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A new method for the demetallation of tricarbonyliron diene complexes by total hydrogenation with Raney nickel. Application to a very short synthesis of (+)-[6]-gingerdiol

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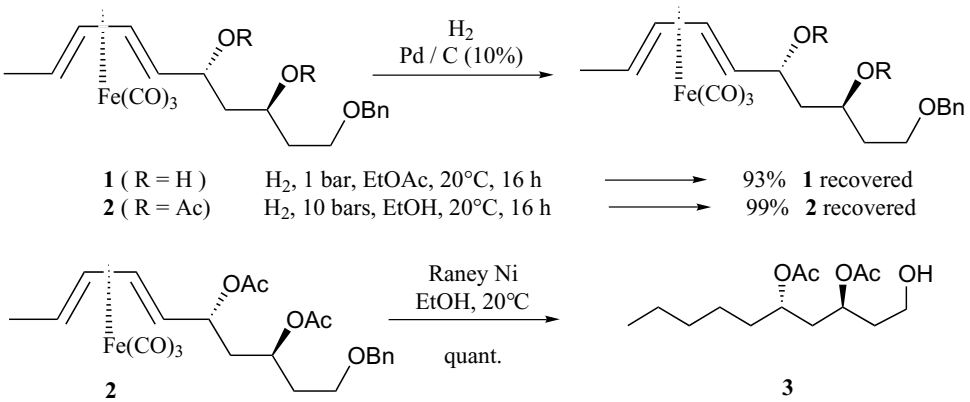
Abstract—Demetallation of tricarbonyliron diene complexes is rapidly achieved by treatment with freshly prepared Raney nickel. The ligands which are totally hydrogenated during the decomplexation are easily isolated in high yields, without racemization, if chiral. A very short and efficient synthesis of (+)-(3*R*,5*S*)-[6]-gingerdiol, based on this novel decomplexation procedure, which also allows the synthesis of the other diastereomers/enantiomers, is described. © 2001 Elsevier Science Ltd. All rights reserved.

Tricarbonyliron complexes of four-electron organic ligands are a useful class of compounds for application to organic synthesis. By coordination to the $Fe(CO)_3$ fragment, various ligands are greatly stabilized, allowing their use in further transformations and, more generally, the complexation results in significant changes in the reactivity (protection, but sometimes also activation). Another important aspect in π-coordination chemistry, is the fact that prochiral ligands give chiral complexes and that such non racemic complexes are relatively easy to obtain. Many reactions of organic tricarbonyliron complexes are highly diastereoselective, and the diastereomers obtained are, in general, easy to separate. The stoichiometric use of such complexes appears therefore very attractive for the synthesis of enantiomerically pure compounds. Now, for the synthesis of purely organic molecules, one of the last steps is always a decomplexation reaction, where the metal is cleaved from the organic fragment.

This is usually achieved by oxidation[1] with liberation of the ligand without structural changes. Another possibility is to liberate the ligand by an exchange reaction, in general with a phosphine,[2] and recently, a mild demetallation method based on a photolytically induced ligand exchange, followed by oxidation with air, was shown to be useful for the cleavage of very reactive free ligands.[3] A completely different method



Scheme 1.

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for cleavage of the metal is photodecomplexation, by irradiation in acetic acid, of functionalized complexes of four-electron ligands. In this case, the four-electron ligand is not obtained unchanged, but is hydrogenated to an alkene, more or less regioselectively[4,5] depending on the substituents.[6] This photoreductive decomplexation, which is useful for the efficient synthesis of deconjugated enones and esters from dienone and dienoic ester complexes,[4] and of chiral unsaturated alcohols,[5] is particularly interesting for complexes of ligands such as cyclobutadienes or trimethylenemethanes, where the simple oxidative decomplexation would lead to hyperreactive species and unwanted secondary reactions (isomerizations, polymerizations, cycloadditions, etc.).

We have now found a different method for the demetallation of tricarbonyliron complexes, which makes use of freshly prepared Raney nickel, with the result that the cleaved ligands are completely hydrogenated.

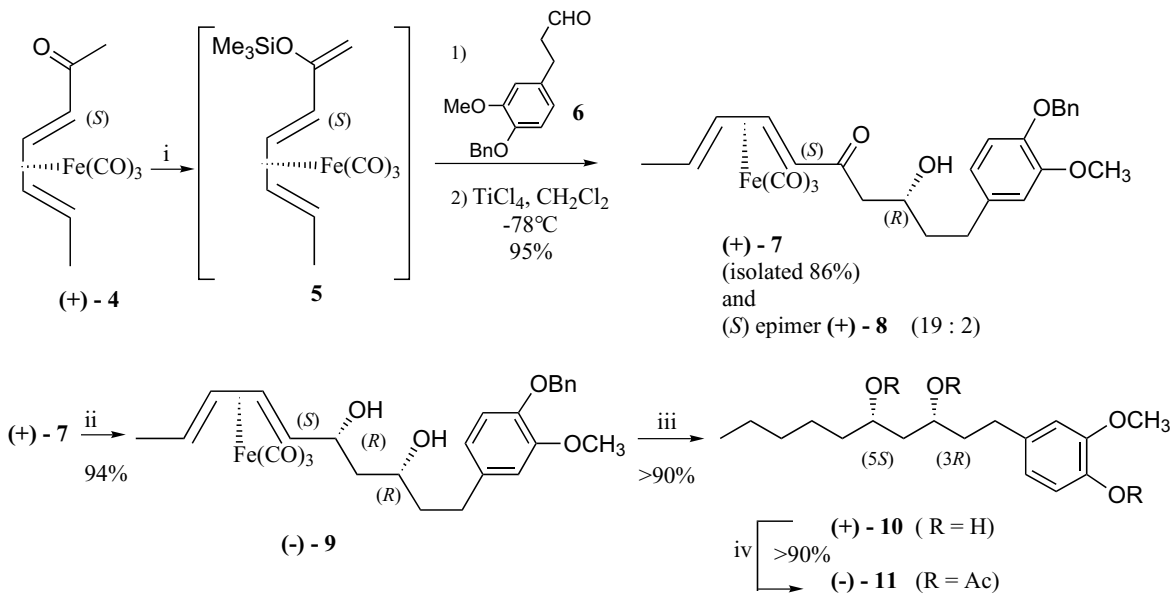
During our investigations on crossed aldol condensation reactions of (3,5-heptadien-2-one) tricarbonyliron,[7] we used *ortho*-methoxybenzyl ethers for the protection of β-hydroxyaldehydes. Deprotection was achieved successfully by oxidation with DDQ (without decomplexation) and acidic cleavage of the acetal formed. The unsubstituted benzyl ethers gave equally good results for the aldol reaction, but we were unable to achieve deprotection by the usual hydrogenolysis, since the benzyl group was not cleaved when complex **1** was submitted to catalytic hydrogenation[8] at atmospheric pressure with 10% palladium on carbon. Even after treatment for 16 h with hydrogen at 10 bars, the corresponding diacetate **2** was quantitatively recovered, using the same catalyst. The same was true for Raney nickel (commercial slurry in water) as catalyst.

On the contrary, when freshly prepared Raney nickel W-2, from the aluminium–nickel alloy,[9] was used, debenzylation occurred, but with decomplexation and hydrogenation of the ligand. Finally, we found that this result was also obtained without gaseous hydrogen, when an excess of a freshly prepared ethanol slurry of Raney nickel was used (ca. 10 g, 50:50 alloy for 1 g complex). The yield was nearly quantitative after a short period of time (ca. 1 h), with a very simple work-up (filtration and evaporation of the solvent), and no epimerization was observed (**2**→**3**, single diastereomer)[10] (Scheme 1).

Of course, with this decomplexation method the chemically versatile diene pattern is lost, but this can be advantageous for the synthesis of saturated target molecules. This is well illustrated in the following very short and efficient synthesis of (+)-[6]-gingerdiol.

The gingerols[11] and gingerdiols[11b,12] are important components of the rhizome of ginger (*Zingiber officinale* Roscoe). Several asymmetric syntheses of the major component, (+)-[6]-gingerol (one asymmetric center), have been previously reported,[13] but to our knowledge, this is not the case for the [6]-gingerdiols (two asymmetric centers), obtained only by non stereoselective reduction of natural [6]-gingerol.[12] Our synthesis is based on a highly diastereoselective crossed aldol condensation reaction using the silyl enol ether/$TiCl_4$ method.

In three simple steps, and an overall yield of nearly 70%, (+)-[6]-gingerdiol was obtained with a high ee from the chiral heptadienone complex (+)-**4**,[7] via the silyl enol ether **5** prepared in situ, and benzyl protected dihydroconiferyl aldehyde **6**.[14]



Scheme 2.

As in previous work with this complex,[7] the aldol reaction was highly diastereoselective (de ~80%) and the diastereomeric hydroxyketones obtained could be easily separated by simple silica gel column chromatography ((+)-**7**, isolated 86%, $[\alpha]_D = +138$ (*c* 0.15, $CHCl_3$); (+)-**8**, isolated 9%). The completely stereoselective reduction of the hydroxy ketone (+)-**7** with KBH_4 yielded the *syn*-diol (−)-**9** (94%, $[\alpha]_D = -6.0$ (*c* 0.3, $CHCl_3$)), the reduction proceeding from the side opposite to the metal, with the 'enone' entirely in the *s-cis* conformation.[7,15]

By treatment with freshly prepared Raney nickel, [6]-gingerdiol (+)-**10** was obtained as a single diastereomer in one practical step (hydrogenolysis of the benzyl ether, demetallation and total hydrogenation of the diene fragment). For the purpose of simpler identification, (+)-**10** was acetylated to the triacetate (−)-**11** (overall 82%, $[\alpha]_D = -1.26$ (*c* = 0.4, $CHCl_3$); lit.[11b] −0.8 (*c* 1, $CHCl_3$); lit.[12] −3.1 (*c* 0.3, $CHCl_3$)) (Scheme 2).

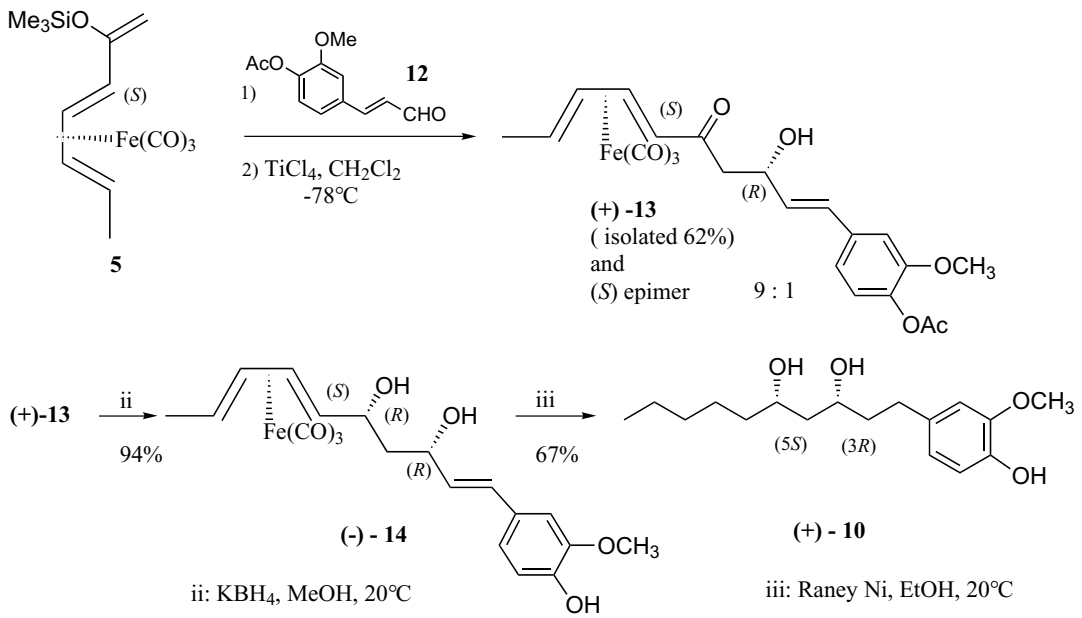
Another very short synthesis of gingerdiol could be achieved directly from commercially available coniferyl aldehyde. Following acetylation, the cinnamaldehyde derivative **12** was obtained, which underwent a crossed aldol condensation with **5** to give primarily the ketol (+)-**13**, readily isolated by simple silica gel column chromatography (80%, $[\alpha]_D = +111$ (*c* 0.3, $CHCl_3$)). Diastereospecific reduction of (+)-**13** with KBH_4 proceeded with concomitant cleavage of the acetyl protecting group[16] to afford the *syn*-diol (−)-**14** (94%, $[\alpha]_D = -6.3$ (*c* 0.1, $CHCl_3$)). Finally, treatment of (−)-**14** with freshly prepared Raney nickel promoted both decomplexation and hydrogenation of the diene substructure and the styrenic double bond to give gingerdiol (+)-**10** (67%, $[\alpha]_D = +11$ (*c* 1, $CHCl_3$); lit. natural product[12] +7.5 (*c* 1.5, $CHCl_3$); lit. less polar reduction product of (+)-(*S*)-[6]-gingerol[12] +10.4 (*c* 1.8, $CHCl_3$)) (Scheme 3).

Since the reduction of the ketocarbonyl group can also be achieved with Raney nickel, the synthesis can be shortened to two steps, by direct treatment of the complexed hydroxyketones with Raney nickel, leading from (+)-**4** and **6** to a mixture of the gingerdiol (+)-**10** (*syn* diol 3*R*,5*S*) and the corresponding *anti* diol (3*R*,5*R*), which can be separated.[12]

When the aldol condensation was performed with the lithium enolate of the complexed heptadienone (+)-**4**, and not under Mukaiyama conditions, the reaction was no longer highly stereoselective but showed the reversed stereoselectivity ((+)-**7** and (+)-**8**, 75%, 2:3), thus allowing straightforward access to (+)-**8** ($[\alpha]_D = +143$ (*c* 0.5, $CHCl_3$)). The other natural [6]-gingerdiol (*anti* diol 3*S*,5*S*) was thus also available, using the same reaction sequence, in particular the novel demetallation and hydrogenation reaction (reduction with KBH_4: complexed *anti* diol, 91%, $[\alpha]_D = -7.0$ (*c* 0.3, $CHCl_3$); Raney nickel reaction: *anti* 3*S*,5*S* gingerdiol, 80%, $[\alpha]_D = -3.8$ (*c* 0.13, $CHCl_3$); lit. natural product[12] $[\alpha]_D = -1.2$ (*c* 0.1, $CHCl_3$)). Obviously, the enantiomers of both natural gingerdiols can be obtained in the same way, if one starts from the enantiomeric heptadienone complex (−)-**4**.

A similar decomplexation with Raney nickel was observed in model studies for the synthesis of macrolactin A by Donaldson and co-workers.[17] However, with the commercial aqueous slurry of Raney nickel they used, the demetallation was very slow (stirring over 48 h under hydrogen, 36% hydrogenated ligand isolated).

Other decomplexation reactions by hydrogenolysis (other main and spectator ligands and other metals) are under investigation.



Scheme 3.

Acknowledgements

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