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Synthesis of [α-Alkyl β-Hydroxy Diene]Iron Tricarbonyl Complexes of Known Configurations via Trisubstituted Epoxides for the Synthesis of Polyenic Macrolactones.

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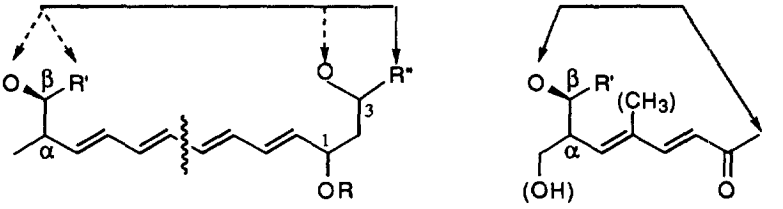
Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Abstract : substituted η^4-(1-oxiranyl-diene) iron tricarbonyl complexes of known configuration are easily synthesized as pure diastereomers. They undergo regiospecific Lewis acid mediated reductions to afford α-alkyl β-hydroxy dienes which represent subunits of various polyenic macrolactones and related natural products. © 1997 Elsevier Science Ltd.

Various antifungal antibiotics are characterized by a conjugated polyenic framework bearing at both ends carbon chains with oxygenated functions, which are connected by lactonization[1].



For a number of the most important of them, an α-alkyl, β-hydroxy carbon chain is located at one end of the polyenic system, the other substituent beginning with a 1,3-diol pattern (Tetrins, Candicidin D, Mepartricins, Partricins, Perimycin, Amphotericin B, Nystatin...) or an α-ketonic chain (Protomycinolide IV, Tylosin, Juvenimicin B_1, Mycinamicins...).

Linear conjugated dienones are readily accessible by Friedel-Crafts acylation of dienes in the form of their tricarbonyl iron complexes[2] and an adjacent 1,3-diol pattern can easily be built up by an aldol reaction between such a dienone complex and an aldehyde[3].

The elaboration of the other pattern is less obvious and we present here our preliminary results in its realization. We have previously reported that $Fe(CO)_3$ complexed dienones can be α-halogenated nearly quantitatively via their silyl enol ethers. In general if diastereomeric α-halodienone complexes are formed, they are easy to interconvert using halide ions, and to separate by simple silica gel chromatography[4]. The highly stereoselective reduction of the ketone carbonyl followed by stereospecific base cyclization yields diastereomerically pure epoxides[4,5]. This led us to investigate the possibility of using such epoxides as intermediates for the synthesis of α-alkyl β-hydroxy dienes, taking advantage of the easy ionization of C-O bonds adjacent to the diene $Fe(CO)_3$ unit[6]. A diastereomerically pure trisubstituted epoxide was however

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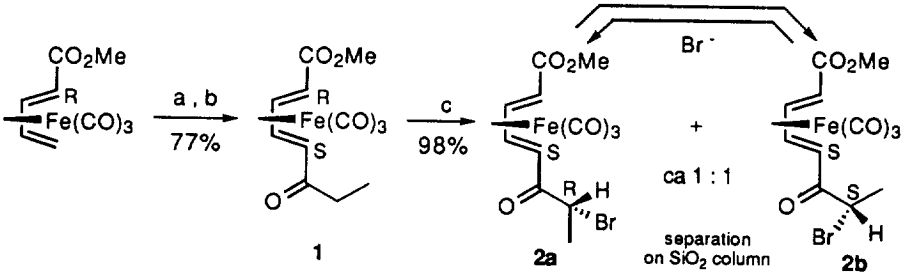
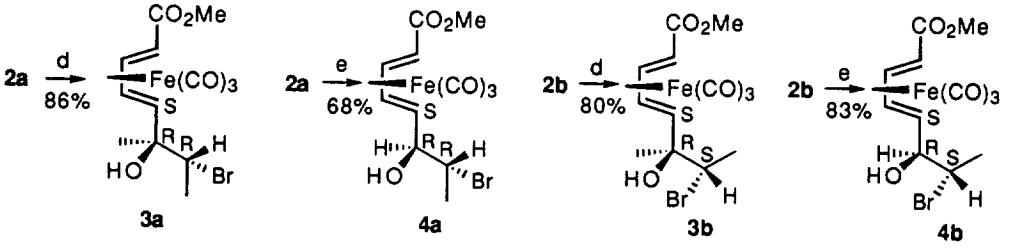
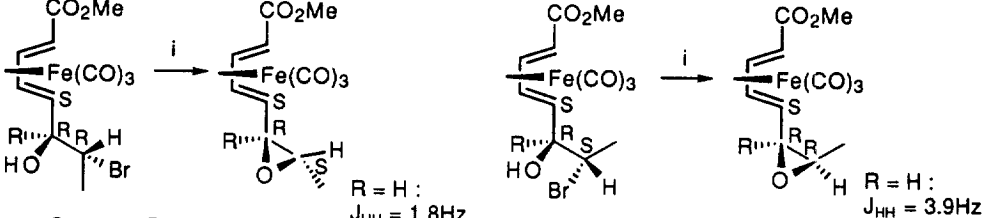
required to give the desired pattern by hydrogenolysis at the α-position (Lewis acid mediated reduction). The reaction of a Grignard or an organolithium reagent with a dienone complex is a highly stereoselective reaction leading to diastereomerically pure tertiary alcohols[7]. However in this case the reaction had to be carried out with α-halogenated dienone complexes bearing also an ester functionality[8]. Methylmagnesium bromide proved to be the reagent of choice here, reacting smoothly at -78° C with both diastereomeric bromodienone complexes **2a** and **2b** to afford solely the corresponding *erythro* and *threo* bromhydrins **3a** and **3b** (to facilitate representation only one enantiomeric series is depicted in the figures). The easily separable bromoketones **2a** (less polar) and **2b** (more polar) were prepared following our usual procedure [reaction of the silyl enol ether with 1,3-dibromo-5,5-dimethylhydantoin (DBA)[4]] from the Friedel-Crafts propionylated product **1** of methyl pentadienoate tricarbonyl iron[2].



a) EtCOCl, $AlCl_3$, 0°C to 20°C ; b) NaOMe, 0°C to 20°C ; c) 1- TfOTMS, Et_3N, CH_2Cl_2, 0°C ; 2- DBA, CH_2Cl_2, -78°C ; d) MeMgBr, THF, -78°C ; e) $NaBH_4$, MeOH, 0°C.



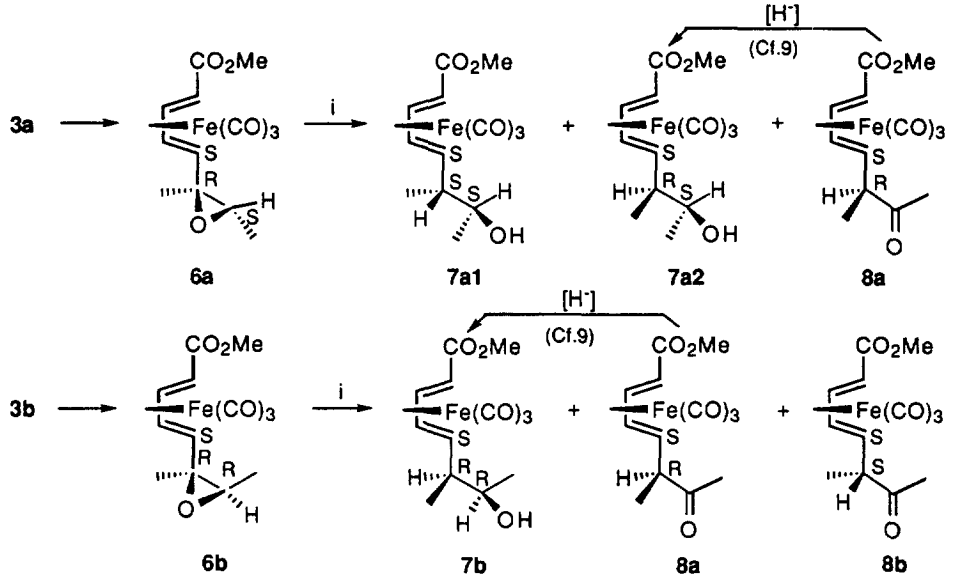
For the assignment of their relative configurations, the bromodienone complexes **2a** and **2b** were reduced completely stereoselectively with $NaBH_4$ to the *erytho* and *threo* bromhydrins **4a** and **4b**, which were cyclized (> 90 % in solution) to the corresponding *trans* and *cis* epoxides **5a** and **5b** (internal S_N2 reaction). Their structure could easily be determined by ^{1}H-NMR.



i) K_2CO_3, 18 crown 6, CH_2Cl_2, 20°C

In view of the critical conditions required for the transformation of tricarbonyl iron coordinated halodienols into disubstituted epoxides[4,5], there was no guarantee that the subsequent cyclization to

trisubstituted epoxides would be successful. However the heterogeneous system K_2CO_3/ether, or better K_2CO_3/CH_2Cl_2, in the presence of 18-crown-6 ether at room temperature worked well, and the cyclization led smoothly to the corresponding *cis*-di-Me and *trans*-di-Me epoxides **6a** and **6b**. The yields are very high (mass balance / NMR, TLC) but the epoxides suffer partial decomposition on concentration of the crude solutions. They were not therefore isolated for the reduction step which followed, but used directly in solution. From several reagents tried, the system $ZnCl_2/NaBH_3CN$[9] gave good results with completely regioselective reduction α to the complexed diene unit.



i): $ZnCl_2$, $NaBH_3CN$, CH_2Cl_2, 20°C, 5-10 min

$ZnCl_2$	$NaBH_3CN$	**7a1**	**7a2**	**8a**	$ZnCl_2$	$NaBH_3CN$	**7b**	**8a**	**8b**
4 eq.	0 eq.	-	-	92%	4 eq.	0 eq.	-	51%	47%
4 eq.	4 eq.	31%	45%	17%	4 eq.	4 eq.	39%	17%	29%
2 eq.	20 eq.	48%	37%	<1%	2 eq.	20 eq.	33%	15%	35%

From the bromhydrin **3a** via the *cis*-di-Me epoxide **6a**, two easily separable diastereomeric monoalcohols **7a1** (less polar) and **7a2** (more polar) were obtained along with the ketone **8a** (single diastereomer). On the other hand, the bromhydrin **3b**, via the *trans*-di-Me epoxide **6b**, gave only one monoalcohol, **7b**, but two diastereomeric ketones, **8a** (more polar, inversion of configuration) and **8b** (less polar, retention of configuration)[10]. The proportion of alcohols to ketones formed is strongly dependent on the ratio of reactants, the ketones being obtained nearly quantitatively by Lewis acid catalysis[11] without addition of a reducing agent. As the ratio $NaBH_3CN$ to $ZnCl_2$ increases, the proportion of ketones formed decreases, disappearing nearly completely in the case of **8a**. In the other series, however, the ketones **8a** and **8b** are always the major products. In the absence of the Lewis acid, no reaction took place under our conditions (CH_2Cl_2, 20° C, 5-10 min reaction time), the work-up yielding only the epoxides. Since the stereochemistry of these reductive openings of epoxides could not be predicted with certitude, the structures of the alcohols **7a1**, **7a2** and **7b** were determined by X-ray diffraction[12]. It appears that the alcohols **7a1** and **7a2** obtained by reduction of the *cis*-

di-Me epoxide complex **6a** are formed respectively with retention (rapid *exo*-reduction of the cation resulting from the ionization of the epoxide in *trans*-antiperiplanar conformation / Fe) and inversion (*exo*-reduction of the cation after rotation, or concerted reduction of the Lewis-acid complexed epoxide) of configuration at the α-carbon atom and that the single alcohol **7b** obtained from the *trans*-di-Me epoxide complex **6b** is formed with inversion. In all cases the oxygen-bearing β-carbon retains its configuration. This work was done in the racemic series, but starting from optically active dienone complexes of known configuration[5,6,13], the reaction sequence would allow the choice of all absolute configurations.

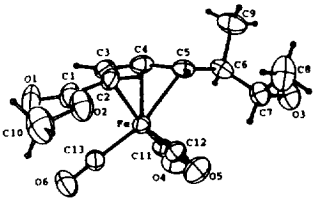
In conclusion, we could achieve the synthesis of diastereomerically pure trisubstituted epoxides bound to a diene iron tricarbonyl fragment and convert them into complexed α-alkyl β-hydroxy dienes of known configurations which are substructures of various polyenic macrolides and related natural products[14].

Acknowledgement : we are grateful to BASF for repeated gifts of $Fe(CO)_5$.

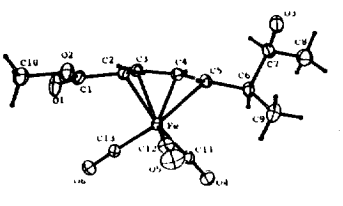
References and Notes:

The indicated yields are for isolated products which gave satisfactory C,H-analysis, IR and ^{1}H-NMR spectra.

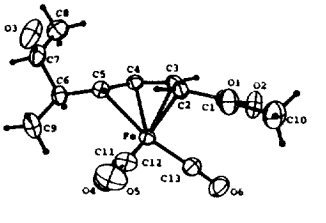
1. Macrolide Antibiotics, S. Omura Ed., Academic Press, Inc. **1984**, Part II : Polyene Macrolides.
2. Unfunctionalized dienes : Graf, R.E.; Lillya, C.P. *J. Organomet. Chem.* **1979**, *166*, 53-56 and ref. ; functionalized dienes : Franck-Neumann, M.; Sedrati, M.; Mokhi, M. *New J. Chem.* **1990**, *14*, 471-480.
3. Franck-Neumann, M.; Bissinger, P. ; Geoffroy, P. *Tetrahedron Lett.* **1997**, *38*, 4477-4478 and ref.
4. Franck-Neumann, M.; Abdali, A.; Colson, P.J.; Sedrati, M. *Synlett* **1991**, 331-334.
5. (-)-LTA_4 methyl ester : Franck-Neumann, M.; Colson, P.J. Synlett **1991**, 891-894.
6. For a recent review, cf : Donaldson, W.A. Aldrichimica Acta 1997, 30, 17-24.
7. Franck-Neumann, M.; Chemla, P.; Martina, D. *Synlett* **1990**, 641-642.
8. The most suitable substituents for the elaboration of the polyenic framework are probably formyl or hydroxymethyl groups, but these groups can not be present from the beginning (incompatibility with Friedel-Crafts conditions[2]). Subsequent transformation of an ester group is however easy[5].
9. This reagent is a reducing agent for aldehydes, ketones and acid chlorides but not for esters : Kim, S.; Oh, C.H.; Ko, J.S.; Ahn, K.H.; Kim, Y.J. *J. Org. Chem.* **1985**, *50*, 1927-1932.
   The reduction of epoxides was not mentioned, but we observed in the present case that it was much more rapid than the reduction of ketones[9].
10. The reaction is rapid at 20° C (5-10 min). Longer times are not suitable since the ketones are then also reduced, in a non stereospecific manner. For instance the isolated ketone **8a** gave after 5 h at 20° C with 4 eq. $NaBH_3CN$ and 4 eq. $ZnCl_2$, the alcohols **7a2** and **7b** (75 %, 1:1) along with minor amounts of the corresponding methyl-epimerized alcohols and ca. 4 % starting material. This allowed the determination of the configuration of **8a/8b**.
11. Cf. for dimethyl styrene oxides : Guyon, R.; Villa, P. *Bull. Soc. Chim. Fr.* **1975**, 2593-2598.
12. The details of the X-ray structure determinations will be given in the full paper. Ortep views of **7a1**, **7a2**, **7b** (Service Commun de Rayons X de la Federation de Recherche Chimie de l'Université Louis Pasteur) :



7a1 F = 86°C



7a2 F = 85°C



7b F = 89°C

13. Franck-Neumann, M.; Briswalter, C.; Chemla, P.; Martina, D. *Synlett* **1990**, 637-640.
14. The same substructure (dienic side chain) is found for instance in some cyanobacteria toxins such as nodularin, microcystin or motopurin (cyclic pentapeptides) : Rinehart, K.L.; Harada, K.I.; Namikoshi, M.; Chen, C.; Harris, C.A. *J. Amer. Chem. Soc.* **1988**, *110*, 8557-8558 ; De Silva, E.D.; Williams, D.E.; Andersen, R.J.; Klix, H.; Holmes, C.F.B.; Allen, T.M. *Tetrahedron Lett.* **1992**, *33*, 1561-1564.

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