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Diastereoselective Elaboration of 2,3,4-Substituted Piperidines Using Diene Iron Tricarbonyl Complexes. Total Synthesis of (±)-Dienomycin C and (±)-4-*epi*-Dienomycin C

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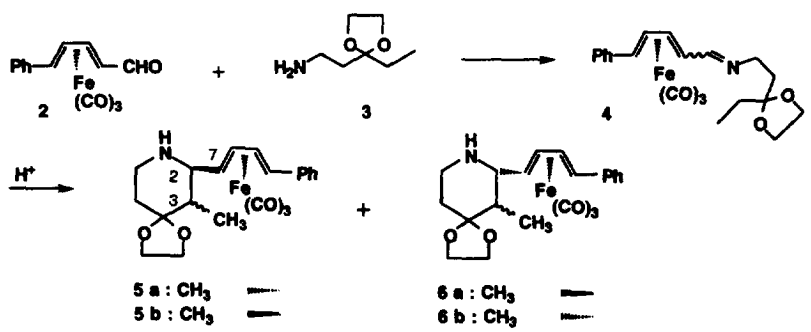
Abstract : The diastereoselective formation of 2,3,4-substituted piperidines is achieved by condensation of the iron dienal complex **2** and the primary amine **3** *via* an intramolecular Mannich-type cyclisation. This method is illustrated by the first total synthesis of (±)- dienomycin C **1** and its C-4 epimer **9**.

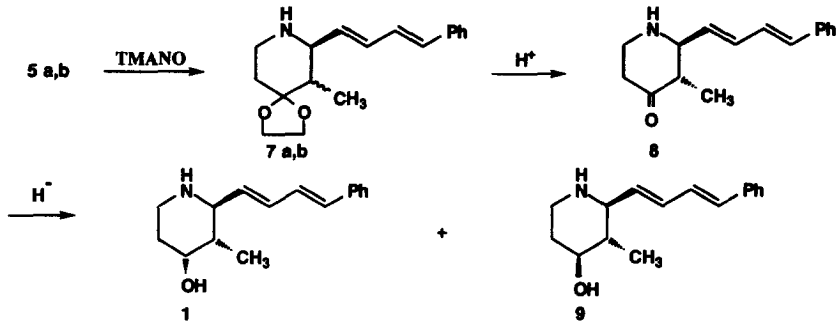
Many heterocyclic compounds of biological interest include in their framework a substituted piperidine moiety. Therefore it is of importance to get an efficient and selective entry to this skeleton. Recently, we have described an enantioselective synthesis of 2-substituted-4-piperidones, using iron tricarbonyl complexes, based upon an intramolecular Mannich-type cyclisation[1].

We wish to report herein, using the same methodology, the first total synthesis of (±)-dienomycin C **1**, a natural alkaloid isolated from a *Streptomyces* strain (MC 67-Cl) which shows antibiotic activity against *Mycobacteria* [2a]. Thus, condensation of the iron dienal complex **2**[3] with the primary amine **3**[4] in dry CH_2Cl_2 led to a mixture of Z and E isomers of the imine **4**. Subsequent treatment with two equivalents of *para*-toluenesulfonic acid at 50°C in dry toluene induced diastereoselective cyclisation into protected Ψ *endo* **5** and Ψ *exo* **6** piperidones[5] (65% overall yield, **5/6** = 9/1), which were easily separated by flash chromatography[6]. Each of the two diastereoisomers of the Ψ *endo* series **5a** and **5b** were isolated (**5a/5b** = 6/1) and fully characterized from their NMR spectra. Particularly relevant was the value of the coupling constant of H-2 with H-3 and H-7 (**5a** : $J_{2,3} = J_{2,7} = 9.6$ Hz; **5b** : $J_{2,3} = 3.0$ Hz, $J_{2,7} = 10.0$ Hz). Concerning the minor Ψ *exo* series, the **6a** and **6b** compounds could not be separated and the 1.5/1 *ratio* of the two isomers was established by relative integration, in the ^1H NMR spectrum, of the doublets of the methyl group in C-3 (1.15 ppm for **6a**, 1.18 ppm for **6b**) (Scheme 1).



Scheme 1

Removal of the $Fe(CO)_3$ unit from **5a,b** was conveniently achieved using trimethylamine *N*-oxide[7] (TMANO) and provided the 4-piperidone acetal **7a,b** in 82% yield. Acidic treatment of **7** furnished the desired piperidone **8**[8] which is transformed into (±)- dienomycin C **1** by stereoselective reduction at -50°C in THF using L-Selectride®[9]. A reverse diastereoselectivity is observed upon $NaBH_4$ reduction at room temperature in MeOH[10]. Dienomycin C **1** and its 4-epimer **9** were easily separated by flash chromatography, the major product being the 4-*epi* dienomycin C **9** as shown in Scheme 2. Total assignments of spectral data for these piperidines including NMR 2D experiments were in good agreement with the proposed structures and with the assignments reported for the natural product[2b].



L-Selectride®, -50°C	98	2	(yield = 90 %)
$NaBH_4$, 20°C	15	85	(yield = 90 %)

Scheme 2

In conclusion, dienal iron tricarbonyl complexes involved with an appropriate primary amine in an intramolecular Mannich-type reaction, provide an efficient and selective pathway for the preparation of piperidine ring having three contiguous asymmetric centers. This method is illustrated herein by the first stereocontrolled total synthesis of alkaloids (±)-dienomycin **1** and (±)-4-*epi*-dienomycin **9**.

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