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Synthesis of the 9-fluoro analogues of disparlure

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Abstract

Starting from a propargylic fluoride, a three step sequence led to syn and anti 9-fluoro analogues of the disparlure pheromone. During these studies an unusual C–C bond cleavage of an epoxide has also been discovered.

Keywords: Propargylic fluoride; Allylic fluoride; DAST; Epoxide; Pheromone; 9-Fluorodisparlure

1. Introduction

The introduction of fluorine in organic molecules strongly modifies their physical, chemical and biological properties [1–8]. It led for instance to new drugs or to useful pharmacological tools [9]. Developments have also appeared in the field of pheromones; Prestwich and Graham for instance reported an elegant study [10] on disparlure **1**, the pheromone of the Gipsy Moth. The synthesis and biological evaluation of a series of analogues allowed them to build a model for the active site of the epoxide hydrolase of this pheromone (Scheme 1).

In particular, they prepared the 6,6-difluoro analogue (**2**) and the corresponding 9,9-difluoro analogue (**3**). The biological tests revealed that **3** was a potent inhibitor in suppressing the metabolism of disparlure by the *L. dispar* epoxide hydrolase. Therefore, it appeared to us important to prepare also the two syn (**4**) and anti (**5**) stereoisomers of the 9-monofluorinated analogues of disparlure.

In this communication we report a short synthesis of both derivatives, in racemic form. A very unusual C–C ring opening of the epoxide has also been observed during these studies.

2. Results and discussion

The synthesis started from the propargylic fluoride **6** easily accessible by reaction of DAST with the corresponding alcohol [11]. Alkylation with 5-methyl-1-bromo hexane gave **7** in 79% yield (Scheme 2). The semi-hydrogenation, using Lindlar's catalyst, gave the olefin **8** with a *Z*-configuration ($^3J_{HH} = 10.5$ Hz). This reaction was rapid, quantitative and easily monitored by ^{19}F NMR (376 MHz, $CDCl_3$) directly on the crude reaction mixture (**7**:$\delta = -170.46$ ppm; **8**:$\delta = -170.69$ ppm).

The epoxidation of **8**, using metachloroperbenzoic acid, gave a 1:1 mixture of syn **4** and anti **5** stereoisomers which could be separated by flash chromatography on silica gel. Their stereochemistry was deduced from the NMR data.[1] In particular, the vicinal coupling constants indicate that these molecules probably adopt the preferred conformations represented in Scheme 2. This appears to be due essentially to the steric interactions produced by both alkyl chains *R* and *R*'. It is worthy to note that epoxidation of allylic fluoride **8** is non stereoselective. This is in sharp contrast with the epoxidation of corresponding alcohol **9** which is known to give **10** in a highly stereoselective process [10,12]. Since C–OH and C–F bonds have similar steric and electronic

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[1] Selected spectroscopic data 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.25 (dtd, 1H, $J_{HF} = 47.8$, $J = 8.0$; $J = 4.2$); 3.02 (tdd, 1H, $J = 5.7$, $J = 4.0$, $J_{HF} = 1.0$); 2.95 (ddd, 1H, $J = 8.0$, $J = 4.0$, $J_{HF} = 3.0$); 1.86−1.65 (m, 2H); 1.65−1.17 (m, 23H); 0.88 (t, 3H, $J = 6.7$); 0.87 (d, 6H, $J = 6.6$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 91.1 ($J_{CF} = 168.2$); 57.5; 56.6 ($J_{CF} = 37.4$); 38.9; 34.0 ($J_{CF} = 21.4$); 32.0; 29.59; 29.56; 29.52; 29.4; 28.0; 27.9; 27.3; 26.8; 24.6 ($J_{CF} = 3.7$); 22.8; 22.72; 22.69; 14.2. ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ: −188.1 (dddd, $J = 47.8$, 30.6, 20.4, 3.0). EIHRMS (M^+) for $C_{19}H_{37}OF$ calcd 300.2828, found 300.2830.

5: ^{1}H NMR (400 MHz, C_6D_6) δ: 4.41(dtd, 1H, $J_{HF} = 49.7$, $J = 8.5$; $J = 3.6$); 2.99 (ddd, 1H, $J_{HF} = 9.9$, $J = 7.9$, $J = 4.4$); 2.76 (tdd, 1H, $J = 7.1$, $J = 4.4$, $J_{HF} = 3.1$); 1.75−1.1 (m, 25H); 1.03 (t, 3H, $J = 6.7$); 0.98 (d, 6H, $J = 6.6$). ^{13}C NMR (100 MHz, C_6D_6) δ: 93.2 ($J_{CF} = 169.8$); 57.7 ($J_{CF} = 24.1$); 55.8 ($J_{CF} = 8.7$); 39.1; 32.7 ($J_{CF} = 22.2$); 32.3; 29.9; 29.8; 29.7; 28.8; 28.3; 27.6; 27.4; 24.9 ($J_{CF} = 3.6$); 23.1; 22.8; 14.4. ^{19}F {^{1}H}NMR (376 MHz, C_6D_6) δ: −187.4 (ddddd, $J = 49.5$, 29.3, 15.8, 9.9, 3.1). EIHRMS (M^+) for $C_{19}H_{37}OF$ calcd 300.2828, found 300.2830.

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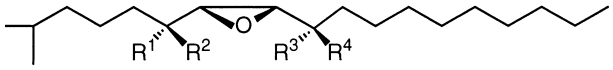


1 : $R^1 = R^2 = R^3 = R^4 = H$
2 : $R^1 = R^2 = F$; $R^3 = R^4 = H$
3 : $R^1 = R^2 = H$; $R^3 = R^4 = F$
4 : $R^1 = R^2 = R^3 = H$; $R^4 = F$
5 : $R^1 = R^2 = R^4 = H$; $R^3 = F$

Scheme 1

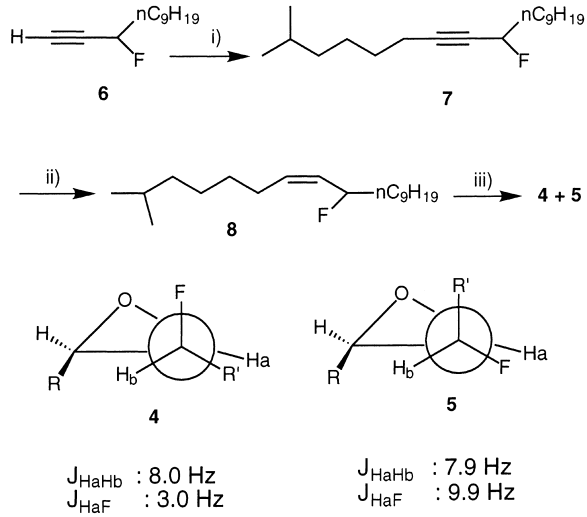
properties, the epoxidation of **8** affords indirect evidence for the role of hydrogen bonding in the transition states of these reactions [13].

Another attractive alternative for the preparation of **5** (and/or **4**) was the direct fluorination of alcohol **10**. The reaction with DAST occured smoothly at room temperature but yielded unexpected results (Scheme 3). Careful examination of the crude reaction mixture using ^{19}F NMR did not give any evidence for **5** (or **4**). Furthermore, there was no evidence for other fluorinated epoxides such as **11** resulting from a well known Payne type rearrangement. The only compound obtained in this reaction was vinylic ether **12** (Scheme 3).

Although somewhat sensitive, **12** could be isolated in 76% yield after flash chromatography on silica gel (Eluent: pentane containing 1% Et_3N), and characterized by spectroscopic data.[2] Noteworthy also was the fact that only the *E* isomer was obtained in this process: the coupling constant $^3J_{HH}$ (12.3 Hz) is characteristic for the trans vinyl ether [14].

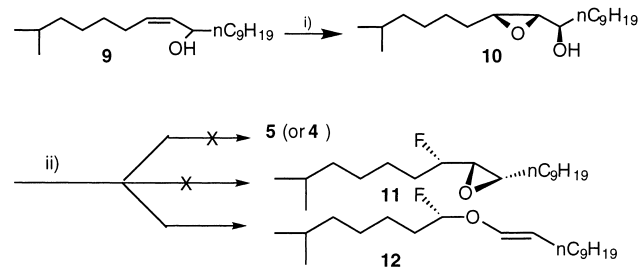
If the C–O bond opening in epoxides is routinely used in synthesis, the C–C bond cleavage is a more rare process. Examples include the formation of 1,3-dipoles (carbonyl yields) but this reaction usually requires high temperature (over 110°C) and electron-withdrawing substituents on the heterocycle [15]. Radical type reactions have also been reported more recently [16]. To the best of our knowledge such a C–C opening of epoxide, at room temperature and under nucleophilic reaction conditions, has not previously been reported. We are currently studying the mechanism of this reaction as well as its scope and limitations.

In conclusion we have designed a short and efficient sequence towards both stereoisomers of 9-fluorodisparlure. Extension to enantiomerically pure compounds appears possible since, starting propargylic fluoride is now accessible in optically active forms [17]. This is under active study



i) BuLi (1.2eq), HMPA, THF -50°C, 1H, then 5- methyl-1-bromohexane, (2eq), 4h, (79%) ; ii) H_2, Lindlar's catalyst, Py/Pentane RT, 3h, (95%) ; iii) m-CPBA (2eq), CH_2Cl_2, 40°C, 5h, (73%).

Scheme 2



i) m - CPBA (2eq), CH_2Cl_2, RT, 4h, (78%)[10] ;
ii) DAST (1.1eq), CH_2Cl_2, RT, 10mn, (76%).

Scheme 3

in order to obtain a better understanding of the structure activity relationship for this important pheromone.

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[2] Selected spectroscopic data 12: ^1H NMR (400 MHz, $CDCl_3$) δ: 6.25 (dd, 1H, $J = 12.3$, $J_{HF} = 1.1$); 5.39 (dt, 1H, $J_{HF} = 64.4$, $J = 5.0$); 5.19 (dt, 1H, $J = 12.3$, $J = 7.4$); 1.93 (q, 2H, $J = 7.0$); 1.83–1.73 (m, 2H); 1.60–1.10 (m, 21H); 0.88 (t, 3H, $J = 6.6$); 0.87 (d, 6H, $J = 6.6$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.6; 111.5 ($J_{CF} = 218.8$); 111.1; 38.8; 34.3; ($J_{CF} = 22.1$); 32.0; 30.1; 29.6; 29.5; 29.4; 29.1; 27.9; 27.4; 27.0; 23.5 ($J_{CF} = 4.8$); 22.7; 22.6; 14.2. ^{19}F {^1H}NMR (376 MHz, $CDCl_3$) δ: −123.7 (dt, $J = 64.4$, $J = 16.0$). EIHRMS (M^+) for $C_{19}H_{37}OF$ calcd 300.2828, found 300.2823.

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