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Aldol Condensation Reactions of Chiral (Dienone) Tricarbonyliron Complexes. 2[1]. Enantioselective Synthesis of the Dienic Polyols Streptenols C and D (Metabolites from *Streptomyces Fimbriatus*).

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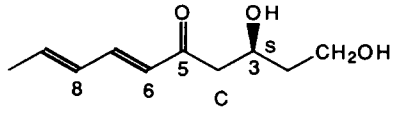
Abstract : The trimethylsilyl enol ether of (3,5-heptadien-2-one) tricarbonyliron **1** undergoes a highly stereoselective cross aldol reaction with $TiCl_4$-coordinated β-o.methoxybenzyloxypropanal yielding after deprotection the ketodiol complex **9**. Direct decomplexation or decomplexation after totally metal induced stereoselective reduction to the triol **10**, led to Streptenols C and D. The natural dextrorotatory enantiomers were obtained from the readily available pure **(+)-1**. © 1997 Elsevier Science Ltd.

Linear conjugated dienones coordinated to iron as tricarbonyliron complexes are converted highly stereoselectively into complexes of 1-dienols by reduction with metal hydrides (ψ endo alcohols)[2a] or reaction with organometallic reagents[2b]. This provides easy access to optically active secondary and tertiary alcohols when the starting material is a resolved chiral complex[2b]. (1-acetyldiene)tricarbonyliron complexes are particularly interesting in this context since they undergo high yield aldol condensation reactions with aldehydes, leading thus to chiral 1,3-diols[1]. Depending on the nature of the aldehyde and the conditions used, the reaction proceeds more or less diastereoselectively, but in general yields pure diastereomers owing to their efficient separation by simple silica gel column chromatography.

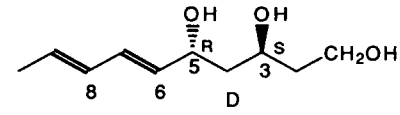
We investigated several modalities of the aldol condensation reaction of (dienone)tricarbonyliron complexes as a key step for the synthesis of chiral polyols, differing in the way the optical activity was introduced :

- resolution of the starting (1-acetyl acyclic diene) tricarbonyliron (this paper)
- use of an optically active hydroxyaldehyde, allowing at the same time the resolution of the racemic starting complex
- use of an enantiomerically pure complex, obtained by completely stereoselective complexation of an optically active ligand (natural product).

In this paper, we describe an efficient synthesis of two metabolites from *Streptomyces Fimbriatus*, the Streptenols **C** [(+)-(3S,6E,8E)-deca-6,8-dien-5-one-1,3-diol] and **D** [(+)-(3S,5R,6E,8E)-deca-6,8-diene-1,3,5-triol][3].



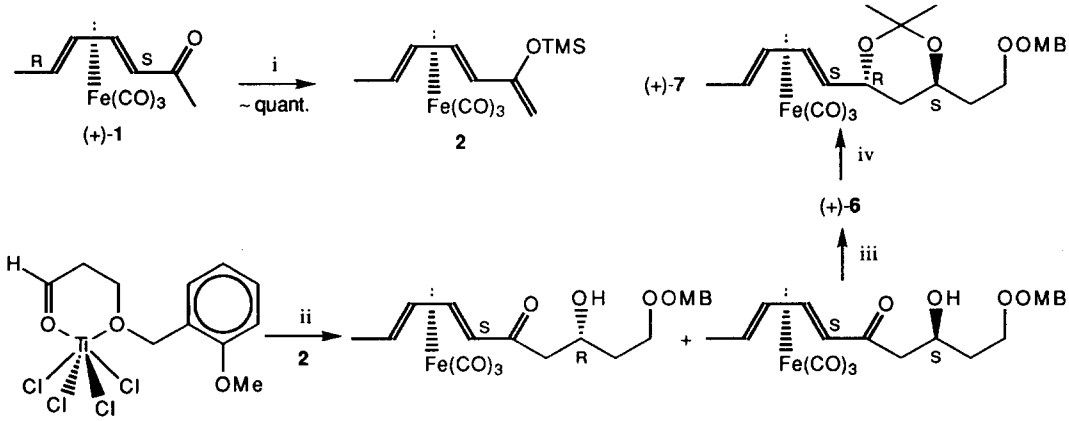
Streptenols



✆ : (33).03.88.41.68.11 ; Fax : (33).03.88.60.42.48 ; e-mail : mfneu@chimie.u-strasbg.fr

For this synthesis, the aldol condensation reaction was to be performed between (3,5-heptadien-2-one) tricarbonyliron **1** and an alcohol-protected β-hydroxypropanal. It quickly became apparent that the greatest diastereoselectivity was obtained using Mukaiyama conditions[4], by chelation of the β-alkoxyaldehyde with $TiCl_4$ prior to reaction with the silyl enol ether[5]. Of several protecting groups tested, o.methoxybenzyl ether (OMB) proved to be the most effective here, in terms of yield, diastereoselectivity and deprotection[6].

The optically active starting complex (+)-**1** ($[\alpha]_D$ = +377, ee > 96 %) of known[2b] absolute configuration (3S,6R) was obtained in 80 % yield by reaction of the readily available (+)-complex of sorbic acid[7] with Meldrum's acid, followed by acidic cleavage[8]. By reaction with trimethylsilyl triflate and triethylamine in CH_2Cl_2, the silyl enol ether **2** was obtained nearly quantitatively. *After purification by evaporation of the solvent, precipitation with ether of the triethylammonium salts, decantation and elimination of the solvent, it was added in solution in CH_2Cl_2 to an equimolecular mixture of the protected β-hydroxypropanal* **3** [9] *and $TiCl_4$ in CH_2Cl_2 at -78° C.* With this order of addition, a mixture of two easily separable (SiO_2 chromatography) diastereomeric ketols (+)-**4** and (+)-**5**[10] was obtained in the ratio 1:10 (ratio of isolated yields). The minor less polar diastereomer (+)-**4** and the major more polar diastereomer (+)-**5** were reduced (100 % ψ endo alcohols) and converted into the acetonides of the obtained 1,3-diols.



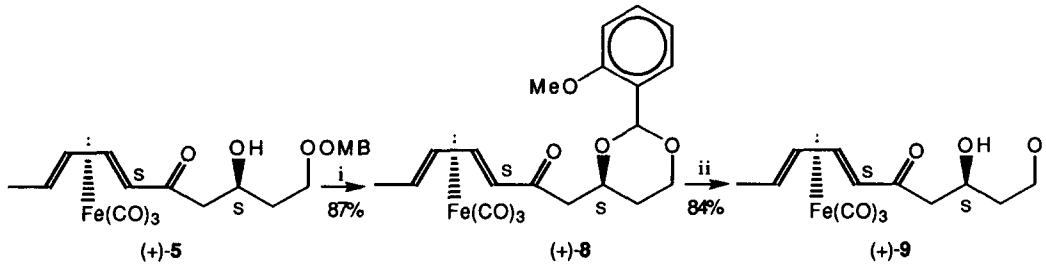
3 (1.1 eq / (+)-**1**) (+)-**4** (8% / (+)-**1**) (+)-**5** (79% / (+)-**1**)

i : TMSOTf (1.1 eq), Et_3N (1.5 eq), CH_2Cl_2, -78°C → +20°C ii : 1) **2**, CH_2Cl_2, -78°C 2) $NaHCO_3$, H_2O

iii : BH_3•Me_2S, THF, 20°C, 58 % iv : $Me_2C(OMe)_2$, acetone, pTsOH, 20°C, 71 %

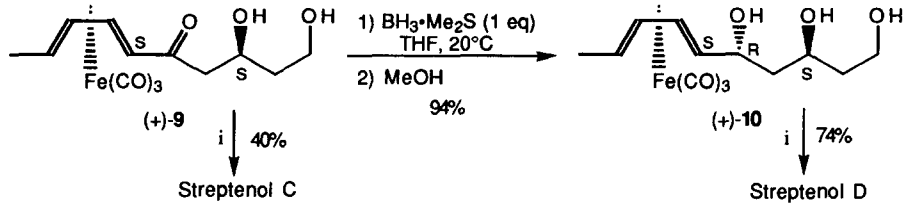
This allowed the unambiguous assignment of their configurations by examination of the ^{13}C NMR spectra, using the method of Rychnovsky *et al.*[11]. The major ketol (+)-**5** yielded the diol (+)-**6** whose acetonide (+)-**7** showed nearly identical δ values for the acetal methyl groups (24.4 and 24.5 ppm), and is therefore of the anti configuration.

The deprotection of the primary alcohol function of (+)-**5** was achieved by intermediate formation of the acetal (+)-**8**[12], followed by acidic cleavage, to give the complexed ketodiol (+)-**9**[10]. Remarkably, although tricarbonyliron complexes are prone to oxidative decomplexation, the use of the oxidant DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as a reagent for the formation of the acetal (+)-**8** was not a problem here[13], the overall yield for (+)-**9** reaching 73 %.



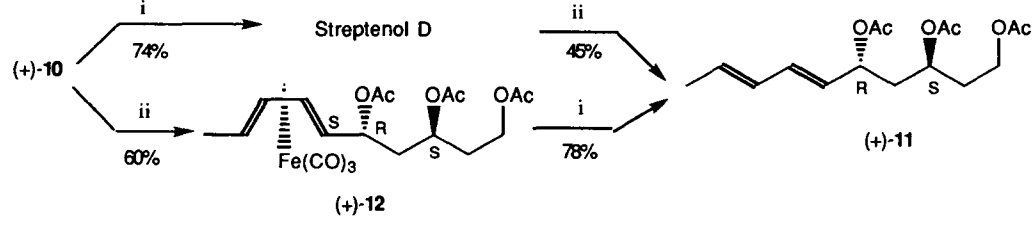
i : DDQ (1.2 eq), CH_2Cl_2, 20°C ii : PPTS, acetone/H_2O, 60° C.

From the complex (+)-**9**, Streptenols C and D were obtained by decomplexation with Ce^{IV} ammonium nitrate (CAN), directly in the case of the former[14], and after completely metal induced stereoselective reduction to the triol complex (+)-**10**[10] for the latter.



i : 1) CAN (5 eq), MeCN/H_2O, 0°C 2) $NaHCO_3$/H_2O

The spectral data of the synthetic Streptenols C and D are consistent with those of the natural products[3a-c]. The $[\alpha]_D$ of our Streptenol C ($[\alpha]_D$ = +24) is also in good agreement with one value reported in the literature ($[\alpha]_D$ = 23.4)[3a], but two other values are given in the literature (+49.3[3b] and +62[3c]) and the situation as to the optical purity is somewhat confusing. However, since the complex (+)-**9** is a pure diastereomer and since partial racemization at the level of the metal-diene attachment is highly improbable, we feel confident that this complex must be nearly optically pure. If partial racemization intervenes, it could only be during the final decomplexation step, which is also unlikely (vide infra). The situation is even more confusing in the case of Streptenol D. Our $[\alpha]_D$ value is low compared to the highest literature values (+4/+8.2[3b] and +35[3c]), but $[\alpha]_D$ values of polyhydroxylated compounds are not always reliable. We therefore prepared the known triacetate (+)-**11**, directly from our Streptenol D and via the complex (+)-**12**. The measured $[\alpha]_D$ were +10 and +15 respectively, which compare well with the literature value of +11.4[3b].



i : 1) CAN (5eq), MeCN/H_2O, 0°C 2) $NaHCO_3$, H_2O ii : Ac_2O, Et_3N, DMAP cat., CH_2Cl_2, 20°C

We can therefore conclude that the Streptenols obtained in our iron mediated synthesis are of at least the same optical purity as the natural products, and are probably nearly enantiomerically pure.

Acknowledgments : we thank the BASF AG, Ludwigshafen, for repeated gifts of pentacarbonyliron.

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5. Different conditions were tested for the aldol reaction of the dienone complex **1** with protected β-hydroxypropanals. The lithium enolate (LDA, THF) gave poor selectivity (nearly 1:1) with the benzyloxyaldehyde and the acetoxyaldehyde. Via the silyl enol ether **2**, the selectivity depended on the protecting group, the Lewis acid used, *and the order of addition of reactants*. With the most convenient order of addition (addition of the aldehyde to the silyl enol ether formed in situ, followed by addition of $TiCl_4$) the β-benzyloxyaldehydes gave mixtures of diastereomeric ketols in excellent overall yields (~ 90 %), but the desired more polar (S,S) diastereomers were always minor products (~ 3 : 1). Under the same conditions, the β-acetoxypropanal gave also mainly the undesired (S,R) diastereomer (~ 10 : 1) which became the *sole* product when the addition order was reversed (addition of the purified silyl enol ether to the preformed aldehyde-Lewis acid complex). With this reversed addition the β-benzyloxyaldehydes gave in excellent yields mixtures of diastereomeric ketols with the desired (S,S) diastereomers now largely major (1 : 5 to 1 : 10) when $TiCl_4$ was the Lewis acid used. With the non chelating $BF_3.Et_2O$, the selectivity was anew reversed in favor of the (S,R) diastereomer (3 : 1) !
6. With the reversed addition and $TiCl_4$, the β-benzyloxypropanals gave mainly the desired (S,S) ketols. However the selectivity was far better with an ortho-methoxybenzyl group (1 : 10), than with a para-methoxybenzyl group (1 : 5). The unsubstituted benzyl ether also gave good selectivity (1 : 10), but we were unable to achieve deprotection by catalytic hydrogenation, and switched therefore to the methoxylated series and oxidative deprotection.
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9. The protected β-hydroxypropanal **3** was prepared in 67 % overall yield via reaction of propane-1,3-diol with o.methoxybenzaldehyde, followed by reductive cleavage of the acetal with Dibal[15] and oxidation (PCC).
10. **(+)-5** : $C_{21}H_{24}FeO_7$ (C,H), orange oil ; **(+)-9** : $C_{13}H_{16}FeO_6$, orange oil ; **(+)-10** : $C_{13}H_{18}FeO_6$, yellow oil ; $[\alpha]_D$ (c=1, $CHCl_3$) : **(+)-5** + 213, **(+)-9** +310, **(+)-10** +2.5 ; IR (CCl_4, cm^{-1}) ν (C≡O) **(+)-5** : 2060, 2000, 1985 ; **(+)-9** : 2061, 2000, 1988 ; **(+)-10**: 2045, 1974 ; ν (C=O) **(+)-5** : 1672, **(+)-9** : 1668; ν (OH) **(+)-5** : 3501, **(+)-9** : 3412, **(+)-10** : 3476 ; ^{1}H-NMR ($CDCl_3$, 200 MHz, ppm/TMS, Hz) : **(+)-5** : δ = 1.22 (dd, 1H, J = 8.2 and 0.7), 1.47 (d, 3H, J = 5.8), 1.54 (m, 1H), 1.72-1.82 (m, 2H), 2.50 (dd, 1H, J = 16.3 and 5.2), 2.60 (dd, 1H, J = 16.3 and 7.3), 3.65-3.78 (m, 2H), 3.84 (s, 3H), 3.86 (d, 1H, J = 2.9), 4.23 (m, 1H), 4.55 (s, 2H), 5.24 (dd, 1H, J = 7.9 and 5.1), 5.79 (ddd, 1H, J = 8.3, 5.1 and 0.8), 6.87-7.29 (4H, arom) ; **(+)-9** : δ = 1.17 (d, 1H, J = 8.3), 1.48 (d, 3H, J = 5.8), 1.57 (m, 1H), 1.63-1.80 (m, 2H), 2.54 (d, 2H, J = 6.1), 2.70 (s, 1H), 3.75 (d, 1H, J = 2.3), 3.81-3.84 (m, 2H), 4.26 (m, 1H), 5.26 (dd, 1H, J = 8.4 and 5.1), 5.79 (dd, 1H, J = 8.8 and 5.6) ; **(+)-10** : δ = 1.08 (t, 1H, J = 7.7), 1.17 (m, 1H), 1.42 (d, 3H, J = 6.2), 1.70-1.90 (m, 4H), 2.28 (s, 2H), 3.33 (s, 1H), 3.70-3.90 (m, 3H), 4.25 (m, 1H), 5.07 (dd, 1H, J = 8.4 and 5.4), 5.14 (dd, 1H, J = 8.3 and 5.3).
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13. The same reaction after decomplexation of **(+)-5** or **(+)-6** gave respectively an acetal which was much more difficult to deprotect than the complex **(+)-8**, and a mixture of monoprotected and acetalized Streptenol C, by oxidation of the allylic alcohol function.
14. Streptenol C was isolated in low yield by decomplexation (40 %). However Streptenol C can also be obtained by oxidation of Streptenol D with MnO_2[3c] or ... DDQ[13].
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