



Highly stereoselective biomimetic polyene cyclizations using chiral pentadienol tricarbonyliron complexes

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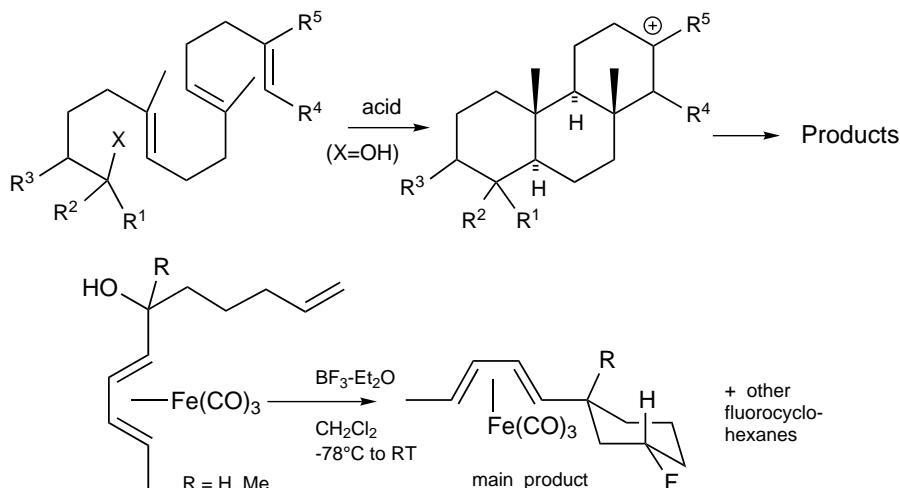
Received 29 October 2001; revised 14 January 2002; accepted 24 January 2002

Abstract—Acyclic *E*-5,9-polyenes linked to chiral 1-pentadienol tricarbonyliron fragments are highly stereoselectively cyclized via cationic intermediates with retention of configuration in chair-like transition states (several X-ray structures). This allows the preparation of diastereomerically pure *trans*-decalinic diene complexes, from which chiral bicyclic sesquiterpenes and tricyclic diterpenes can be synthesized. © 2002 Elsevier Science Ltd. All rights reserved.

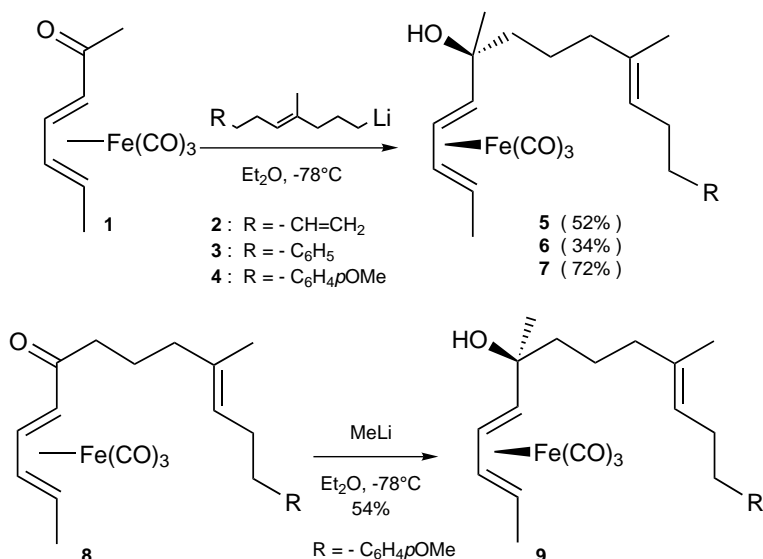
The well known approach to steroids and polycyclic terpenes from *E*-1,5-polyenic acyclic precursors makes use of a non enzymatic biogenetic like cationic cyclization which generates several asymmetric centers stereospecifically.^{1,2} The crucial step is the formation of a carbocation from a C=C double bond by protonation,^{1b} or, mainly mediated by a Lewis acid, from an alcohol, an acetal,^{1a} or an epoxide.²

We were interested in the use of such biomimetic cyclizations, starting from chiral pentadienol tricarbonyl iron complexes as precursors of cationic intermediates that maintain the stereochemical integrity of the alcohols [$\sim R^1=C_4H_5Fe(CO)_3$, X=OH]. Oxygenated

functions such as acetates, alcohols or epoxides adjacent to 4-electron ligands coordinated to the $Fe(CO)_3$ group, are easily cleaved by Lewis acids to transient metal stabilized cations, which react in general stereospecifically with retention of configuration with weak nucleophiles.³ Tertiary pentadienol complexes of high enantiomeric purity result from the totally stereoselective reaction of organometallics, principally alkyllithiums, with the enantiomers of pentadienone complexes.⁴ We therefore investigated the reaction of several ω -pentenylpentadienol tricarbonyl iron complexes with $BF_3 \cdot Et_2O$ as Lewis acid. Monofluorinated cyclohexane derivatives were obtained^{5,6} by a rather unusual fluorocyclization reaction.



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The secondary diastereomeric *psi-endo* and *psi-exo* alcohols gave in the approximate ratio 10:4:1 *cis*-3-fluoro dienylcyclohexanes in a stereospecific manner, *trans*-3-fluoro dienylcyclohexanes (non stereospecific: de ca. 75%) and minor amounts of other fluoro dienylcyclohexanes.⁵ Similar results were reported by A. J. Pearson and co-workers.⁶ The tertiary diastereomeric alcohols led also mainly to *cis*-3-fluoro dienylcyclohexanes, but the reaction was no longer stereospecific (de 74 and 38%). However, no *trans*-3-fluoro dienylcyclohexanes were present, but *trans*-2-fluoro dienylcyclohexanes (de 50 and 20%) and 4-fluoro dienylcyclohexanes were formed in the approximate ratio 12:1:1.⁵

We have now investigated the possibility of polycyclizations, with special attention to the stereochemical outcome.

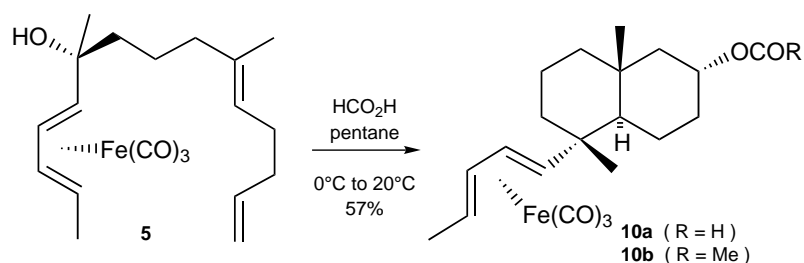
Several tertiary alcohols bearing polyunsaturated side chains were obtained as highly pure diastereomers by reaction of hepta-2,4-dien-6-one tricarboxylate iron **1** with the unsaturated organolithium reagents **2–4**,⁷ or by reaction of methylithium with the complexed pentadienyl ketone **8** bearing an unsaturated chain.⁸

separated. However, by treatment of **5** with formic acid in pentane at 0°C, only one cyclization product was observed, the bicyclic formate **10a**, easily obtained as the pure diastereomer. Saponification followed by acetylation gave the acetate **10b**, from which single crystals were obtained which allowed confirmation of the structure by X-ray diffraction.⁹

Under the same conditions, the tertiary alcohol **6**, with an aromatic ring instead of a simple C=C terminal double bond, gave only the tricyclic product **11** (69%). Better results for cyclization were obtained, when an activating OMe substituent was present, with BF₃·Et₂O than with the protic acid. The tricyclic products **11–13** were obtained as crystallized single diastereomers, allowing structure determination by X-ray diffraction.⁹

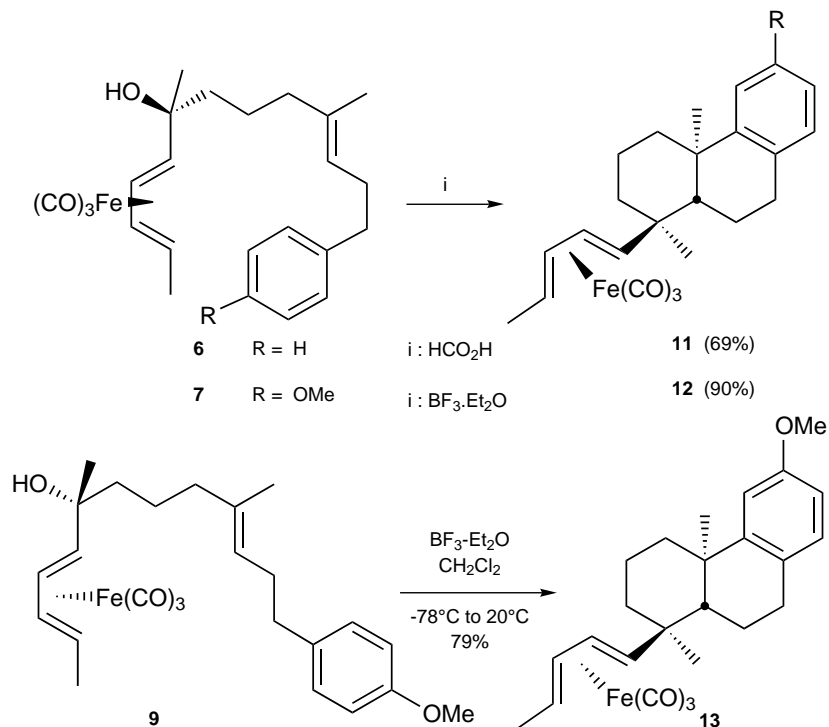
The diastereomers **12** and **13** differ only by the attachment of the Fe(CO)₃ fragment (same *cis*-di-Me diene obtained by decomplexation in the racemic series).

As shown by these results, cationic polycyclizations are possible with pentadienol tricarboxylate iron complexes as cation precursors. The reactions proceed fully



When the polyolefinic alcohol **5** was treated with BF₃·Et₂O in CH₂Cl₂, first at -78°C then at 20°C, a mixture of cyclized elimination products was obtained in 78% yield, but the products were too nonpolar to be

stereospecifically and the cyclohexanic products obtained result from cyclizations via chair-like transition states, with the larger diene tricarboxylate iron substituent in an equatorial orientation and with reten-



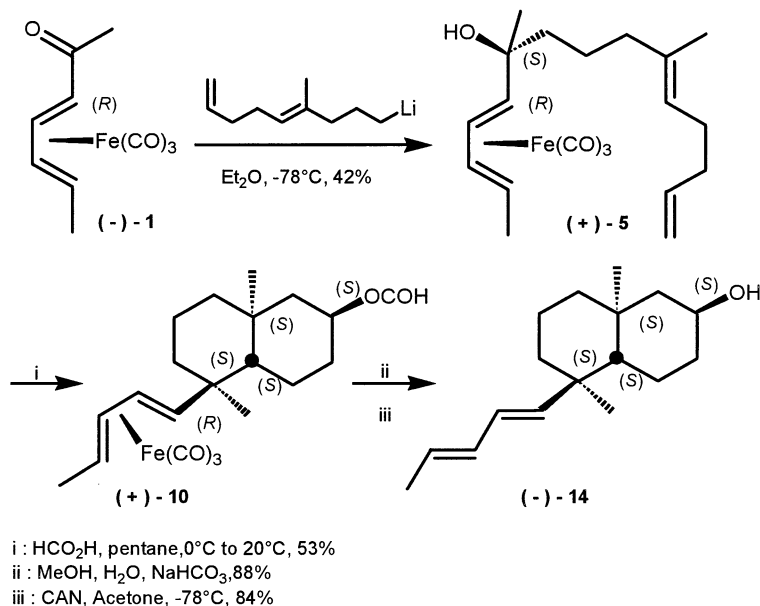
tion of configuration of the hydroxyl bearing carbon atom.

Since all products were obtained as very pure single diastereomers, this means that polycyclic enantiomers of high enantiomeric purity can be obtained if one starts from the enantiomeric dienone complexes (+) or (-)-**1** [(**-1**, $[\alpha]_{\text{D}} -364$ (*c* 0.5, CHCl_3); (+)-**5** [$\alpha]_{\text{D}} +25$ (*c* 0.5, CHCl_3); (+)-**10** [$\alpha]_{\text{D}} +86$ (*c* 0.6, CHCl_3); (-)-**14** [$\alpha]_{\text{D}} -19$ (*c* 0.5, CHCl_3)].

The *psi-endo* and *psi-exo* secondary alcohols, which resulted from the reaction of the organolithium reagent **4** with the complexed sorbic aldehyde,⁸ were

similarly cyclized by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$. They gave respectively, in 86 and 89% yields, single tricyclic diastereomers which were different (NMR, HPLC), but gave the same diene by decomplexation.

By oxidative cleavage of the dienic side chain liberated by decomplexation,^{5,10} various substituted decalins are accessible, with a high degree of stereochemical control. Since the cyclization reaction seems to be general in the polycyclic series,¹¹ the synthesis of natural products such as sesqui-, di-, triterpenes and steroids, of high enantiomeric purity, mediated by iron tricarbonyl cationic species, can now be considered.

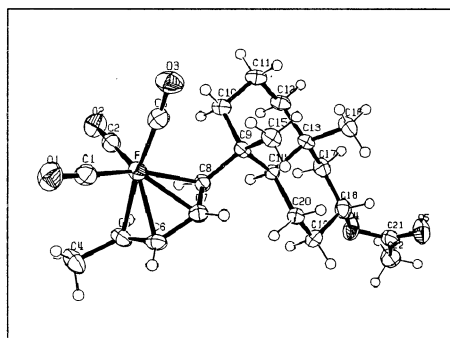


Acknowledgements

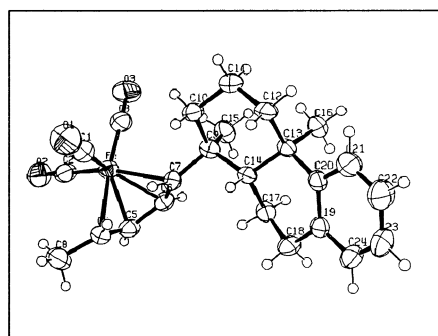
We are grateful to BASF for gifts of $\text{Fe}(\text{CO})_5$.

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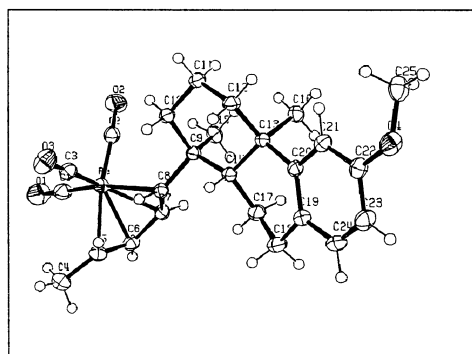
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- The δ,ϵ -unsaturated hexadienone– $\text{Fe}(\text{CO})_3$ complex **8** was obtained in 59% yield by oxidation with 1,1-(azodicarbonyl)-dipiperidine¹³ of the magnesium alcoholate of the *psi-endo* alcohol resulting from the reaction of the organolithium reagent **4** with the complexed sorbic aldehyde (78%, *psi-endo/psi-exo* 1:1.3, easily separated).
- The details of the X-ray structure determinations will be given in the full paper. Service, Commun de Rayons X de la Faculté de Chimie, ULP, Strasbourg, October 2000–March 2001)
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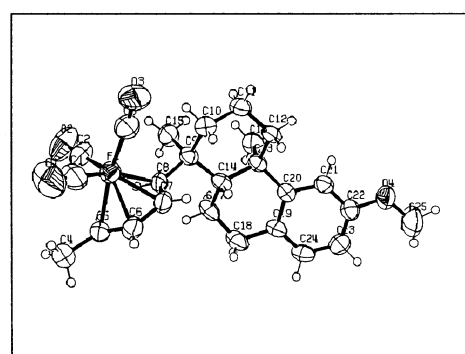
ORTEP view of **10b**



ORTEP view of **11**



ORTEP view of **12**



ORTEP view of **13**