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Aldol condensation reactions of tricarbonyliron complexes. Towards building blocks for the synthesis of carbomycin B/ tylosin macrolide antibiotics and fluorinated analogs

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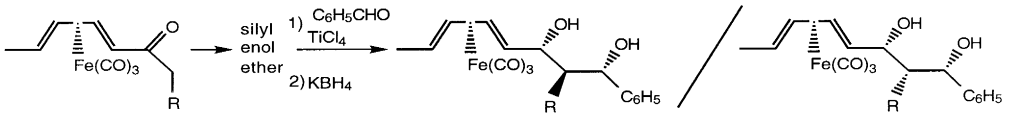
Abstract

Tricarbonyliron complexes of α-methoxyheptadienone **3** and octadienone **8** were reacted as silyl enol ethers with protected β-hydroxypropanal and $TiCl_4$, to give the *syn–syn* aldol condensation products **4** and **11** as major, isolated diastereomers (61 and 45%). Products **4** and **11** were converted into key intermediates of previous total syntheses of carbonolide B and tylonide, in a few steps, including the iron-directed reduction to *syn* diols and partial ozonolysis. The same methodology was used for the high yielding synthesis of a monofluorinated analog.

Diastereomerically pure, easily isolated, 1,2,3-trisubstituted 1,3-diols were obtained by aldol condensation reaction of tricarbonyliron complexes of α-substituted dienones, as silyl enol ethers, and benzaldehyde, in the presence of $TiCl_4$, followed by totally stereoselective reduction (Scheme 1).[1]



Scheme 1.

This promising reaction sequence has now been investigated for the preparation of the advanced building blocks **1** and **2** of previous syntheses of carbonolide B and tylonide (Scheme 2).[2]

The aldol condensation reaction of the trimethylsilyl enol ether of tricarbonyliron α-methoxyheptadienone **3** with *o*-methoxybenzyl-protected β-hydroxy propanal,[3] gave a mixture of diastereomers (78%) when performed simply as a one-pot reaction in the presence of $TiCl_4$ (successive addition of the aldehyde and $TiCl_4$ to the preformed silyl enol ether), according to our previous work.[1] The major *syn–syn*

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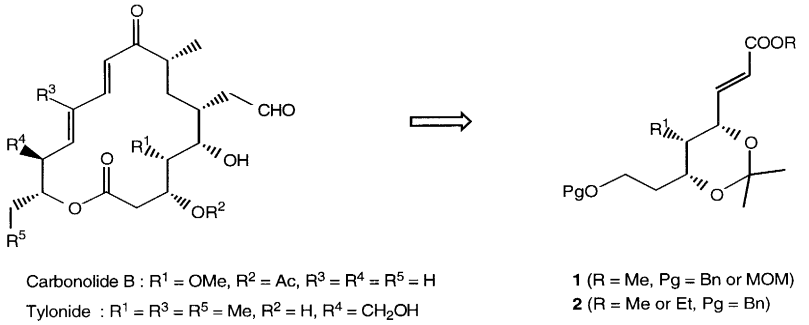
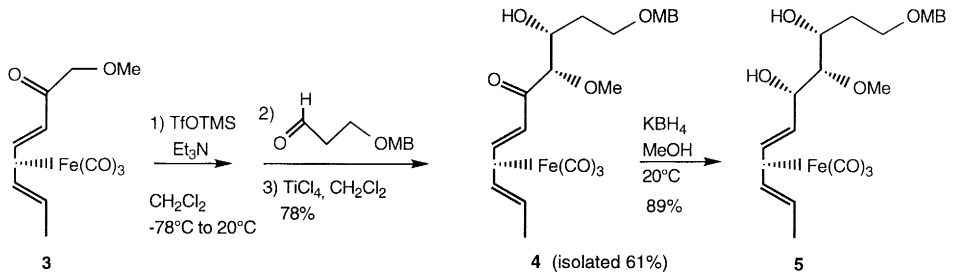


Scheme 2.

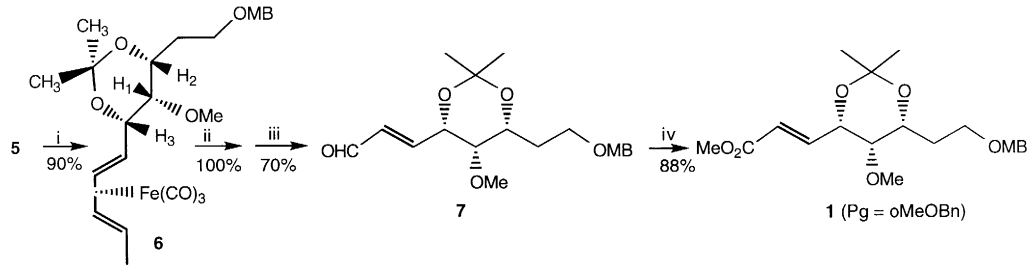
diastereomer **4** could easily be isolated by simple silica gel column chromatography (61%). A subsequent completely stereoselective reduction, which was entirely directed by the iron, gave the polyol derivative **5** with the correct configurations for carbonolide B (Scheme 3).



(The products reported in this preliminary paper have been prepared in racemic form, and stereoisomers drawn in the schemes depict only relative configurations).

Scheme 3.

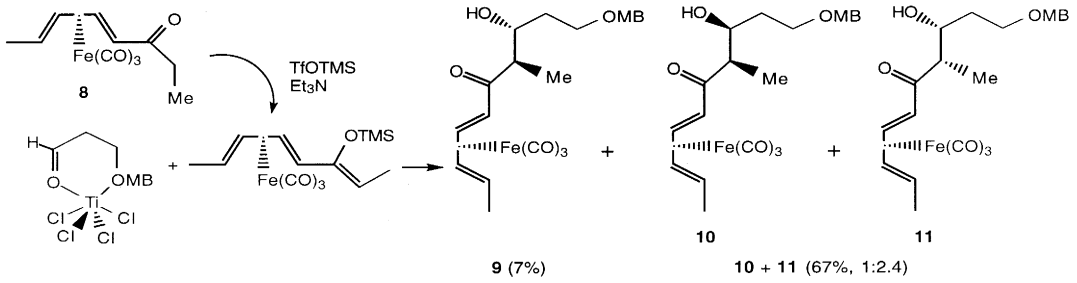
From there, in a few steps, the building block **1** (Pg=*o*-MeOBn) was obtained in 56% overall yield. Alcohol protections afforded the *syn* acetonide **6** (90%), with a *syn* methoxy group (δ $^{13}CH_3$=18.7/29.7; $J_{H1–H2}$ and $J_{H1–H3}$ <2 Hz, ax–eq couplings[1]), which was decomplexed [cerium^{IV} ammonium nitrate (CAN), quant.] and submitted to partial ozonolysis (O_3, CH_2Cl_2/pyridine,[4] −78°C, 70%) to give the pure *E* unsaturated aldehyde **7**. The latter, which is closely related to the structure of the southeastern part of carbonolide B, was transformed into the unsaturated ester **1** (Pg=*o*MeOBn) by Corey's procedure[5] (88%) (Scheme 4).



Scheme 4. (i) $Me_2C(OMe)_2$, acetone, *p*-TsOH cat. 20°C; (ii) CAN, acetone, −78°C; (iii) (1) O_3, pyridine, CH_2Cl_2, −78°C; (2) Me_2S; (iv) KCN, AcOH, MnO_2, MeOH, 20°C

In our model studies of the aldol condensation reaction of tricarbonyliron octa-2,4-dien-6-one **8** with benzaldehyde under Mukayiama conditions, the principal diastereomeric ketol isolated (60%) gave by reduction and protection a *syn* acetonide; however, with an *anti* methyl substituent.[1] On the contrary,

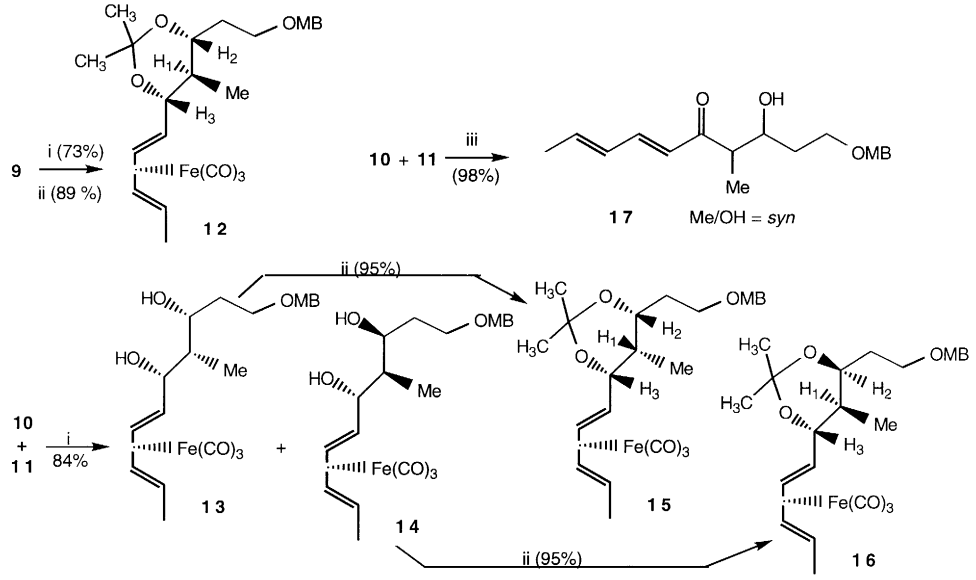
the aldol condensation reaction of the isolated silyl enol ether of **8** with the complex $TiCl_4$/protected β-hydroxypropanal in CH_2Cl_2 at −78°C, essentially gave a mixture of ketols, the major diastereomer **11** now bearing the methyl substituent in a *syn* orientation (Scheme 5).



Scheme 5.

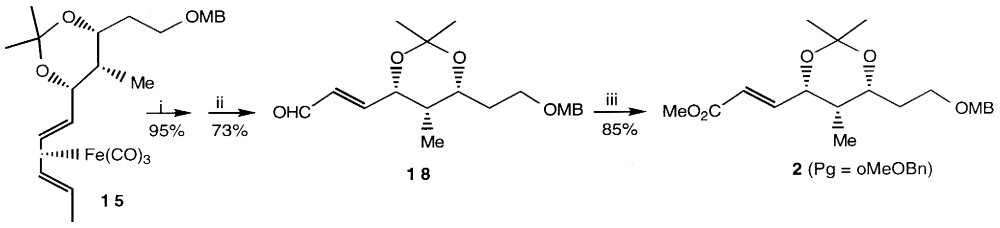
The less polar, minor diastereomer **9** could easily be separated by simple column chromatography (silica gel, hexane/ether; 7%), but the separation of the major products **10** and **11** was difficult under such chromatographic conditions. Fortunately, after reduction, the corresponding diols **13** and **14** were much easier to separate (column chromatography: silica gel, benzene+7% EtOAc), so that the more polar major diol **13** could be isolated in 40% yield, based on the starting ketone complex **8**.

The structures of the different ketols were determined, as usual[1] by reduction to diols and conversion to acetonides which were analyzed by ^{13}C and ^{1}H NMR. The *syn* acetonides **12** and **15** were obtained from the ketols **9** and **11**, respectively, with an *anti* methyl (**12**: δ $^{13}CH_3$=19.3/29.8; J_{H1-H2} and J_{H1-H3} ~10 Hz) and a *syn* methyl substituent (**15**: δ $^{13}CH_3$=19.3/29.8; J_{H1-H2} and J_{H1-H3} ~2 Hz). The ketol **10** gave an *anti* acetonide, **16** (δ $^{13}CH_3$=23.9/24.4). Since the decomplexation (CAN, 98%) of the ketols **10** and **11** gave the same product **17** (racemic compounds), the orientation of the methyl substituent must be *syn* to the hydroxyl group in both series (Scheme 6).



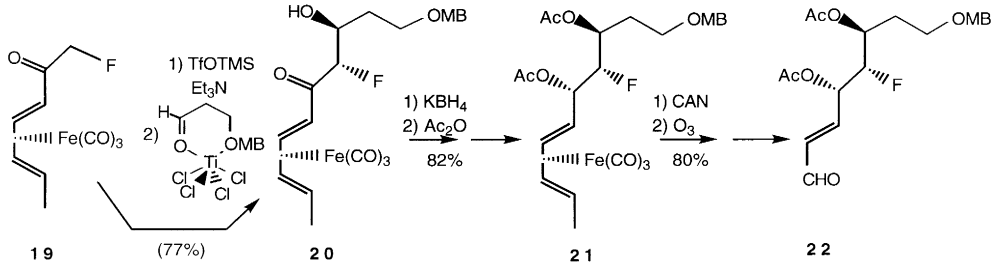
Scheme 6. (i) KBH_4, MeOH, 20°C; (ii) $Me_2C(OMe)_2$, acetone, *p*-TsOH, 20°C; (iii) CAN, acetone, −78°C

By decomplexation and partial ozonolysis of the acetonide **15**, from the major ketol **11**, the *E*-unsaturated aldehyde **18** was obtained, which was similarly converted into the corresponding methyl ester **2** (overall 59%; Pg=oMeOBn) (Scheme 7).



Scheme 7. (i) CAN, acetone, −78°C; (ii) (1) O_3, pyridine, CH_2Cl_2, −78°C; (2) Me_2S; (iii) KCN, AcOH, MnO_2, MeOH, 20°C

The general interest for fluorinated analogs of bioactive compounds led us finally to investigate the aldol condensation reaction of the fluorodienone complex **19**.[1] Under the same reaction conditions (isolated silyl enol ether added to the $TiCl_4$/β-hydroxypropanal complex), one single diastereomer[6] was formed (**20**, isolated 77%), which was converted, via the diacetate **21** (82%) into an *E*-unsaturated aldehyde (**22**, 80%) (Scheme 8).



Scheme 8.

Acknowledgements

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2. The building block **1** was obtained from glucose diacetonide in nine steps with an overall yield of 42%, (Pg=Bn[7]), or 34% (Pg=MOM[8]). The building block **2** was more tedious to obtain, and was prepared in 11 steps with 28% overall yield (methyl ester, Pg=Bn[9]) from a 3-*C*-methyl-D-glucoside which was obtained from D-glucose in 40% overall yield,[10] or in 19 steps from glucose diacetonide in 11% overall yield (ethyl ester, Pg=Bn).[11] Mixtures of *E*- and *Z*-isomers were always obtained.
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6. Which gave an *anti* acetonide (δ $^{13}CH_3$=23.7/24.7; $J_{H1–H2}$ ~6.5 Hz and $J_{H1–H3}$ ~3.4 Hz).
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