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Conjugate addition of organozinc reagents to enones linked to a tricarbonyl iron diene unit. Asymmetric synthesis of a building block of amphotericin B

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Abstract—Conjugate addition of organometallics to enones linked by the ketocarbonyl to tricarbonyliron diene units can be successfully achieved with dialkylzinc reagents, when used in the presence of trimethylsilyl triflate. Organocopper reagents are not well suited, giving only incomplete and partially destructive reactions. The enone complexes are easily obtained by dehydration of aldol condensation products, which is particularly interesting when the aldol reaction is also a resolution (chiral aldehydes). The conjugate addition is not highly diastereoselective, unless the enones are substituted with polar groups (de up to 88% for γ-alkoxylated enones). This conjugate addition reaction was used to synthesize, in two practical steps from the enone **14** (two asymmetric centers), the chlorohydrin **25** (54%, five asymmetric centers), an elaborate intermediate for the synthesis of amphotericin B. © 2002 Elsevier Science Ltd. All rights reserved.

Tricarbonyliron dienone complexes are useful intermediates for the synthesis of chiral products of high enantiomeric purity such as α-functionalized tertiary alcohols[1] or α-functionalized 1,3-diols.[2]

In the first case, highly diastereoselective reactions of the ketocarbonyl with organometallic reagents was turned to account for the synthesis of tertiary pentadienols as single diastereomers (substitution α to the diene).

In the second case, stereoselective aldol condensation reactions of enolates, or more diastereoselectively of silyl enol ethers of alkyldienones, were shown to lead to easily separable diastereomeric ketols, which were reduced highly stereoselectively to 1,3-diols (substitution β to the diene).

We were now interested in the possibility of introducing a substituent γ to the diene by 1,4 addition to tricarbonyliron diene complexes bearing enone side chains.

The conjugate addition of organometallic nucleophiles to α,β-unsaturated esters and ketones is a well documented reaction, whose synthetic utility is largely demonstrated,[3] and diastereoselectivity in conjugate addition to prochiral enones is widely used for asymmetric synthesis. In the iron complexed series, this was illustrated by the addition of alkyllithiums to chiral α,β-unsaturated iron acyls[4] and organolithium and Grignard reagents onto alkylidene malonate substituted tricarbonyliron dienyl complexes.[5,6]

In the general case, hard nucleophiles such as organolithium and organomagnesium reagents give mainly 1,2-addition and copper catalysis or the use of dialkylcuprates or similar copper based reagents is necessary to achieve 1,4-addition.

In the present case, only poor and non reproducible results were recorded when dimethyllithiocuprate or methylcopper BF_3 were reacted with enones linked to a $Fe(CO)_3$ coordinated diene such as **1**, **2** or **3**. Under the original conditions for the conjugate reaction,[7] no 1,4-addition was observed, the starting enones were partially recovered (up to 30%), and only decomplexed enones and unidentified degradation products were formed. These negative results could be due to reactions of the cuprate with the CO ligand[8] or the metal,[9] followed by demetallation. Similar negative results were observed in the tentative reaction of organocuprates with tricarbonyliron tropone[10] and reactive higher order cyanocuprates with a tricarbonyliron benzylidene dienone complex.[11]

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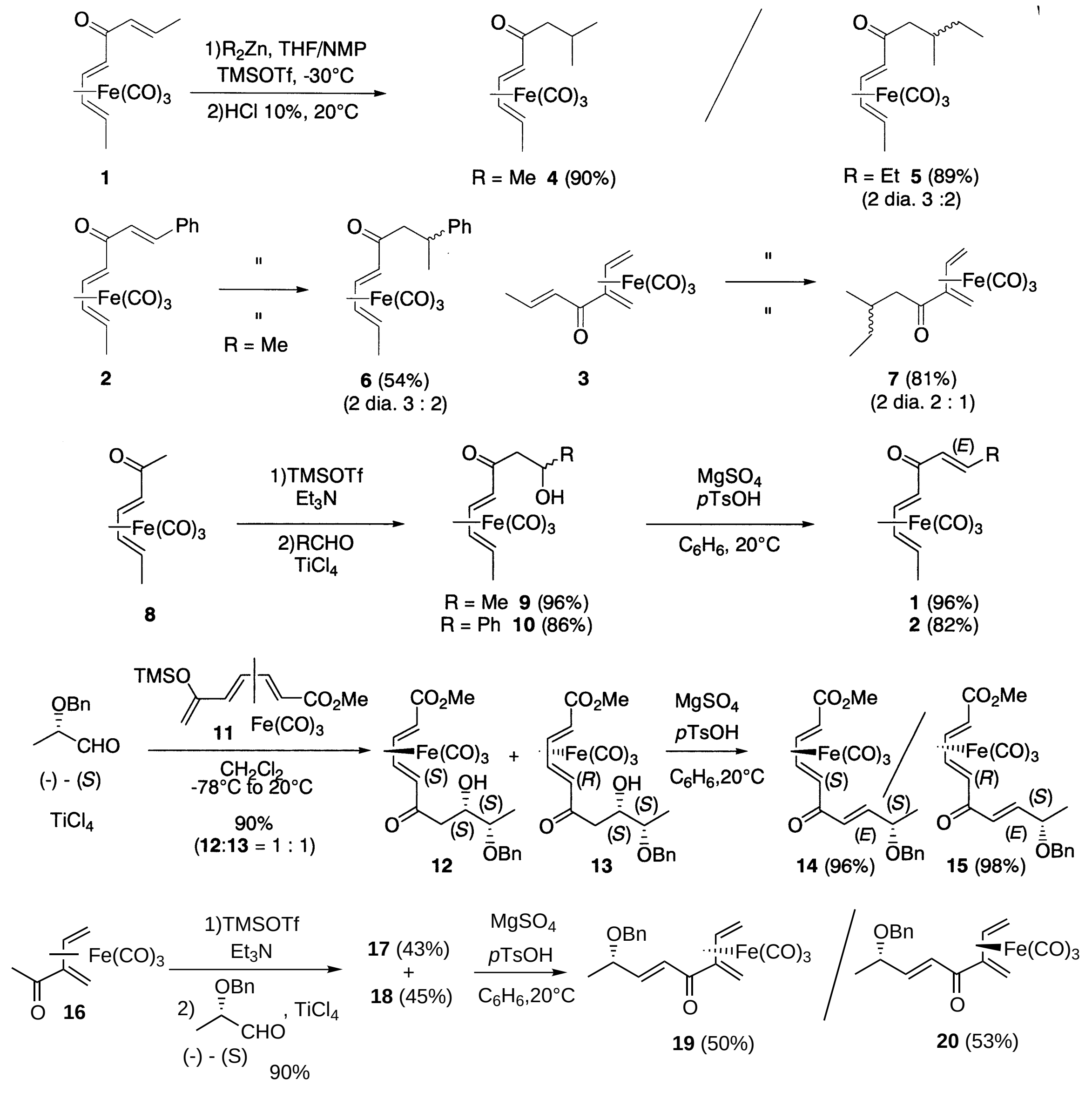
In the presence of trimethylchlorosilane (TMSCl) and triethylamine, 1,4-additions could finally be achieved; however, the methylated silyl enol ethers were obtained in 10–20% yield only, along with decomplexed enones and other non identified decomplexed products (up to 50%). The use of trimethylsilyl triflate (TMSOTf) instead of TMSCl roughly doubled the yield of the 1,4-addition products, but the reaction was still incomplete and partially destructive.

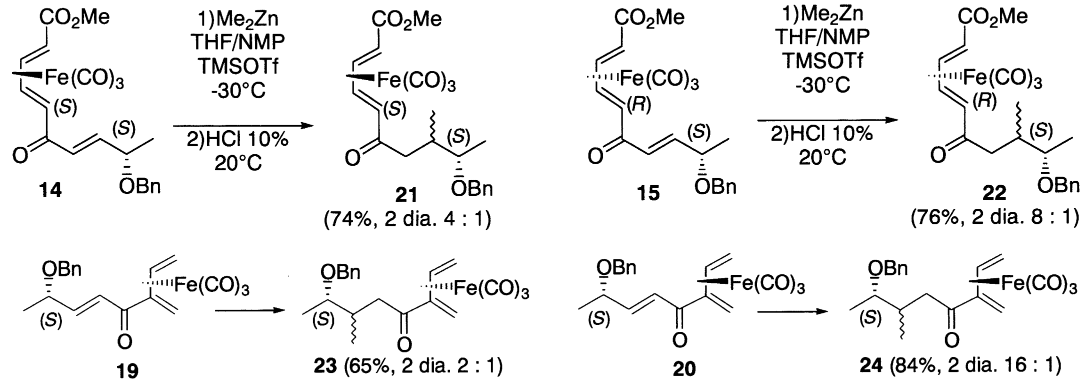
Organocopper reagents seemed therefore not well adapted for reaction with tricarbonyliron coordinated substrates, and we went to diakylzinc reagents, used in the presence of *N*-methylpyrrolidone (NMP) and TMSCl.[12] However, no addition reaction was observed at all between −30 and +20°C under these conditions. In view of our results with organocopper reagents, we used TMSOTf instead of TMSCl and obtained a clean and complete 1,4-addition reaction *when the enone complex, dissolved in THF/NMP (2:3), was successively reacted with dialkylzinc and immediately after with TMSOTf*: The yields were high in general: 80–90%, dropping to ca. 50% for the benzylidene ketone **2**.

The starting enone complexes could be obtained in a number of cases by acylation of tricarbonyliron diene complexes with α,β-unsaturated acid chlorides (Friedel–Crafts reaction at the terminal position[13]), but they were more conveniently prepared, exclusively as *E*-olefins, by dehydration of the ketols which result in high yields from aldol condensation reactions (**9**, **10**). This is particularly interesting when the aldol reaction is performed with chiral functionalized aldehydes such as protected lactaldehydes, and yields resolved complexes, for instance the easily separable complexes **12** and **13**, obtained from the racemic TMS enol ether **11**.

In the butadiene complex series substituted in position 2, enone complexes can be obtained from 2-stannylated precursors by palladium-catalyzed substitution (complex **3**[14]), or from aldol condensation products (**17**, **18**[2a]).



Under our conditions, the complexes **14**, **15**, **19** and **20** with a γ-alkoxyenone side chain, underwent smooth conjugate addition with dimethylzinc to give, with variable diastereoselectivities, the methylated ketones.



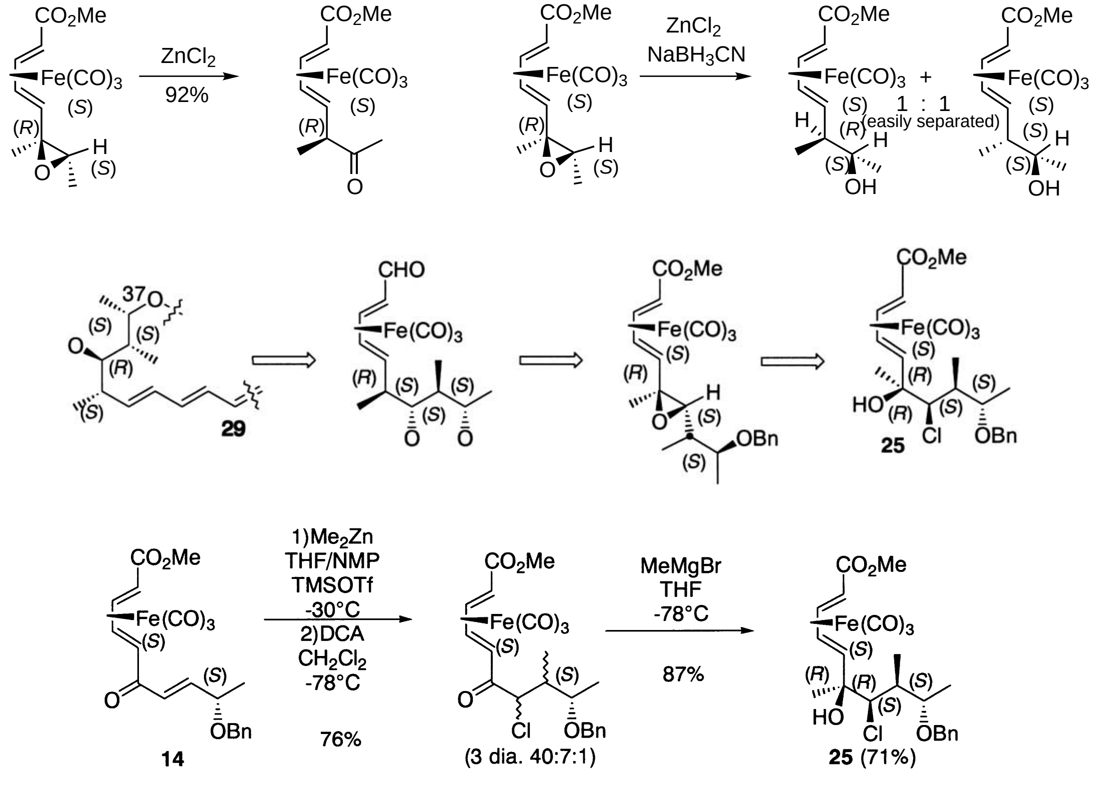
When the inducing effects of the *O*-benzyl and of the $Fe(CO)_3$ groups were cooperative, diastereoselectivities of 8:1 (**22**) and 16:1 (**24**) were observed (NMR). The diastereoselectivities in these favorable cases compare well with the best selectivities reported for 1,4-additions of cuprates on similar non complexed substrates (γ,δ-dialcoxyacrylates ratio = 1:10 to 1:14,[15] γ,δ,ε-trialkoxyacrylate ratio = 1:13[16]) and are far better than with other simple γ-*O*-benzylated electrophilic alkenes (ratio = 1:2[17]).

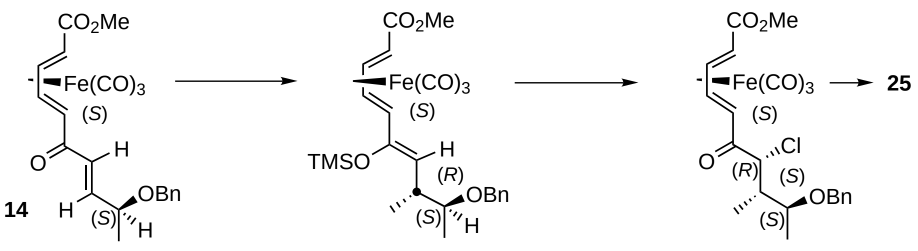
We now made use of this conjugate addition to achieve the synthesis of an elaborate intermediate for the synthesis of the C29–C37 fragment of the antifungal polyenic macrolide antibiotic amphotericin B.

Previous investigations had shown that η_4-(1-oxiranyldiene) tricarbonyliron complexes undergo regiospecific Lewis acid mediated opening of the epoxide ring to give, mainly with inversion of configuration, ketones or, in the presence of reducing reagents such as $NaBH_3CN$, alcohols.[18]

The chlorohydrin **25** would therefore be a suitable precursor for the synthesis of the C29–C37 part of amphotericin B.

As shown, the conjugate addition of dimethylzinc on the enone **14** gave, with a good stereoselectivity, a major β-methylketone, but this major diastereomer could unfortunately not be separated from the minor product. Since more polar diastereomeric complexes such as α-haloketones and alcohols are often easy to separate, we achieved in a one-pot procedure the conjugate addition and the halogenation of the ketone, first





formed as a silyl enol ether, with 1,3-dichloro-3,5-dimethylhydantoin (DCA). The overall reaction (76%) showed a good diastereoselectivity, giving three diastereomers with the major one predominant to more than 80%. Since their separation was still difficult, the mixture was treated directly with methylmagnesium bromide to give three chlorohydrins in the same ratio of ca. 40:7:2. The major, more polar, diastereomer could now be easily isolated by simple SiO_2 column chromatography (yield 71%, yellow crystals, $F = 71°C$, $[\alpha]_D = -75$ (c 1, $CHCl_3$) and completely characterized by X-ray diffraction.[19] It was the required chlorohydrin **25**.[20]

This fortunate outcome can be rationalized if one admits that the methyl and the halogen are both introduced on the less hindered face, opposite to the metal and the *O*-benzyl group, the dienone and the enone parts of **14** being mostly in the *s-cis* conformations, with a completely staggered arrangement of the carbon side chain (cf. X-ray structure[19]).

Acknowledgements

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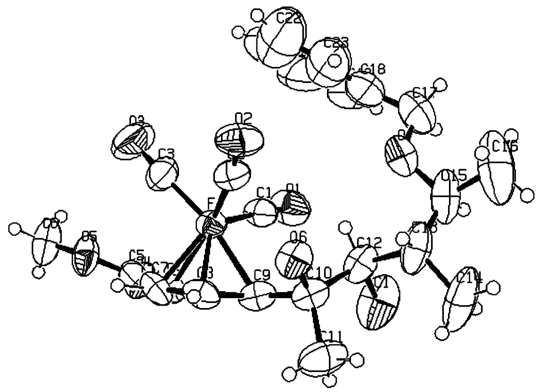
19. The details of the X-ray structure determination will be given in the full paper. (Service Commun de Rayons X de la Faculté de Chimie, ULP, Strasbourg).
Ortep view of **25**:



20. Anal. calcd for $C_{23}H_{27}ClFeO_7$: C, 54.51; H, 5.37. Found: C, 54.62; H, 5.14. IR (CCl_4) ν: 3465, 2063, 2002, 1718 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.97 (1H, m), 1.01 (3H, d, $J = 6.9$ Hz), 1.21 (3H, d, $J = 6.1$ Hz), 1.40 (3H, s), 1.76 (1H, d, $J = 9.1$ Hz), 2.17 (1H, m), 2.27 (1H, s), 3.38 (1H, dq, $J = 9.1$ and 6.1 Hz), 3.64 (3H, s), 4.33 (1H, d, $J = 1.7$ Hz), 4.48 (1H, d, $J = 11.7$ Hz), 4.64 (1H, d, $J = 11.7$ Hz), 5.52 (1H, ddd, $J = 9.1$, 5.2 and 0.9 Hz), 5.80 (1H, ddd, $J = 8.1$, 5.2 and 0.9 Hz), 7.25–7.40 (5H, m). ^{13}C NMR ($CDCl_3$, 50.323 MHz) δ: 13.4, 16.7, 26.4, 69.7, 45.4, 51.7, 71.1, 71.1, 74.4, 75.6, 77.3, 81.8, 84.2, 127.7, 128.0, 128.5, 138.2, 172.7.