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CHIRAL SYNTHESIS OF A KEY INTERMEDIATE IN *THE PREPARATION OF THE AF TOXIN IIc*

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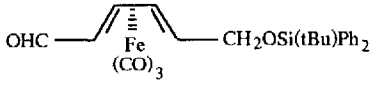
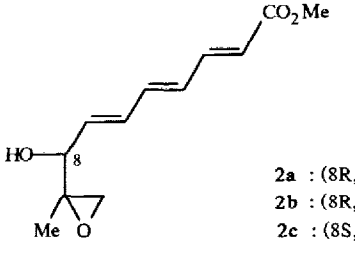
Abstract : The epoxytriene **2a**, which is a key intermediate in the synthesis of the host-specific AF Toxin IIc, is efficiently prepared from the chiral butadiene-tricarbonyliron complex **1**.

The chemical basis of host recognition of plant pathogenic fungi constitute an important problem in plant biology [1]. Several toxins, called AK and AF toxins [2,3] have been isolated recently from Japanese pears and strawberries infected by *Alternaria species*. These toxins appear highly specific, not only for the fruit species, but also for the fungus. The mechanism of action of these messengers has not yet been elucidated, though preliminary studies have established strong correlations between stereostructures and toxicities [4]. It thus appears of much interest to design efficient and stereocontrolled approaches towards these polyenic toxins and syntheses using vitamin C as chiral starting material have been reported recently [4-6].

As part of our program dealing with the use of functionalized and chiral butadiene-tricarbonyliron complexes, such as **1**, in organic synthesis [7], we now describe a short chiral synthesis of the epoxytriene **2a**, a key intermediate in the preparation of the AF toxin IIc [6], and the synthesis of its isomers **2b** and **2c**.

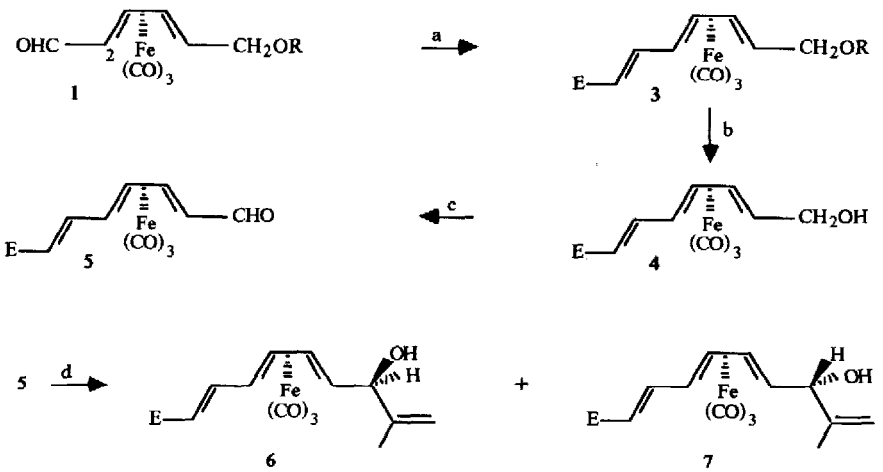


1



2a : (8R,9S)
2b : (8R,9R)
2c : (8S,9R)

The selectively complexed polyenic alcohols **6** and **7** are obtained as indicated in scheme 1. The Wittig-Horner reaction of **1** [of known 2R, 5S absolute configuration [8]] gives the triene **3**.
After desilylation and oxidation, the aldehyde **5** is obtained in 47 % overall yield from **1**. Reaction with the Grignard derivative gives a 2/1 mixture of the alcohols **6** and **7** which are easily separated by chromatography. The φ exo structure with the indicated (S) absolute configuration for the newly created stereogenic center is assigned to the more polar isomer [6, 7, 9] and this was confirmed later by the synthesis of **2a** and **2b**.



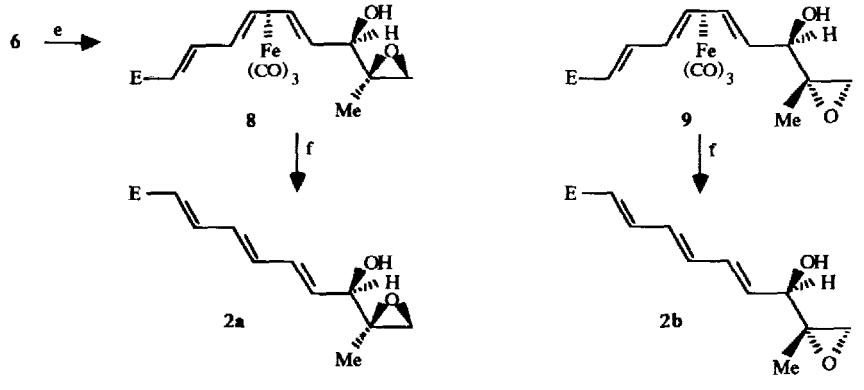
R = -Si(tBu)Ph_2

E = CO_2Me

a : $ECH_2P(O)(OMe)_2$, NaH, THF, -40°C, 165 min., 97 % ; b : $Bu_4N^+F^-$, THF, 0°C, 89 % ; c : PDC, 4Å Mol. sieves, - 40°C, 3 h 45, 60 % ; d : CH_2 = C(Me) MgBr, THF, - 55°C, 75 %.

Scheme 1

In agreement with earlier results [10], the Sharpless epoxidation procedure [$Vo(acac)_2$, tBuOOH] was found to be compatible with the organometallic complex ; as expected from the substitution pattern of this allylic alcohol [11], the reaction proceeds with a high stereoselectivity to give a 93/7 mixture (77 % overall yield) of **8** and **9** which are separated by chromatography (scheme 2) [12]. The erythro configuration

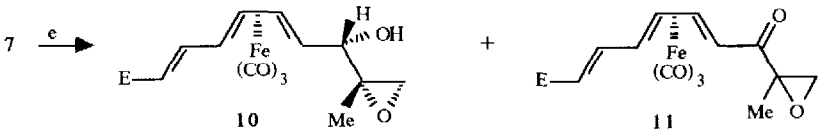


e : tBuOOH, $VO(acac)_2$, toluene, 20°C, 6 h, 77 % ; f : $Ce(NH_4)_2(NO_3)_6$, K_2CO_3, MeOH, 0°C, 1 h, 89 %.

Scheme 2

is attributed to the major diastereoisomer **8** [11] and this was confirmed by decomplexation leading to the (8R,9S) derivative **2a** whose physical and spectroscopic data are in full agreement with those obtained by Irie [4, 13]. The threo (8R, 9R) derivative is obtained in the same way by decomplexation of **9**. Since the AF toxin IIc has already been prepared from **2a** [6], this represents a new formal total synthesis of this compound.

The epoxidation of the diastereoisomeric alcohol **7** also proved to be highly stereoselective giving, after chromatography, the epoxide **10** [14] (72 % yield) together with a small amount (13 %) of the epoxyketone **11** [15] (scheme 3). Decomplexation of **10** under the same conditions (Ce^{4+}, MeOH, -15°C, 89 % yield) give the (8S,9R) derivative **2c**.



Scheme 3

In conclusion, the butadiene-tricarbonyliron complexes are versatile starting materials for the preparation of these polyunsaturated toxins and their structural analogs. The synthesis of the other isomers of the AF toxin is under active investigation in this laboratory [16].

Acknowledgments : We thank Prof. H. Irie, Dr. J.P. Lellouche and Dr. D. Bremner for very fruitful and stimulating discussions.

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7 - For a recent review see R. Grée, Synthesis, 1989, 341.

8 - Due to changes in the priority order, this becomes an (R) stereocenter in **2a** and **2b**.

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10 - J.P. Lellouche, Breton P., Beaucourt J.P., Toupet L., Grée R. Tetrahedron Lett., 1988, 29, 2449.

11 - See for instance : K.B. Sharpless, T.R. Verhoeven, Aldrichimica Acta, 1979, 12, 68.

12 - **8** : ^{1}H NMR (90 MHz ; $CDCl_3$; δ) : 6.84 (d.d. ; J_{23} = 15.3, J_{34} = 10.3 ; H_3) ; 5.89 (d ; H_2) 5.52 to 5.44 (m ; 2H ; H_5 and H_6) ; 3.71 (s ; 3H ; $CO_2C\underline{H}_3$) ; 3.62 (d.d. ; J_{78} = 5.0 ; J_{68} = 2.2 ; H_8) ; 2.87 (d ; J = 4.6 ; H_{10}) ; 2.66 (d ; 1H ; H_{10}) ; 2.39 (d ; 1H ; J = 1.5 ; O<u>H</u>) ; 1.66 (d.d. ; J_{45} = 7.4 ; H_4) ; 1.45 (s ; 3H ; $C\underline{H}_3$) ; 1.36 (d.d. ; J_{67} = 7.5 ; H_7).

I.R. (Nujol, ν cm^{-1}) : 3260 (broad, OH) ; 2060, 2000 and 1960 (C≡O) ; 1705 (C=O) ; 1630 (C=C).

$[\alpha]^{25}_D$ = - 195° (c = 3.1, MeOH).

9 : ^{1}H NMR (90 MHz ; $CDCl_3$; δ) : 6.85 (d.d. ; J_{23} = 15.3, J_{34} = 10.2 ; H_3) ; 5.91 (d ; H_2) 5.61 to 5.40 (m ; 2H ; H_5 and H_6) ; 3.72 (s ; 3H ; $CO_2C\underline{H}_3$) ; 3.28 (d ; J_{78} = 6.0 ; H_8) ; 2.80 (s ; 2H ; H_{10}) ; 2.50 (broad s ; O<u>H</u>) ; 1.74 (d.d. ; J_{45} = 7.8 ; H_4) ; 1.43 (s ; 3H ; $C\underline{H}_3$) ; 1.35 (d.d. ; J = 7.4 ; H_7).

I.R. (film, ν cm^{-1}) : 3270 (broad, OH) ; 2060, 2000 and 1965 (C≡O) ; 1705 (C=O) ; 1630 (C=C).

$[\alpha]^{25}_D$ = - 138° (c = 1, MeOH).

13 - We thank Prof. Irie for sending us copies of the spectra (IR, NMR) of **2a** and **2b**.

14 - **10** : ^{1}H NMR (90 MHz ; $CDCl_3$; δ) : 6.84 (d.d. ; J_{23} = 15.4, J_{34} = 10.4 ; H_3) ; 5.98 (d ; H_2) 5.50 to 5.35 (m ; 2H ; H_5 and H_6) ; 3.71 (s ; 3H ; $CO_2C\underline{H}_3$) ; 3.60 (d ; J_{78} = 4.9 ; H_8) ; 2.85 (d ; J = 4.5 ; H_{10}) ; 2.65 (d ; 1H ; H_{10}) ; 2.38 (s ; 1H ; O<u>H</u>) ; 1.56 (d.d. ; J_{45} = 7.3 ; H_4) ; 1.45 (s ; 3H ; $C\underline{H}_3$) ; 1.35 (d.d. ; J_{78} = 7.7 ; H_7).

I.R. (film, ν cm^{-1}) : 3460 (broad, OH) ; 2040, 1970 (C≡O) ; 1700 (C=O) ; 1620 (C=C).

$[\alpha]^{25}_D$ = - 212° (c = 4.4, MeOH).

15 - The absolute configuration of this epoxide has not been established ;

11 : ^{1}H NMR (90 MHz ; $CDCl_3$; δ) : 6.85 (d.d. ; J_{23} = 15.3, J_{34} = 10.4 ; H_3) ; 6.01 (d ; H_2) 5.92 (d.d. , J_{45} = 8.5 ; J_{56} = 5.2 ; H_5) ; 5.63 (d.d. ; J_{67} = 8.6 ; H_6) ; 3.73 (s ; 3H ; $CO_2C\underline{H}_3$) ; 2.88 (s ; 2H ; H_{10}) ; 2.35 (s ; 1H ; O<u>H</u>) ; 2.13 (d.d. ; J_{45} = 8.5 ; H_4) ; 1.72 (d ; H_7) ; 1.52 (s ; 3H ; $C\underline{H}_3$).

I.R. (nujol, ν cm^{-1}) : 2040, 1990 and 1975 (C≡O) ; 1700, 1660 (C=O) ; 1620 (C=C).

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