 cm⁻¹. ¹H-NMR δ : 1.1 (3H, s), 1.3—1.7 (6H, m), 2.15 (2H, d, J =6 Hz), 2.85 (1H, s), 5.95 (1H, brs), 6.20 (1H, d, J =6 Hz). ¹⁹F-NMR ppm: -3.16 (d, J =9 Hz). The ketone 7 was also isolated as the most polar oil (240 mg, 10%).

Hydration of 6a A hexane solution (2 ml) of 6a (270 mg, 1.1 mmol) was added to a vigorously stirred solution of Hg₂O (yellow) (30 mg, 0.14 mmol) in H₂O—H₂SO₄ (20/1, 15 ml) and the resulting mixture was stirred at 40 °C for 4 h. The mixture was then extracted with ether and the organic phase was washed with H₂O, saturated NaHCO₃ and brine before being dried (MgSO₄). Concentration of the filtrate and the purification of the residue by silica gel TLC plate (hexane—EtOAc=20:1) gave 7 (150 mg, 51%). IR (CCl₄): 1670 cm⁻¹. ¹H-NMR δ : 1.0 (3H, s), 1.2—1.9 (10H, m), 2.3 (3H, s), 7.45 (1H, s). ¹⁹F-NMR ppm: 6.0 (s). CI-MS m/z : 259 (M+1).

(2E)- and (2Z)-3-(1,2,6,7,8,8a-Hexahydro-8a-methyl-5-trifluoromethylnaphthalene-3-yl)-2-butenal (9a and 9b) Diethyl cyanomethylphosphonate (102 mg, 0.58 mmol) was added to a suspension of 60% NaH in mineral oil (23 mg, 0.58 mmol) in THF—DMF (7/1, 2.4 ml) at 0 °C. The mixture was stirred for 10 min at the same temperature. To the resulting clear solution was added a solution of 7 (150 mg, 0.58 mmol) in THF (1 ml) at 0 °C and the whole was stirred at room temperature for 1 h. After being quenched with 1 N HCl, the mixture was extracted with ether. The combined organic layer was washed with H₂O, saturated NaHCO₃ and brine before being dried (MgSO₄). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane—EtOAc=10:1) to give a stereoisomeric mixture of 8 (87 mg, 53%). A stereoisomeric mixture of 8 was employed in the next step without further separation. A solution of 8 (40 mg, 0.142 mmol) in hexane (1 ml) was treated with a hexane solution of DIBAL-H (0.21 mmol) and the mixture was stirred at 0 °C for 0.5 h. A mixture of silica gel (260 mg), H₂O (50 μ l) and ether—hexane (1/1, 0.6 ml) was added to the reaction mixture. After being

stirred for 30 min at 0 °C, the mixture was filtered through Celite–MgSO₄. Concentration of the filtrate and the purification (silica gel TLC plate, hexane–EtOAc = 10:1) of the residue gave a mixture of two stereoisomers (**9a** and **9b**, ratio 4.6/1). Less polar oil (**9b**) (6 mg, 14%). ¹H-NMR δ: 1.1 (3H, s), 1.2–1.85 (10H, m), 5.9 (1H, dd, *J* = 1.5, 7.5 Hz), 6.45 (1H, br s), 9.65 (1H, d, *J* = 7.5 Hz). ¹⁹F-NMR ppm: 6.0 (s). EI-MS *m/z*: 284. High-resolution MS *m/z*: Calcd for C₁₆H₁₉F₃O: 284.1387. Found: 284.1397. More polar oil (**9a**) (26 mg, 64%). ¹H-NMR δ: 1.03 (3H, s), 1.2–1.9 (10H, m), 2.3 (3H, s), 6.15 (1H, d, *J* = 7.5 Hz), 7.0 (1H, br s), 10.2 (1H, d, *J* = 7.5 Hz). ¹⁹F-NMR ppm: 6.0. EI-MS *m/z*: 284. High-resolution MS *m/z*: Calcd for C₁₆H₁₉F₃O: 284.1387. Found: 284.1412.

Methyl (2E,4E,6E)-3,7-Dimethyl-7-(1,2,6,7,8,8a-hexahydro-8a-methyl-5-trifluoromethylnaphthalene-3-yl)-2,4,6-heptatrienoate (11) A solution of methyl 4-diethylphosphono-3-methyl-2-butenate (**10**)⁷ (45 mg, 0.18 mmol) in THF (0.5 ml) was treated with *n*-BuLi in hexane (0.12 mmol) at –78 °C and the solution was stirred for 10 min at the same temperature. A solution of **9a** (26 mg, 0.09 mmol) in THF (0.5 ml) was added to the above solution and the mixture was stirred at room temperature for 1 h. After addition of saturated NH₄Cl, the mixture was extracted with ether. The organic layer was washed with H₂O, saturated NaHCO₃ and brine before being dried (MgSO₄). The filtrate was concentrated and the residue was purified by MPLC (hexane–EtOAc = 10:1) to give **11** (34 mg, 98%). ¹H-NMR³ δ: 1.03 (3H, s, 1-Me), 2.07 (3H, s, 9-Me), 2.34 (3H, s, 13-Me), 1.2–2.4 (10H, m), 3.71 (3H, s, COOMe), 5.8 (s, 1H, 14-H), 6.36 (1H, d, *J* = 15 Hz, 12-H), 6.44 (1H, d, *J* = 11 Hz, 10-H), 6.76 (1H, br s, 7-H), 7.03 (1H, dd, *J* = 11, 15 Hz, 11-H). EI-MS *m/z*: 380 (M⁺). High-resolution MS *m/z*: Calcd for C₂₂H₂₇F₃O₂: 380.1961. Found: 380.1947.

(2E,4E,6E)-3,7-Dimethyl-7-(1,2,6,7,8,8a-hexahydro-8a-methyl-5-trifluoromethylnaphthalene-3-yl)-2,4,6-heptatrienal (1) A solution of DIBAL-H in hexane (0.28 mmol) was added to a solution of **10** (27 mg, 0.07 mmol) in hexane–ether (1/2, 1 ml) at –78 °C, and the mixture was stirred for 10 min at the same temperature. A mixture of silica gel (300 mg), H₂O (50 μl) and hexane–ether (1/1, 0.2 ml) was added to the reaction mixture at –78 °C and the whole was stirred at room temperature for 1 h. The mixture was

then filtered through Celite–MgSO₄ and the filtrate was concentrated to dryness to give a residue. The residue was dissolved in ether (5 ml) and stirred with active MnO₂ (170 mg, 1.9 mmol) for 5 min at room temperature. Filtration of the mixture through Celite and concentration of the filtrate gave a crude oil, which was purified by MPLC (hexane–EtOAc = 15:1) to give **1** (15 mg, 66%). UV λ_{max}^{MeOH} nm (log ε): 382 (4.62). ¹H-NMR³ δ: 1.03 (3H, s, 1-Me), 2.07 (3H, s, 9-Me), 2.34 (3H, s, 13-Me), 1.2–2.5 (10H, m), 5.99 (1H, d, *J* = 8 Hz, 14-H), 6.44 (1H, d, *J* = 15 Hz, 12-H), 6.48 (1H, d, *J* = 11 Hz, 10-H), 6.8 (1H, br s, 7-H), 7.16 (1H, dd, *J* = 11, 15 Hz, 11-H), 10.1 (1H, d, *J* = 8 Hz, 15-H). ¹³C-NMR ppm: 13.18, 14.32, 17.52, 22.93, 23.27, 25.45, 32.65, 36.59, 36.79, 122.12, 122.45, 126.66, 127.60 (*J*_{C–F} = 188 Hz), 129.50, 132.60, 136.06, 140.31, 141.53, 144.58, 154.44, 191.09. ¹⁹F-NMR ppm: 4.99 (s). EI-MS *m/z*: 350. High-resolution MS *m/z*: Calcd for C₂₁H₂₅F₃O: 350.1856. Found: 350.1841.

References and Notes

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