Remote asymmetric induction by using the 1,3-migration reaction of (diene)iron tricarbonyl complexes

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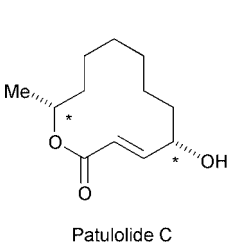
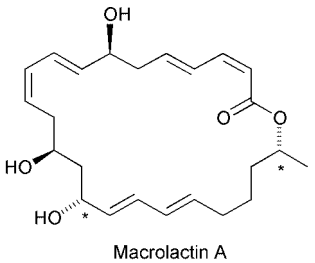
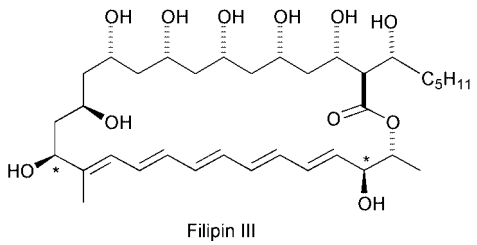
Novel strategies for the stereoselective synthesis of molecules with remote stereogenic centers across double bonds have been developed *via* organoiron methodology allowing highly diastereoselective syntheses of 1,8- and 1,10-diol $Fe(CO)_3$ complexes using the stereospecific 1,3- and 1,5-migration of an $Fe(CO)_3$ group; this strategy could be used for stereoselective functionalization of remote terminal substituents on acyclic polyene compounds.

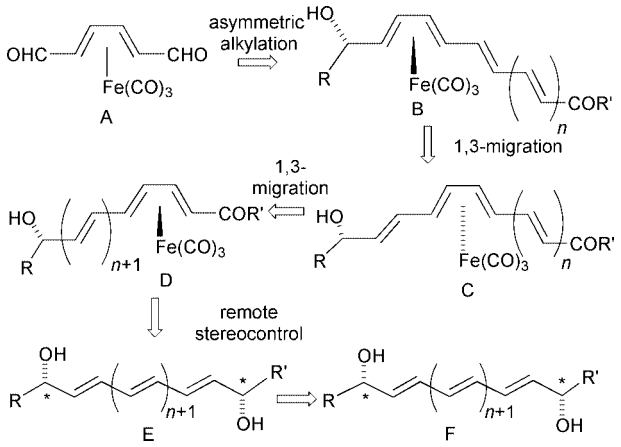
One of the more challenging aspects of organic synthesis is the stereoselective construction of molecules with remote (*i.e.* greater than 1,3-related) stereogenic centers with high levels of diastereo- and enantioselectivity.[1] A particularly challenging goal would be the development of a general strategy for the control of remote stereogenic centers related across double bonds of fixed configuration, because this moiety is present in many natural products, including polyene macrolide antibiotics such as filipin III.





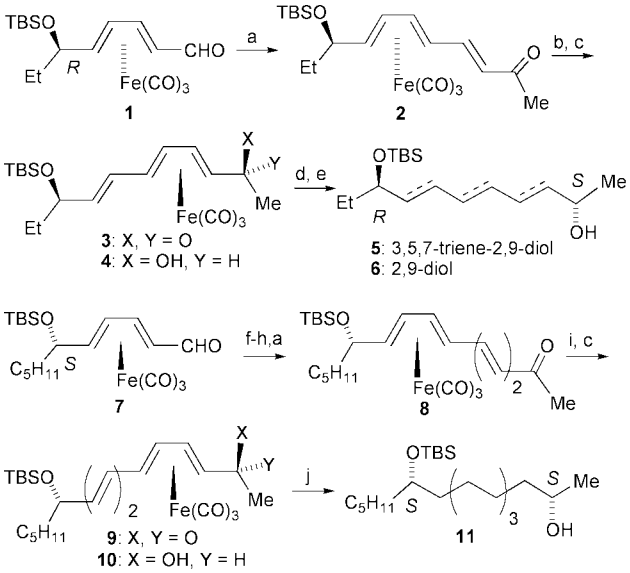


In the course of our studies on the mobility of the $Fe(CO)_3$ group on polyenes with the aim of constructing several stereogenic centers using a single chiral auxiliary,[2] we have found that the $Fe(CO)_3$ moiety of (triene)$Fe(CO)_3$ complexes shifts to the electron-deficient double bond stereospecifically on treatment with a base such as potassium bis(trimethylsilyl)-amide (KHMDS) and NaH. By taking advantage of this 1,3-migration of the $Fe(CO)_3$ group, the (polyenone)$Fe(CO)_3$ complexes **B** could be converted *via* **C** into the corresponding migrated complexes **D**, where the $Fe(CO)_3$ groups are situated in the ideal position for controlling several reactions of the ketone (Scheme 1). We herein report a novel strategy for highly diastereoselective preparation of polyene- and saturated 1,8- and 1,10-diols **E** and **F** by a combination of the 1,3- or 1,5-migration of the $Fe(CO)_3$ group and subsequent hydride reduction of the ketone, together with a formal asymmetric synthesis of epipatulolide C.



Scheme 1 Remote stereocontrol based on the 1,3-migration concept of an $Fe(CO)_3$ group.

The requisite (trienone)- and (tetraenone)$Fe(CO)_3$ complexes **2** and **8** were prepared from the chiral aldehydes **1** and **7** (Scheme 2).[3] We first examined the 1,2-reduction of the α,β-unsaturated ketone **2** *via* 1,4-asymmetric induction. In contrast to the reduction of (dienone)$Fe(CO)_3$ complex,[4] the reduction of **2** with sodium borohydride in methanol in the presence of $CeCl_3{\cdot}6H_2O$ gave a nearly equimolar ratio of the two diastereomeric trienol complexes.[5] To overcome this problem, we next



Scheme 2 *Reagents and conditions*: (a) $CH_3COCH_2P(O)(OMe)_2$, $LiOH{\cdot}H_2O$, MeOH (90% for **1**, 78% for **7**); (b) NaH, THF (81%), (c) $NaBH_4$, MeOH (91% for **3**, 72% for **8**); (d) H_2O_2, 1 M NaOH, MeOH, 0 °C (83%); (e) H_2, PtO_2, AcOEt (85%); (f) $(EtO)_2P(O)CH_2CN$, NaH, THF, 0 °C (69%); (g) DIBAL-H, −50 °C (49%); (h) n-Bu_3P, CH_2Cl_2 (71%); (i) $KN(SiMe_3)_2$, THF, 0 °C (70%); (j) H_2O_2, 1 M NaOH; H_2, PtO_2 (89%).

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investigated the 1,2-reduction of the 1,3-migrated complex **3**, which was easily accessible from **2** by the stereospecific 1,3-migration of the $Fe(CO)_3$ group. According to the reported procedure,[2] **2** was treated with 1.5 equiv. of NaH in THF at 0 °C to give the desired product **3** in 81% yield along with the recovered starting material (2%). The stereochemistry of **3** was deduced from the previous result, namely, that the 1,3-migration of the $Fe(CO)_3$ group proceeded with inversion of configuration. In contrast to **2**, the reduction of the migrated product **3** with $NaBH_4$ provided the alcohol **4** as the single isomer in 91% yield. The desired 3,5,7-triene-2,9-diol **5** was easily synthesized by reaction of **4** with 30% hydrogen peroxide in the presence of 1 M NaOH solution. Furthermore, subsequent hydrogenation of **5** on platinum oxide in AcOEt gave the 1,8-*anti*-diol **6** in 85% yield. To confirm the absolute stereochemistry, the diastereomerically pure alcohol **6** was converted into the corresponding (*R*)- and (*S*)-MTPA esters, respectively. As expected, the absolute stereochemistry of the C2 position was revealed to be (*R*)-configuration by comparing their ^1H NMR spectra.[6]

To extend the applicability of this method, we next examined the reduction of the (tetraenone)$Fe(CO)_3$ complex **8**, which was prepared stereoselectively from **7** in 4 steps. The key reaction in this case would be a double 1,3-migration reaction of the $Fe(CO)_3$ group (*i.e.*, 1,5-migration). Then we investigated the migration reaction of **8** with several bases. Although we could not obtain the migration product by treatment of **8** with NaH, the reaction of **8** with 0.3 equiv. of KHMDS in THF at 0 °C provided the 1,5-migration product **9** in 70% yield along with the recovered starting material (7%). In the latter case, the 1,3-migration product of the $Fe(CO)_3$ group, an intermediate of the 1,5-migration reaction, could not be observed in the crude reaction mixture. Similarly, the reduction of **9** with $NaBH_4$ in methanol gave rise to the alcohol **10** in 72% yield as a single isomer. The transformation of **10** into **11** was performed by the same reaction sequence as that of **4** to give the 1,10-*syn*-diol **11** in 89% yield. The absolute stereochemistry was also determined by the MTPA-ester method.[6] The result revealed that the 1,5-migration of the $Fe(CO)_3$ group should occur with retention of configuration as a result of a double inversion mechanism.

Finally, we applied this method to a formal asymmetric synthesis of epipatulolide C (Scheme 3).[7] By a similar 5-step sequence, the chiral aldehyde **12** was transformed into the (2*S*,9*R*)-triol derivative **13** as a single isomer. After protection and deprotection of the hydroxy groups of **13**, the resulting alcohol was oxidized, and Wittig condensation of the aldehyde so obtained and subsequent removal of the TBS group gave the unsaturated ester **14**, which had been converted into racemic epipatulolide C in three steps.

This work shows how a combination of the mobility and the stereodirecting ability of the $Fe(CO)_3$ group can be used to prepare stereoselectively compounds with remote stereogenic centers. Further applications to the construction of more remote stereogenic centers across double bonds are underway in these laboratories.

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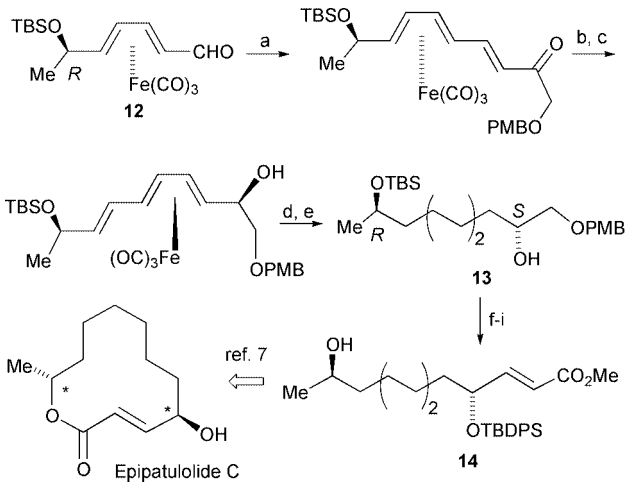

Scheme 3 *Reagents and conditions*: (a) $PMBOCH_2COCH_2P(O)(OEt)_2$, *t*-BuOH, toluene (54%); (b) KHMDS (0.1 eq.), THF, 0 °C (62%); (c) $NaBH_4$, MeOH (83%); (d) H_2O_2, NaOH; (e) H_2, PtO_2 (89%); (f) TBDPSCI, imidazole (64%), (g) DDQ (72%); (h) Swern oxidation; $Ph_3P{=}CHCO_2Me$ (69%); (i) AcOH, THF, H_2O (74%).

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