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A stereoselective synthesis of ethyl 9-*cis*-7,8-didehydro-19-trifluoromethylretinoate

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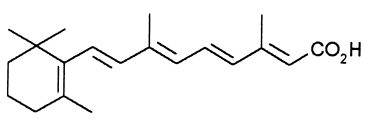
Abstract

The design and synthesis of ethyl 9-*cis*-7,8-didehydro-19-trifluoromethylretinoate was described. The key step is the Sonogashira reaction of ethyl 3-iodo-4,4,4-trifluoro-2(*Z*)-butenoate **2** with terminal alkyne **3**.

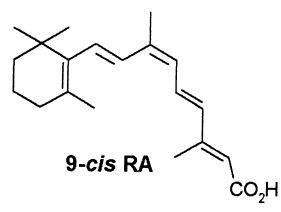
Keywords: Trifluoromethylated; Retinoids

1. Introduction

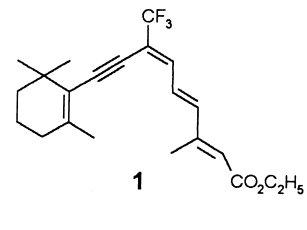
Retinoids, natural and synthetic analogs of vitamin A, are potent molecules that can effect a variety of fundamental biological processes including cell differentiation and proliferation and apoptosis [1,2]. The nuclear receptors, the RARs and RXRs have retinoic acid (RA) and 9-*cis*-retinoic acid (9-*cis* RA) as ligand molecules, respectively. Current research efforts in this field have focused on searching for conformationally restricted retinoids in order to elucidate the biological functions of each receptor [3,4]. With a view towards replacing the disubstituted double bonds with alkynes to provide rigidity [5] and to explore the effect of a trifluoromethyl group on chemical and physical properties [6,7], we were interested in designing and preparing of ethyl 9-*cis*-7,8-didehydro-19-trifluoromethylretinoate **1**.



RA



9-*cis* RA



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2. Results and discussion

Liu et al. have reported the synthesis of 9-*cis*-19,19,19-trifluororetinal by using the Reformatsky reaction of cyclocitral with trifluoromethylated bromo C_5 ester ($BrCH_2(CF_3)C{=}CHCO_2R$) in the key step [8], but the yield of this reaction was low (30% yield). Following our previous work describing the regio- and stereo-specific preparation of ethyl 3-iodo-4,4,4-trifluoro-2(*Z*)-butenoate **2** [9,10], we decided to employ **2** as building block for the preparation of **1** (Scheme 1). The Sonogashira reaction of **2** with terminal alkyne **3** afforded the conjugated (2*Z*)-en-ynoic acid derivative containing a trifluoromethyl group **4** in 85% yield. This ester underwent dehydration with phosphorus oxychloride in pyridine to the diene-yne ester **5**. The ester **5** was converted to the aldehyde **6** by DIBAL-H reduction and subsequent MnO_2 oxidation. The configuration of trisubstituted double bond in **6** was assigned by ^{19}F NMR spectroscopy ($\delta_F = -9.8$ ppm for trifluoromethyl group in **6** (using CF_3CO_2H as an external standard, upfield positive)). The δ_F value for the CF_3 group was close to -10.0 ppm which is diagnostic for the CF_3 group and CHO group being *trans* oriented. Under classical conditions using *n*-butyl lithium as base [11], the reaction of **6** with the C_5-phosphonate **7** did not proceed satisfactorily. The Emmons-Hoener reaction was carried out successfully using LDA to give the target

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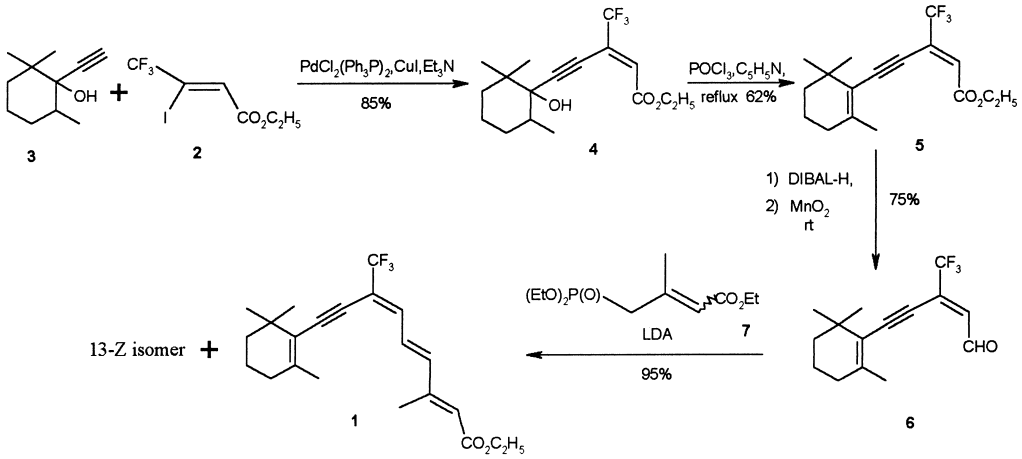

Scheme 1. Synthesis of **1**.

molecule **1** and its 13-*Z* isomer (**1** : 13-*Z* = 1 : 1), which can be separated by column chromatography. The stereochemistry (*E*-form) of the 11,12-double bond in **1** and its 13-*Z* isomer was determined on the basis of the coupling constants of the 11-H signal in the NMR spectrum.

3. Experimental

^{19}F NMR spectra (56.4 Hz) were recorded on a Varian-360A instrument using CF_3CO_2H as an external standard, upfield positive. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer with tetramethylsilane as the internal standard. All chemical shifts are expressed in ppm. The mass spectra were recorded on a Finnigan-MAT-8430 mass spectrometer. IR spectra were recorded as KBr discs on a Shimadzu IR-440 Spectrometer. Terminal alkyne **3** was prepared by a literature procedure [12]. Light petroleum ether refers to the fraction with distillation range 60–90°C.

3.1. Preparation of compound 4

To a three-necked, round-bottomed flask were added ethyl 3-iodo-4,4,4-trifluoro-2(*Z*)-butenoate **2** (360 mg, 1.2 mmol), alkyne **3** (220 mg, 1.3 mmol), CuI (13 mg, 0.07 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.03 mmol) and triethylamine (5 ml) under nitrogen. The reaction mixture was stirred at room temperature for 24 h. Diethyl ether (10 ml) and 5% aqueous HCI (10 ml) were added to the flask. The organic layer was washed with brine (2 × 20 ml), dried (Na_2SO_4), and flash chromatographed (petroleum–ethyl acetate = 20 : 1) to yield **4** (330 mg, 85%). ^{19}F NMR ($CDCl_3$) δ: −10.0 (s); ^{1}H NMR ($CDCl_3$) δ: 1.00–1.58 (m, 15H), 1.29 (t, J = 7.0 Hz, 3H), 1.90–1.93 (m, 1H), 2.65 (br, 1H), 4.25 (q, J = 7.0 Hz, 2H), 6.58 (s, 1H); MS (*m/e*): 332 (M^+, 17.0), 303 (25.0), 259 (66.9), 69 (100.0), 55 (90.8); IR: 3495, 2934, 2873, 2217, 1733, 1635, 1464, 1370, 1328, 1307, 1287, 1259, 1191, 1030 cm^{-1}; HRMS Calcd for $C_{17}H_{23}F_3O_3$; 332.1599, Found: 332.1599.

3.2. Preparation of compound 5

The hydroxyalkynoate **4** (0.55 g, 1.6 mmol) was added to a solution of phosphorus oxychloride (0.38 g, 2.5 mmol) in pyridine (8 ml) at room temperature. After 15 min of stirring at room temperature and 7 h at reflux, the reaction was cooled to 0°C and saturated aqueous sodium bicarbonate was added (10 ml). After extraction with ether, the combined organic layers were washed with 10% aqueous hydrochloric acid and brine, dried (Na_2SO_4), and evaporated in vacuo to give, after flash chromatography (petroleum–ethyl acetate = 50 : 1) **5** (0.31 g, 62%). ^{19}F NMR ($CDCl_3$) δ: −10.0 (s); ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 6H), 1.30 (t, J = 7.0 Hz, 3H), 1.47–1.52 (m, 2H), 1.57–1.67 (m, 2H), 2.00 (s, 3H), 2.09(t, J = 7.0 Hz, 2H), 4.26 (q, J = 7.0 Hz, 2H), 6.48 (s, 1H). MS (*m/e*): 315 (M^+ + 1,21.0), 313 (M^+, 17.3), 299 (26.0), 285 (100.0), 271 (42.0) 163 (40.0). IR: 2963, 2937, 2870, 2184, 1730, 1634, 1602, 1459, 1462, 1364, 1286, 1255, 1196 cm^{-1}. HRMS Calcd for $C_{17}H_{21}F_3O_2$: 314.1494, Found: 314.1476.

3.3. Preparation of compound 6

DIBAL-H (3.0 ml, 5.7 mmol, 1.5 M in toluene) was added to a solution of **5** (0.7 g, 2.23 mmol) in toluene (5 ml) at −78°C. After 30 min of stirring at room temperature, the reaction was cooled to 0°C and 20% aqueous hydrochloric acid (10 ml) was added. After extraction with ether, the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the alcohol which was used in the next reaction without further purification. A mixture of the alcohol (0.44 g, 1.06 mmol), activated MnO_2 (1.0 g) and dichloromethane (16 ml) was stirred at room temperature for 6 h under nitrogen. Then the reaction mixture was diluted with dichloromethane and filtered. The inorganic solid was washed with dichloromethane. The combined filtrates were evaporated in vacuo to give pure **6**. ^{19}F NMR ($CDCl_3$) δ: −9.8 (s): ^{1}H NMR ($CDCl_3$) δ: 1.12 (s, 6H), 1.51 (t, J = 5.7 Hz, 2H), 1.60–1.68

(m, 2H), 1.94 (s, 3H), 21.11 (t, $J = 6.0$ Hz, 2H), 6.58 (d, $J = 7.8$ Hz, 1H), 10.19 (d, $J = 7.8$ Hz, 1H). MS (*m/e*): 271 ($M^+ + 1$, 24.3), 270 (M^+, 42.2), 255 (100.0), 241 (29.7), 200 (71.2). IR: 2694, 2871, 1693, 1590, 1364, 1262, 1194, 1154 cm^{-1}. HRMS Calcd for $C_{15}H_{17}F_3O$: 270.1231, Found: 270.1232.

3.4. Preparation of compound **1**

To a solution of triethyl 3-methyl-4-phosphonocrotonate (184 mg, 0.69 mmol) in THF (10 ml) at −78°C was added LDA (0.7 ml, 0.7 mmol, 1 M in THF). After stirring for 15 min, the solution containing the ylide of triethyl phosphonocrotonate was added to a solution of **6** (150 mg, 0.55 mmol) in THF (10 ml) at −78°C. The reaction mixture was warmed to room temperature, and quenched with saturated aqueous NH_4CI (15 ml). After extraction with ether, the combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give, after flash chromatography (petroleum-ether = 50 : 1) **1** (95 mg). ^{19}F NMR ($CDCI_3$) δ: −12.0 (s); ^1H NMR ($CDCI_3$) δ: 1.25 (s, 6H), 1.29 (s, 3H), 1.32 (t, $J = 7.0$ Hz, 3H), 1.48–1.53 (m, 2H), 1.59–1.68 (m, 2H), 1.95, (s, 3H), 2.05–2.11 (m, 2H), 2.32 (s, 3H), 4.19 (q, $J = 7.0$ Hz, 2H), 5.90 (s, 1H), 6.58 (d, $J = 15.3$ Hz, 1 h), 6.89 (d, $J = 11.0$ Hz, 1H), 7.11 (dd, $J = 15.3$, 11.0 Hz, 1H). MS (*m/e*): 380 (M^+, 19.9), 365 (30.0), 334 (20.6), 291 (60.9), 277 (35.2), 251 (100.0), 23.7 (70.6). 211 (41.2), 165 (36.3), 122 (37.2), 69 (46.2), 41 (42.2); IR: 2964, 2183, 1713, 1616, 1570, 1455, 1373, 1292, 1264, 1226, 1159, 1133, 1049, 801, 706 cm^{-1}. HRMS: Calcd for $C_{22}H_{27}F_3O_2$: 380.1973, Found: 380.1974.

Acknowledgements

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