Iron(III)–Copper(II) and Manganese(III)–Copper(II) Promoted Cyclizations: a New Stereoselective Approach towards α-Methyl Substituted Penicillin Derivatives

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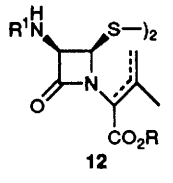
The stereoselective synthesis of α-methyl substituted penicillin by Fe^{III}–Cu^{II} and Mn^{III}–Cu^{II} promoted cyclizations and its relationship with the Baldwin's INPS (isopenicillin N synthase) mechanistic hypothesis on the biosynthesis of penicillin is described.

Recently we have reported our results on a metal-catalysed and -promoted cyclization for the synthesis of β-lactam antibiotics based on a sequence of single-electron transfer oxidations performed by Fe^{III} and Mn^{III} salts. When the reaction was carried out in the presence of $Fe(NO_3)_3$ or $Mn(OAc)_3$ the only products isolated were cephams **4**.[1] This observation prompted us to explore the possibility to intercept the stabilized radical **3**, which is the key intermediate of the cyclization process, using other metals in order to obtain over-oxidized products. Herein, we report our preliminary results on the stereoselective synthesis of α-methyl substituted penicillin by Fe^{III}–Cu^{II} and Mn^{III}–Cu^{II} promoted cyclization of thiol **2**.

Thiazoline **1**, obtained by the known procedure from 6-APA,[2] afforded by acidic treatment the corresponding thiol **2** (Scheme 1).[3] Compound **2** was subjected to the metal-promoted cyclization without purification. The couple $Fe(NO_3)_3$–$Cu(NO_3)_2$ in MeCN at 0 °C afforded α-ONO_2 methyl penicillin **7a**† in a 40% overall yield from **1** and the cyclization promoted by $Mn(OAc)_3$–$Cu(OAc)_2$ in $MeCO_2H$ at room temp. afforded α-OAc-methyl penicillin **7b** in a 45% overall yield from **1**. The only side product present in the final reaction mixtures of the two cyclization processes was disulfide **12** in *ca.* 30% yield. A blank experiment showed that **12** resulted from the direct oxidation of thiol **2** by the Cu^{II} salts.[4] The stereochemistry at C(2) of compounds **7a,b** was determined by NOE enhancement between the 2β-methyl on the C(2) and the H-3 proton, the observed enhancements were 10 and 12% for **7a** and **7b**, respectively. In the case of compounds **9a** and **9b**,‡ the NOE enhancement between the 2α-methyl on the C(2) and the H-3 proton was consistently lower (<2%).

From a mechanistic point of view, the stereoselective outcome of the reaction allowed the formation of the stabilized cation **8** by oxidation of **3** be ruled out. In fact, it is well known that the nucleophilic attack of acetate, nitrate or halide anions to **8** affords the cephalosporins **10** and **11** under thermodynamic control and β-methyl substituted penicillin **9a,b** under kinetic control.[5] Therefore, the stereoselective formation of **7a,b** by a 5-*exo* cyclization can be explained only with a mechanism centred on the trapping of stabilized radical **3** by Cu^{II} with formation of the organometallic intermediate **5** followed by insertion (**5** → **6**) and reductive elimination (**6** → **7**).

It is worth noting that the only related result was obtained by Baldwin during his investigation on the biosynthesis of penicillins and cephalosporins. In fact, incubation of the modified tripeptide **13** with isopenicillin N synthase (INPS) afforded exomethylene cepham **17** and α-hydroxymethyl penicillin **19** in a 1:3 ratio (Scheme 2).[6] Compound **19** is supposed to derive from rotamer **15** by *syn* [2π + 2π] cycloaddition followed by reductive elimination and the overall process is a 5-*exo* cyclization. Our results support the



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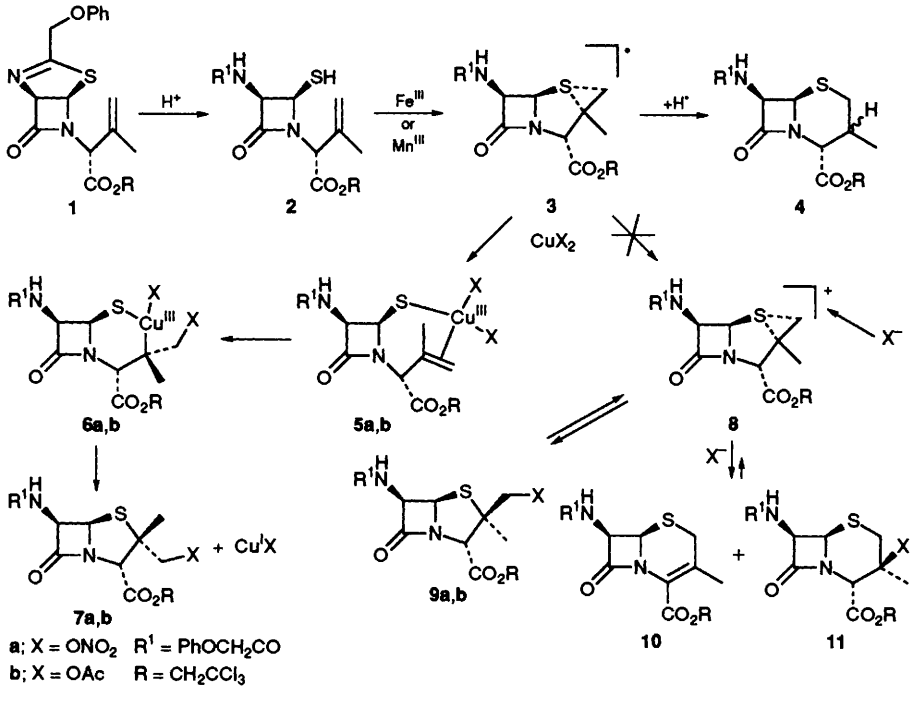
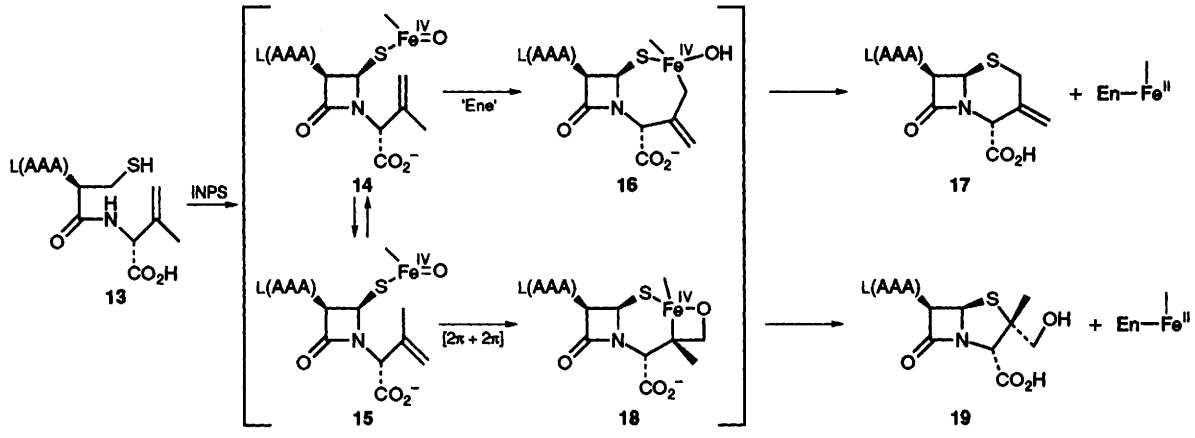


a; X = ONO_2 R^1 = $PhOCH_2CO$
b; X = OAc R = CH_2CCl_3

Scheme 1



Scheme 2

hypothesis that an organometallic intermediate in which the metal is able to perform a two-electron oxidation [**5** → **7** (Cu^{III} → Cu^{I}) is equivalent to **15** → **19** (Fe^{IV} → Fe^{II})] is generated in the active site of INPS and that the preferential formation of **7** and **19** is related to the high reactivity of the corresponding rotamers **5** and **15** in a cyclization process involving a metal centre. In fact, both reaction mechanisms are based on the irreversible formation of metallacycles **6** (Scheme 1) and **18** (Scheme 2).

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Footnotes

† *Selected spectroscopic details* for compound **7a**: waxy solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–6.82 (m, 6H), 5.79 (dd, *J* 4.3, 9.0 Hz, 1H), 5.63 (d, *J* 4.3 Hz, 1 H), 4.77 (s, 2H), 4.70 (d, *J* 11.6 Hz, 1H), 4.63 (s, 1H), 4.54 (s, 2H), 1.71 (s, 3H); $[\alpha]_D^{22}$ +116.0 (*c* 1, $CHCl_3$).

For **7b**: white solid: mp 49–51 °C; ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.38–7.25 (m, 3H), 7.08–6.80 (m, 3H), 5.78 (dd, *J* 4.2 Hz, 1H), 5.61 (d, *J* 4.2 Hz, 1H), 4.74 (s, 2H), 4.64 (s, 1H), 4.54 (s, 2H), 4.41 (d, *J* 12.0 Hz, 1H), 4.22 (d, *J* 12.0 Hz, 1H), 2.07 (s, 3H), 1.68 (s, 3H). $[\alpha]_D^{22}$ + 108.9 (*c* 1 in $CHCl_3$).

‡ Compounds **9a,b** were synthesized following known procedures; see ref. 5.

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