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New Organoiron-Mediated Synthesis of Oxocenes

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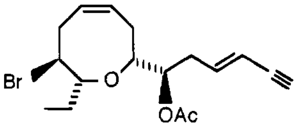
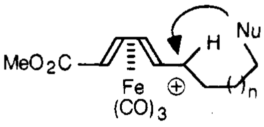
Medium ring ethers are common key structural fragments of various natural products isolated from marine species. The metabolites from the alga *Laurencia*, such as laurencin, or several toxins like the brevetoxins or ciguatoxin are representative examples.



Laurencin

The synthesis of such medium-sized cyclic ethers is still a difficult problem although significant progress have been achieved recently,[1] culminating in elegant total syntheses of some of these natural products.[2] Three main strategies have been developed for the preparation of these cyclic ethers. The use of lactones as starting materials and their subsequent elaboration to the required ethers was successfully applied in the total synthesis of laurencin[2a,b] and brevetoxins.[3] A second strategy involved cyclization processes by formation of a C–C bond wherein intramolecular capture of oxonium ions by suitable double bonds proved to be a very efficient technique[2c,4] and a new approach using radical chemistry has also been reported.[5] Ring closure by formation of a C–O bond is a third strategy which has not been used very often. The ring expansion of δ-lactones into oxocenones has been reported,[6] and a rhodium-mediated cyclization of α,ω-diazo alcohols was also useful.[7] Intramolecular nucleophilic substitution reactions led, in some cases, to oxepanes and oxocanes[8] while iodoetherification gave only low yields of such ethers.[9] It is interesting to point out that C–O bond cyclizations have been rarely used under acidic conditions,[10–12] probably due to the known instability of these medium ring ethers toward acids or Lewis acids.

It is well established that some organometallic complexes strongly stabilize vicinal positive charges, and this effect has already found many applications in organic synthesis.[13,14] As part of our program dealing with the use of dienetricarbonyliron complexes in organic synthesis[15] we have reported previously the preparation of various five- and six-membered heterocycles, using intramolecular trapping of pentadienylcations complexed to $Fe(CO)_3$.[16]



Nu = OH,[16a,16c] NH-CO_2Ph,[16b] SH,[16d]; n = 1,2

In this paper we describe a new stereospecific synthesis of oxocenes which demonstrates that this methodology can be extended to the more challenging case of medium-sized cyclic ethers (Scheme 1).

Our synthesis starts from the easily accessible Ψ-exo[17] homoallylic alcohol **1a**,[16c] in racemic form,[18] which is first protected as its TBDMS ether **2a**, before being submitted to a hydroboration–oxidation sequence leading to **3a**. Oxidation of the primary alcohol using Swern's procedure gives aldehyde **4a** in 74% yield. In agreement with

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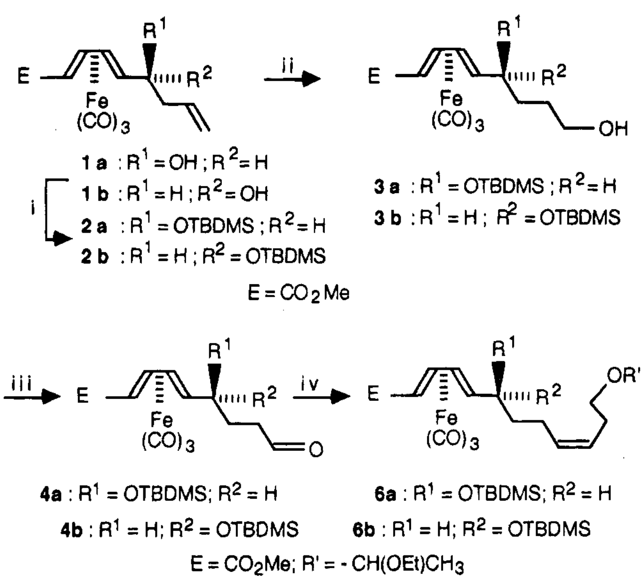
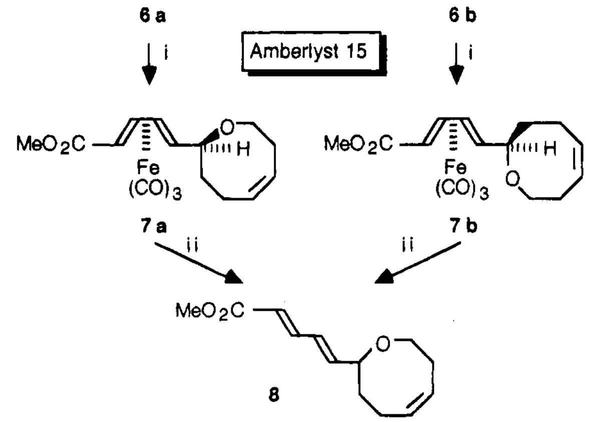
Scheme 1



[a] Reagents and conditions: (i) TBDMSOTf, 2,6-lutidine, THF, 15 min, −40 °C, **2a** (95%), **2b** (92%); (ii) BH_3:THF complex, hexane, 0 °C, 1 h, then NaOH and H_2O_2, **3a** (70%), **3b** (67%); (iii) Swern, **4a** (71%), **4b** (67%); (iv) $Ph_3P^+(CH_2)_3OCH(OEt)CH_3Br^-$ (**5**), BuLi, THF −80 °C to −20 °C, then HMPA and **4a** (or **4b**) −80 °C to −20 °C, 1 h, **6a** (72%), **6b** (81%).

Scheme 2

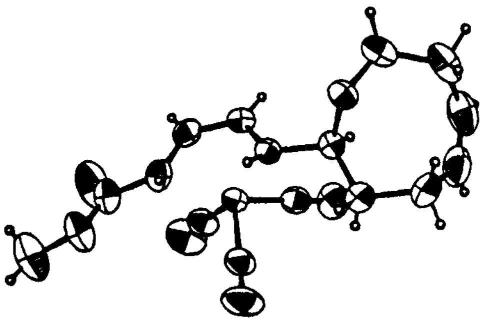


[a] Reagents and conditions: (i) Amberlyst 15, CH_2Cl_2, rt, 1 h, **7a** (61%), **7b** (41%); (ii) $Ce(NH_4)_2(NO_3)_6$, MeOH, −15 °C, 30 min, **8** (72%).

previous results,[15] both steps are compatible with the organometallic moiety and there is no significant decomplexation. A Wittig reaction with the phosphorane obtained from **5**,[19] under[20] *cis* olefination conditions, gives the *Z* olefin **6a**.[21] The same sequence of reactions was carried out starting from the Ψ-endo alcohol **1b**, leading to the diastereoisomeric bis ether **6b**.

We have discovered that the heterocyclization process can be carried out directly on the bis-ether derivatives **6a** and **6b** using the acidic resin Amberlyst 15, without any need for the deprotection of the alcohol functions. Furthermore, the reaction is stereospecific: **6a** gives exclusively the oxocene **7a** while its diastereoisomer **7b** is the only heterocycle obtained from **6b** (Scheme 2).[22]

The reaction occurs with retention of configuration, as unambiguously established by the X-ray diffraction analysis of oxocene **7a**.[23]



Nucleophilic additions to $Fe(CO)_3$-complexed acyclic pentadienylcations are strongly dependent on the nature of substituents on the cations and also the nucleophiles.[15] However, retention of configuration is usually preferred, especially in the case of the *in situ* formation of the cation.[16,24] It should be noted also that, contrary to the case of the corresponding tetrahydrofurans,[16c] there is no equilibration between **7a** and **7b**: longer reaction times gives only decomposition products with no evidence for epimerization.

The key role of the acidic resin in this process should also be noted:[25] the use of various protic or Lewis acids ($BF_3{\cdot}OEt_2$ or TMS triflate for instance) gives only very low yields of oxocenes. The nature of R′ seems also to be important: no cyclization products could be isolated starting either from the corresponding alcohols (R′ = H) or from other derivatives (R′ = $SiPh_2tBu$, −THP, $-CH_2C_6H_4pOMe$). Decomplexation of **7a** or **7b** under the classical conditions (Ce^{4+}, MeOH) gives the, racemic, dienyloxocene **8** in good yields.

In conclusion, this new preparation of oxocenes is further confirmation of the great potential of diene tricarbonyl iron complexes in organic synthesis. This heterocyclization occurs under very mild reaction conditions and, furthermore, is stereospecific and can be extended to optically active derivatives since the starting organometallic complexes can be resolved easily.[15,18] Finally, these oxocenes **7** and **8**, with the intracyclic double bond and one chain already in the correct position, are good models for the preparation of natural products or their structural analogs.

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Supplementary Material Available: Experimental procedures and characterization data for all compounds (8 pages).

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[19] The phosphonium salt **5** was prepared by reaction of ethyl vinyl ether with (3-hydroxypropyl)triphenylphosphonium bromide, using pyridinium paratoluene sulfonate as catalyst (see supplementary material). This compound gave better results than the corresponding, more labile, 2-methoxy-2-propyl ether used previously, for instance in the LTB_4 synthesis.[20]

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[21] This olefin, as well as **6b**, is isolated as a mixture of diastereoisomers due to the presence of an extra stereogenic center.

[22] Careful TLC and NMR analysis of the crude reaction mixtures indicate, in each case, the presence of a single heterocycle. The only other isolated products are the primary alcohols (deprotection of the acetal group) and smaller amounts of the bis ethers (in situ reprotection of these alcohols by a silyl group).

[23] The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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