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Metal-Catalyzed and -Promoted Cyclizations for the Synthesis of Cephalosporins: A Possible DAOC/DAC Synthetase Biomimetic Process.

Walter Cabri,* Daniela Borghi, Emanuele Arlandini, Piero Sbraletta and Angelo Bedeschi

Farmitalia Carlo Erba, via Giovanni XXIII,23 20014-Nerviano (MI), Italy.

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Abstract: *A thiyl radical cyclization approach to the sulphur containing ring of cephams is described The reaction was carried out using metals able to perform a single-electron oxidation process under stoichiometric [Fe(III), $Mn(OAc)_3$] or catalytic [Fe(III)] conditions. Furthermore, the $FeCl_3$ or $Mn(OAc)_3$/LiX promoted reactions afforded, by a double single-electron oxidation process, over oxidized compounds The relationship with the mechanistic hypothesis proposed by Baldwin for the DAOC/DACS-catalyzed ring expansion from Penicillin N to Desacetoxy cephalosporin C is discussed.*

INTRODUCTION

The comprehension of the molecular processes involved in the oxidations catalyzed by iron-dependent heme and non-heme oxidase has increased during the past several years.[1] On the basis of the mechanistic models proposed for these enzymatic reactions, the research carried out in several academic and industrial laboratories allowed to define new methodologies for the oxidation of synthetic organic molecules.[2,3] In addition, the emulation *in vitro*, under controlled conditions, of the enzymatic activity can provide insights into the molecular mechanism involved in the *in vivo* reaction.[4]

The superb studies of Baldwin and coworkers on the two non-heme oxidase (INPS and DAOC/DAC Synthetase)[5] involved in the biosynthesis of penicillins and cephalosphorins[6] suggested to us a new approach to the synthesis of the sulphur containing ring of cephalosporin derivatives.[7] Herein, we wish to report the results of our studies on the development of a catalytic procedure for the thiyl radical approach to cephams **5** and **6** using Fe(III) salts (Scheme 1) and the synthesis of over oxidized products by $FeCl_3$- or $Mn(OAc)_3$/LiX-promoted cyclizations (Scheme 2). Furthermore, the relationship between these results and the DAOC/DAC Synthetase catalyzed ring expansion from penicillin N to desacetoxy cephalosporin C (DAOC) will be discussed.

RESULTS AND DISCUSSION

Thiazoline **2** was synthetized from 6-aminopenicillanic acid (6-APA) **1** by known procedure.[8] The opening of **2** by standard procedure ($HClO_4$ 30% in water/CH_3COCH_3/CH_2Cl_2, rt, 1-2h),[9] afforded the unstable thiol **3**. The organic solution of **3** obtained from the reaction work up, was concentrated and directly used for the metal catalyzed or promoted cyclizations.

Single-electron oxidation.

The cyclization of thiol **3** under acid or basic conditions was reported to fail.[9] In contrast, we found that the reaction carried out in the presence stoichiometric amounts of metal able to give a single-electron transfer oxidation[10] gave cephams **5** and **6** by a radical mechanism (Scheme 1, Table 1).[7] On the basis of the assumption that thiyl radicals follow the same rules as carbon centred radicals,[11] the cyclization of **4a** should take place in a 5-exo-trig fashion forming **4b**.[12] However, radical species **4a-d** are in equilibrium, as shown by Baldwin,[13] and the reduction of the thermodynamically stable tertiary carbon radical **4d** by a hydrogen donor affords **5** and **6**.

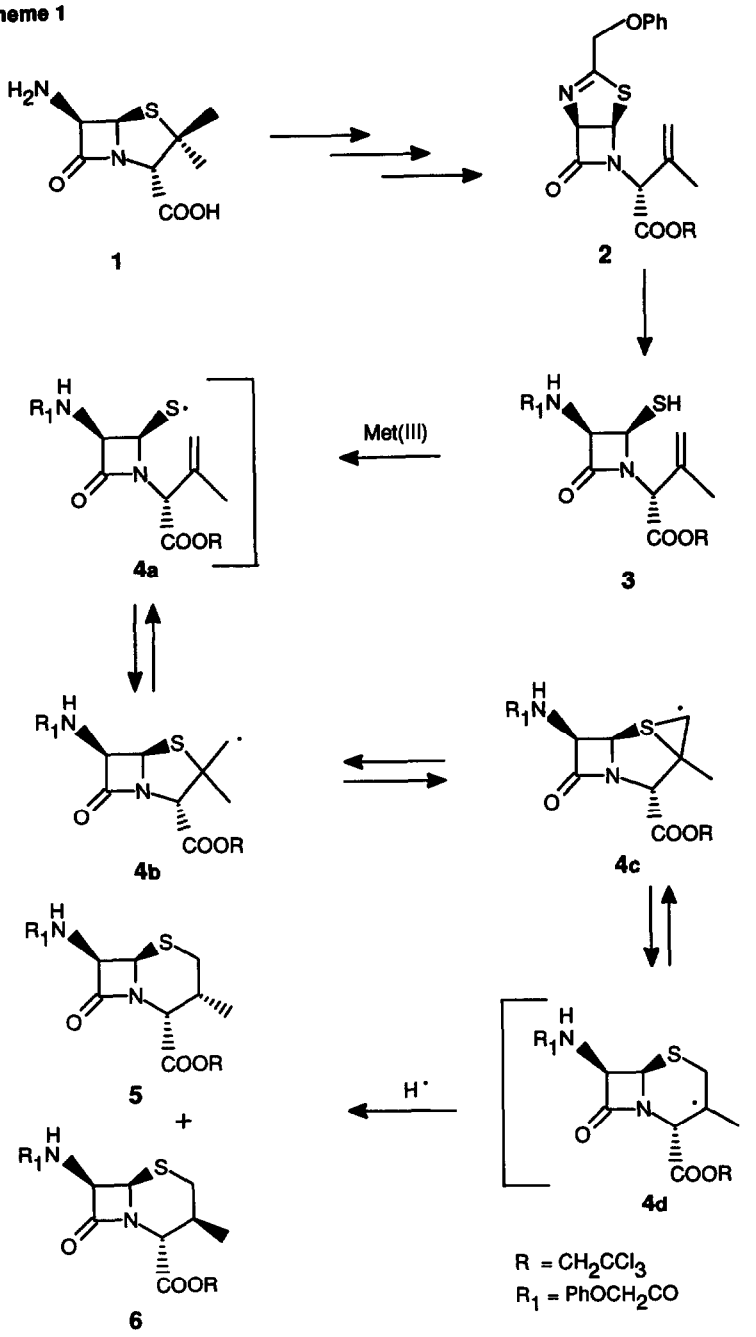
Table 1. Metal-promoted cyclization of thiol **3**.[a]

Entry	Promoter	Additive(eq)	5 + 6, yield %[b]
1	$Fe(ClO_4)_3 9H_2O$	-	10
2	$Fe(ClO_4)_3 9H_2O$	Ac_2O (10)	42
3	$Fe(ClO_4)_3 9H_2O$	AcOH (20)	30
4	$Fe(ClO_4)_3 9H_2O$	Ac_2O(10)/Phen(3)	-
5	$Fe(NO_3)_3 9H_2O$	-	29
6	$Fe(NO_3)_3 9H_2O$	Ac_2O (10)	34
7	$Fe(NO_3)_3 9H_2O$[c]	Ac_2O (10)	49
8	$Fe(NO_3)_3 9H_2O$	Phen (3)	-
9	$Mn(OAc)_3 2H_2O$	-	37
10	$Mn(OAc)_3 2H_2O$	AcONa (10)	3

a. See Experimental Part. b. Isolated yields of the **5/6** mixture. The **5/6** ratios, determined by HPLC and ^1H NMR, were for the Fe(III)-promoted reactions 80/20 and for the Mn(III)-promoted reactions 75/25. c. The reaction was carried out under high dilution.

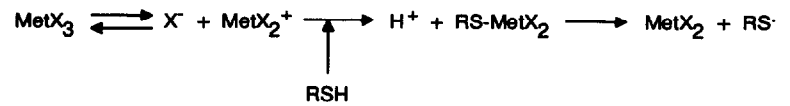
The results of the Fe(III)-promoted reaction are difficult to understand due to the overlap of different effects: modification of the redox potential, coordination capability and salt solubility. However, some considerations can be made on the basis of the results described in Table 1 (entries 1-8). The best yields of cephams **5** and **6** (80/20 ratio) were obtained using $Fe(ClO_4)_3 9H_2O/Ac_2O$ (entry 2) and $Fe(NO_3)_3 9H_2O/Ac_2O$ (entry 7) as promoters. The addition of acetic acid to the $Fe(ClO_4)_3 9H_2O$ reaction

Scheme 1


H2N
S
N
O
COOH
1
OPh
N
S
O
COOR
2
R1N
H
SH
3
Met(III)
S·
4a
4b
4c
4d
H·
5
6
+
R = CH2CCl3
R1 = PhOCH2CO

increased the yield from 10% to 30% (cf entries 1 and 3), suggesting that acetate anion was involved in the coordination sphere of the metal when the reaction was carried out in the presence of Ac_2O (entries 2,6,7). On the other hand, the addition of phenanthroline suppressed the cyclization (entries 4,8). In this case the coordination of **3** was hampered by the neutral ligand that surrounds the metal in the $Fe(phen)_3^{3+}$ complex.[14] These data clearly indicate that the oxidation process, takes place by coordination of the thiol onto a cationic metal-complex followed by homolytic cleavage of the Fe(III)-sulphur bond (eq 1).[10]

Equation 1



The $Mn(OAc)_3$-promoted reactions follows the same radical pathway. In fact, cephams **5** and **6** were isolated as a 75/25 mixture in 37% yield (entry 9) and the reaction was practically suppressed when the coordination of **3** onto the metal was hampered by addition of AcONa (entry 10).

The diastereoselectivities of the cyclizations reported in Table 1 were not dependent on the metal and the reaction conditions, indicating that the hydrogen source was always the same. The best hydrogen donor present in the reaction media was thiol **3**[15] and the goal of a catalytic reaction was achieved by a modification of the reaction conditions. In fact, all the Fe(III)-promoted reactions were carried out by addition of thiol **3** (0.1M in CH_2Cl_2/ CH_3CN) to a 0.1M solution of the iron salt in CH_3CN with or without the additive at 0-5°C. In contrast, the iron-catalyzed reaction were performed by dropwise addition of a 0.007M solution of the iron salt in CH_3CN, with or without the additive, to a 0.1M solution of thiol **3** in CH_3CN at rt (Table 2). The yields and the diastereoselectivities were not dependent on the iron salt used and the usual 80/20 mixture of **5** and **6** was isolated in up to 58% yield from **2** (entry 3). At present time we can not explain the failure of the reaction carried out in the presence of catalytic amounts of $Mn(OAc)_3$.

Table 2. Iron(III)-catalyzed cyclization of thiol **3**.[a]

Entry	Catalyst	Additive	5 + 6,yield[b]
1	$Fe(ClO_4)_3 9H_2O$	-	56
2	$Fe(ClO_4)_3 9H_2O$	Ac_2O (10)	53
3	$Fe(NO_3)_3 9H_2O$	-	58
4	$Fe(NO_3)_3 9H_2O$	Ac_2O (10)	50

a. See the experimental part. b. Isolated yields of the 80/20 **5/6** mixture.

Double single-electron oxidation.

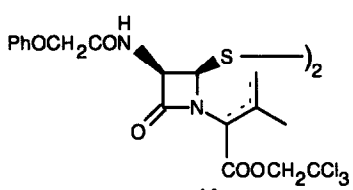
In contrast to the results shown in Table 1, the cyclization promoted by $FeCl_3$ afforded, albeit in very low yield (3.5%), a 69/31 mixture of 3-β-chloro cepham **8** and Δ^3-cephem **10** (Scheme 2, Table 3 entry 1). The overall process was a double single-electron oxidation.

The addition of halide anions to $Mn(OAc)_3$ gave similar results. In fact, the reaction promoted by $Mn(OAc)_3$, carried out in the presence of LiCl in CH_3COOH, afforded a mixture of **8**, **9**, and **10** in high yield (entry 2). Due to the instability of 3-α-chloro-cepham **9**, which in solution afforded spontaneously and rapidly Δ^3-cephem **10**, the **8/9/10** ratio was not reproducible. However, the **8/9,10** ratio was 51/49. It is worth noting that in spite of the number of publications on 3-halo-substituted cephams[8,16] the 3-α-halocepham derivatives were never isolated. The acidic media (CH_3COOH) possibly plays an important role in hampering the elimination of HCl from **9**. The $Mn(OAc)_3$-promoted reaction carried out in the presence of LiBr gave a 71/14/15 mixture of 2-bromomethyl penam **12**, 3-β-bromo cepham **13** and Δ^3-cephem **10**. In this case the yield range from 50% to 55% and the product ratio was not reproducible (entry 3). In fact, compound **12** was unstable under the reaction conditions and it gave spontaneously **10** and **13** (Scheme 2).[17] When LiI was added to the $Mn(OAc)_3$ promoted reaction the corresponding disulphide **14** was isolated (entry 4). This result seems to be a typical Mn(III) reaction with thiols.[18] The system $Mn(OAc)_3$/LiI in acetic acid generates iodine, however, a blank experiment (I_2/**3**/CH_3COOH/rt) showed that the formation of **14** was not due to the direct reaction between iodine and thiol **3**.

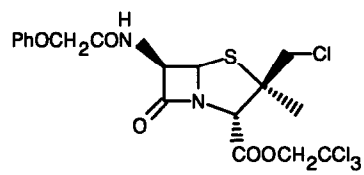
Table 3. Metal-promoted cyclization of thiol **3**. Synthesis of over oxidized products.[a]

Entry	Promoter	Products[b]	Overall yield[c]
1	$FeCl_3$	**8,10**	3.5
2	$Mn(OAc)_3 2H_2O$/LiCl	**8,9,10**	80
3	$Mn(OAc)_3 2H_2O$/LiBr	**10,12,13**	50-55
4	$Mn(OAc)_3 2H_2O$/LiI	**14**	76

a. See Experimental Part. b. See text for the product ratio. c. Isolated yields.



14

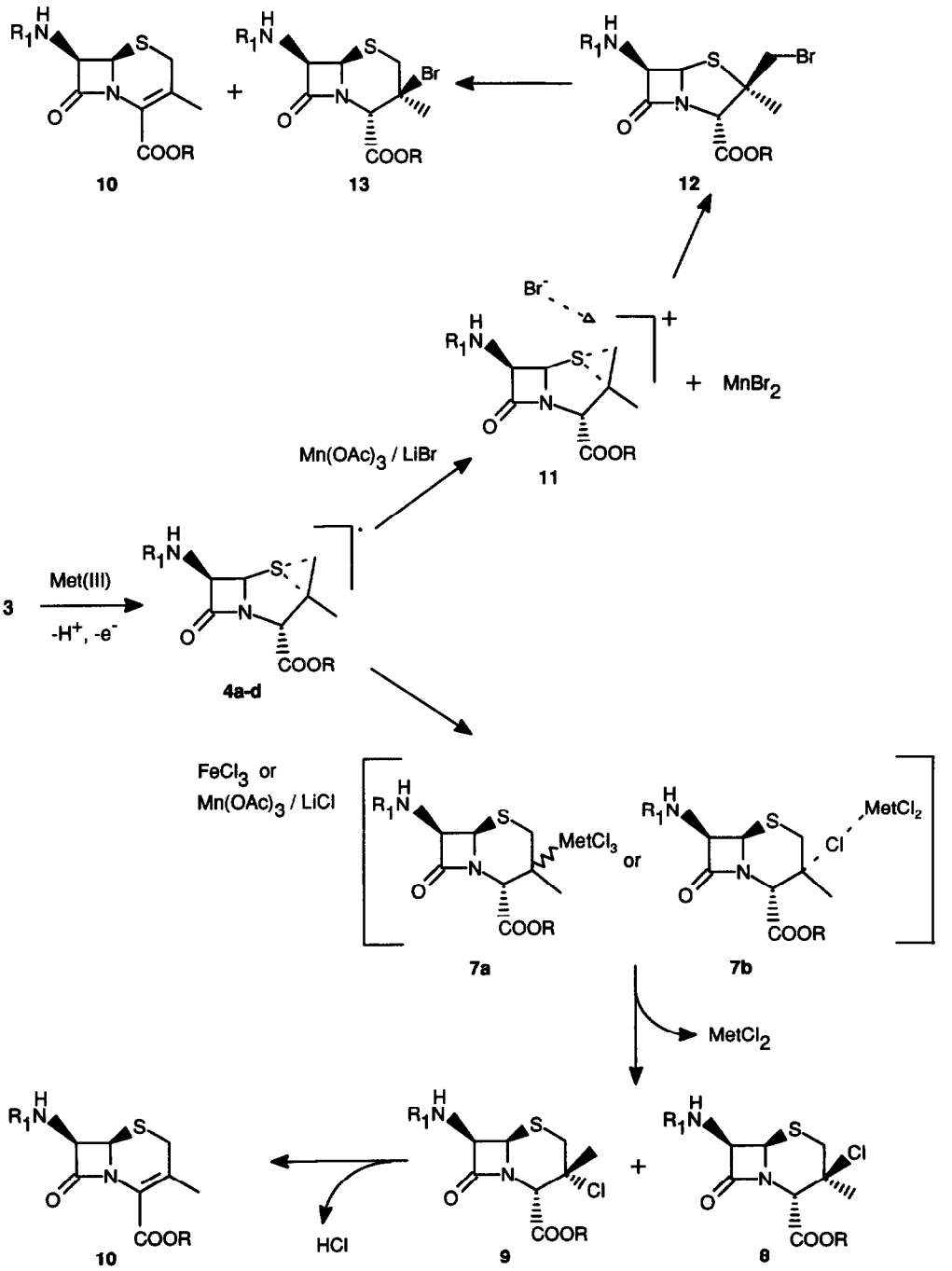


15

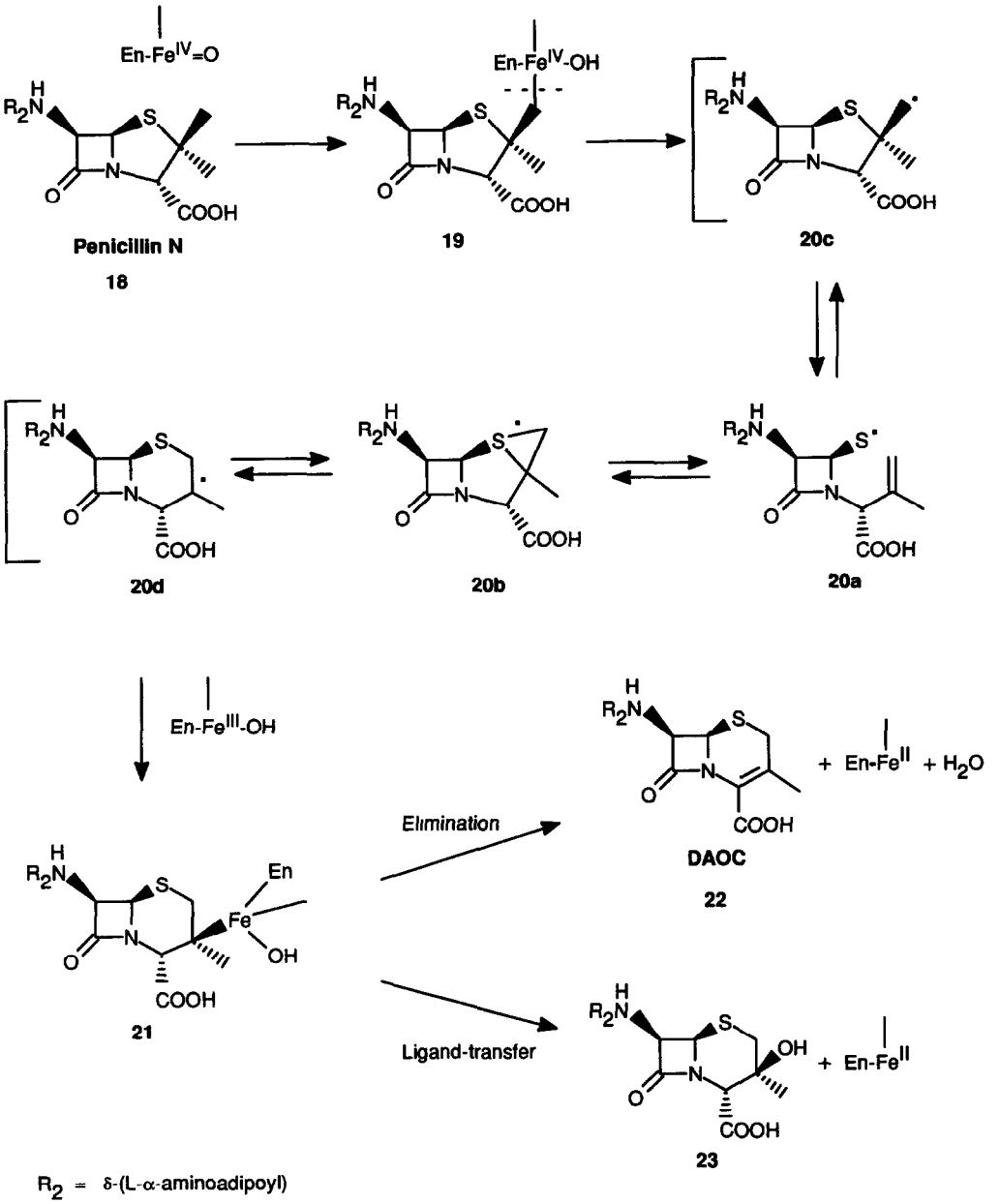
The double single-electron oxidation processes and the biosynthesis of Desacetoxy Cephalosporin C (DAOC).

The result of the $Mn(OAc)_3$/LiBr promoted reaction can be easily rationalized on the basis of the well know fate of the nucleophilic attack of a bromide anion to episulfonium ion **11** under kinetic conditions with formation of 2-β-bromometyl penam **12**.[16,17] It is worth noting that **11** has never been obtained by oxidation of the corresponding radical.[19] In contrast, the $FeCl_3$ and $Mn(OAc)_3$/LiCl cyclization did not afford the kinetic product of the nucleophilic attack of a chloride anion to **11**, 2-β-

Scheme 2


10
13
12
11
+ MnBr2
Mn(OAc)3 / LiBr
3
Met(III)
-H+, -e-
4a-d
FeCl3 or
Mn(OAc)3 / LiCl
MetCl3
or
MetCl2
7a
7b
MetCl2
HCl
9
8
10

Scheme 3


En-Fe^{IV}=O
Penicillin N
18
En-Fe^{IV}-OH
19
20c
20d
20b
20a
En-Fe^{III}-OH
21
Elimination
DAOC
22
+ En-Fe^{II} + H_2O
Ligand-transfer
23
+ En-Fe^{II}
R_2 = δ-(L-α-aminoadipoyl)

chloromethyl penam **15**.[16] A blank experiment showed that **15** was stable under the reaction conditions. Consequently, **8** and **9** come from direct chlorination of radical **4a-d** *via* a ligand transfer process. However, we cannot discriminate between the two possible inner sphere processes one occurring at the metal centre **7a** and the other on the ligand site **7b** (Scheme 2).[20]

In the DAOC/DAC Synthetase catalyzed ring expansion of penicillin N **18** to desacetoxy cephalosporin C (DAOC) **22**, the presence a small quantity of a shunt product, 3-β-hydroxy cepham **23**, is reported (Scheme 3). Interestingly, on incubation of the C-3 deuterated penicillin N, the amount of shunt product increases up to a third of the final mixture as a result of a primary isotopic effect. Furthermore, the incubation under an atmosphere of $^{18}O_2$, showed that the oxygen of the OH incorporated in **23** came partly from the stoichiometric oxidant, $^{18}O_2$.[21] On the basis of these observations and other studies, Baldwin proposed a mechanism centred on the trapping of radical **20a-d** by a Fe(III)-complex that generates the organometallic specie **21**. The composition of the final mixture can depend on the competition between elimination and ligand transfer (Scheme 3).[6c,21]

The biosynthetic pathway requires a two electron oxidation [Fe(IV) + $2e^-$ →Fe(II)]. We have reproduced the same overall process using two equivalents of a metal, Fe(III) or Mn(III), able to give a single-electron oxidation [2Me(III) + $2e^-$ → 2Me(II)]. The stabilized radical intermediate **4a-d** was obtained by a different starting reaction, inner sphere oxidation of a thiol (Scheme 1, eq 1) instead of insertion on a C-H bond and homolitic cleavage (Scheme 3). However, the cyclization carried out in the presence of $FeCl_3$ or $Mn(OAc)_3$/LiCl, **4a-d** afforded Δ^3-cephem **10** and 3-substituted cepham **8** *via* a ligand-transfer process and elimination. The fate of the radical intermediate **4a-d** and the reaction products, **8** and **10**, were similar to the one described by Baldwin for the DAOC/DAC Syntetase-catalyzed ring expansion of **18** (Scheme 3). [6c,21]

There are two major differences between the chemical (Scheme 2) and the enzymatic (Scheme 3) oxidation of the stabilized radical species: a. The metal ligands were different and consequently "Cl" was incorporated into the cephalosporin instead of "OH". b. The action of a basic residue in the active site of DAOC/DACS could be responsible for the effectiveness of the elimination pathway. The $FeCl_3$ or $Mn(OAc)_3$/LiCl promoted reactions were carried out in acidic media, because the presence of a base was not compatible with the use of thiol **3**.[22] However, 3-α-chloro cepham **9** was unstable and quantitatively gave Δ^3-cephem **10**, that is equivalent to the main product of the biosynthetic route, DAOC **22**.

CONCLUSION

Fe(III) proved to be the metal of choice for the metal-catalyzed thiyl radical cyclization for the synthesis of cephams **5** and **6**. In contrast, the $Mn(OAc)_3$/LiX systems were effective in the double single-electron oxidation process. Furthermore, we have suggested a mechanism that explains the results of the double single-electron oxidation process performed by $FeCl_3$ or $Mn(OAc)_3$/LiCl. Noteworthy, the reaction products and the mechanistic hypothesis were similar to the Baldwin results on the DAOC/DACS-catalyzed ring expansion of penicillin N to DAOC, that is the key step in the biosynthesis of cephalosporins.

EXPERIMENTAL SECTION

All compound were identified and characterized through their ^1H NMR spectra in $CDCl_3$ (Bruker 200-MHz) mass spectra (EI/ms spectra for the exact mass were recorded on a VG Analytical 70-70 EQ and FD/ms spectra were recorded on a Varian Mat 311-A), mp (Kofler apparatus and are uncorrected). Thiazoline **2** was synthetized by a known procedure.[8] Compounds **5**,[23] **6**,[23] **8**,[24] **10**,[25] **12**,[16] and **13**[24] were identified by comparison with a pure sample.

General procedure for the Fe(III)-promoted thiyl-radical cyclization. Table 1, entry 2.

Acetic anhydride (0.944mL, 10mmol) was added to a stirred solution of $Fe(ClO_4)_3 9H_2O$ (0.516g, 1mmol) in CH_3CN (10mL) at 0°C under Ar. After 0.7h a solution of **3** in 10mL of a 1/1 mixture of CH_3CN/CH_2Cl_2 obtained by standard procedure from **2** (0.463g, 1mmol),[9] was dropwise added in 0.2h. The reaction mixture was diluted after 3h with CH_2Cl_2 (40mL) and sequentially washed with HCl 10% (15mL) and water till neutrality. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure affording after purification by flash chromatography (hexane/ethyl acetate 7/3 by volume) 0.212g of a 80/20 mixture of **5** and **6** (42% yield).

The reaction described in entry 8 was carried out using 30mL of CH_3CN for the preparation of the promoter.

General procedure for the Mn(III)-promoted thiyl-radical cyclization. Table 1, entry 11.

To a stirred solution of $Mn(OAc)_3 2H_2O$ (0.268g, 1.0mmol) in CH_3COOH (30mL) at rt under Ar, a solution of **3** in 10mL of CH_2Cl_2 obtained by standard procedure from **2** (0.463g, 1mmol),[9] was dropwise added in 0.5h. After 2h the reaction was diluted with CH_2Cl_2 (40mL). Subsequent standard work-up and purification afforded 0.178g of a 75/25 mixture of cephams **5** and **6** (37% yield).

General procedure for the Fe(III)-catalyzed thiyl-radical cyclization. Table 2, entry 3.

To a stirred solution of thiol **3** in CH_3CN (10mL), obtained by standard procedure from **2** (0.463g, 1mmol),[9] at rt under argon a solution of $Fe(NO_3)_3 9H_2O$ (0.028g, 0.07mmol) in CH_3CN (10mL) was added over 10min. After 3h and standard purification 0.279g of a 80/20 mixture of cephams **5** and **6** (58% yield).

Pure samples of **5** and **6** were isolated by preparative HPLC.

2,2,2-Trichloroethyl (3R,6R,7R)-3-methyl-7-[(phenoxyacethyl)amino]-8-oxo-5-thia-1-azabicyclo [4.2.0]octane-2-carboxylate (**5**). White solid: mp 110-112°C; ir ($CHCl_3$) 3410, 2965, 1775, 1760, 1695, 1600, 1495 cm^{-1}; ^1H NMR δ 7.42-7.26 (m, 3H), 7.09-6.92 (m, 3H), 5.73 (dd, J=4.5, 9.9Hz, 1H), 5.38 (d, J=4.5Hz, 1H), 4.80 (s, 2H), 4.78 (d, J=6.0Hz, 1H), 4.55 (s, 2H), 3.12 (dd, J=11.8, 14.1Hz, 1H), 2.54 (dd, J=2.9, 14.1Hz, 1H), 2.31-2.17 (m, 1H), 1.12 (d, J=7.3Hz, 3H). MS calcd for $C_{18}H_{19}Cl_3N_2O_5S$: 480.0080. Found: 480.0008. $[\alpha]_D^{20} = +72.3$ (c 0.86 in $CHCl_3$).

2,2,2-Trichloroethyl (3S,6R,7R)-3-methyl-7-[(phenoxyacethyl)amino]-8-oxo-5-thia-1-azabicyclo [4.2.0]octane-2-carboxylate (**6**). White solid: 85-87°C. ir ($CHCl_3$) 3410, 2965, 1775, 1760, 1695, 1600, 1495 cm^{-1}; ^1H NMR δ 7.46 (bd, J=9.5Hz, 1H), 7.38-7.12 (m, 2H), 7.08-6.93 (m, 3H), 5.71 (dd, J=4.4,

9.5Hz, 1H), 5.28 (d, J=4.4Hz, 1H), 4.87 (d, J=11.4Hz, 1H), 4.80 (d, J=11.4Hz, 1H), 4.57 (s, 2H), 4.51-4.48 (m, 1H), 3.23-3.12 (m, 1H), 2.60-2.49 (m, 2H), 1.34 (d, J=6.6Hz, 3H). MS calcd for $C_{18}H_{19}Cl_3N_2O_5S$: 480.0080 . Found: 480.0010. $[\alpha]_D^{20}$= +72.8 (c 1.2 in $CHCl_3$).

General procedure for the Mn(III)/LiX-promoted cyclization .

To a stirred solution of $Mn(OAc)_3 2H_2O$ (0.536g, 2.0mmol) and LiX (10mmol) in CH_3COOH (10mL) at rt under Ar, a solution of **3** in 10mL of CH_2Cl_2 obtained by standard procedure from **2** (0.463g, 1mmol),[9] was dropwise added in 1h. After 2h the reaction was diluted with CH_2Cl_2 (40mL). The pure products were isolated by standard work up and flash chromatography while their ratios were determined by ^1H NMR of the crude.

2,2,2-Trichloroethyl (3S,6R,7R)-3-chloro-3-methyl-7-[(phenoxyacethyl)amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylate (**8**). Foam. ir ($CHCl_3$) 3415, 2930, 1790, 1765, 1700, 1605, 1500 cm^{-1}; ^1H NMR δ 7.53 (bd, J=9.8Hz, 1H), 7.40-7.26 (m, 2H), 7.10-6.89 (m, 3H), 5.75 (dd, J=4.5, 9.8Hz, 1H), 5.35 (d, J=4.5Hz, 1H), 4.92 (s, 1H), 4.86 (d, J=11.9Hz, 1H), 4.78 (d, J=11.9Hz, 1H), 4.58 (s, 2H), 3.67 (d, J=14.7Hz, 1H), 2.78 (dd, J=1.0, 14.7Hz, 1H), 1.79 (s, 3H). MS calcd for $C_{18}H_{18}Cl_4N_2O_5S$: 513.9691. Found: 513.9698. $[\alpha]_D^{20}$= +16 (c 0.97 in $CHCl_3$).

2,2,2-Trichloroethyl (3R,6R,7R)-3-chloro-3-methyl-7-[(phenoxyacethyl)amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylate (**9**) was unstable. The ir, ^1H NMR and ms spectra were recorded in the presence of **10**. ir ($CHCl_3$) 3420, 2930, 1790, 1765, 1700, 1610, 1500 cm^{-1}; ^1H NMR δ 7.48-7.22 (m, 3H), 7.08-6.87 (m, 3H), 5.68 (d, J=4.6, 12.5Hz, 1H), 5.38 (d, J=4.6Hz, 1H), 4.86 (d, J=11.9Hz, 1H), 4.79 (d, J=11.9Hz, 1H), 4.77 (s, 1H), 4.57 (s, 2H), 4.05 (d, J=14.0Hz, 1H), 2.80 (d, J=14.0Hz, 1H), 1.94 (s, 3H). MS calcd for $C_{18}H_{18}Cl_4N_2O_5S$: 513.9691. Found: 513.9705.

2,2,2-Trichloroethyl (6R,7R)-3-methyl-7-[(phenoxyacethyl)amino]-8-oxo-5-thia-1-azabicyclo [4.2.0]-octan-2-ene-2-carboxylate (**10**). White Solid: mp 97-99°C. ir ($CHCl_3$) 3400, 1790, 1740, 1595, 1495 cm^{-1}; ^1H NMR δ 7.42-7.21 (m, 3H), 7.08-6.83 (m, 3H), 5.88 (dd, J=4.8, 9.2Hz, 1H), 5.01 (d, J=4.8Hz, 1H), 4.97 (d, J=11.9Hz, 1H), 4.83 (d, J=11.9Hz, 1H), 4.56 (s, 2H), 3.54 (dd, J=0.8, 18.5Hz, 1H), 3.25 (d, J=18.5Hz, 1H), 2.20 (s, 3H). MS calcd for $C_{18}H_{17}Cl_3N_2O_5S$: 477.9924. Found: 477.9854. $[\alpha]_D^{20}$=+52.8 (c 0.96 in $CHCl_3$).

2,2,2-Trichloroethyl (3R,5R,6R)-3-bromomethyl-3-methyl-6-[(phenoxyacethyl)amino]-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate (**12**). White solid: mp 53-55°C. ir ($CHCl_3$) 3400, 1795, 1765, 1695, 1600, 1495 cm^{-1}; ^1H NMR δ 7.40-7.27 (m, 3H), 7.12-6.90 (m, 3H), 5.67-5.58 (m, 2H), 5.16 (s, 1H), 4.80 (s, 2H), 4.58 (s, 2H), 3.44 (s, 2H), 1.69 (s, 3H). FD/ms 566 [$(M+8)^+$,6%], 564 [$(M+6)^+$,20%], 562 [$(M+4)^+$,60%], 560 [$(M+2)^+$,100%], 558 [M^+,50%], 478 [$(M-HBr)^+$,28%]. $[\alpha]_D^{20}$=+108.0°C (c 0.96 in $CHCl_3$).

2,2,2-Trichloroethyl (3S,6R,7R)-3-bromo-3-methyl-7-[(phenoxyacethyl)amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylate (**13**). White solid: mp 110-112°C. ir ($CHCl_3$) 3410, 1795, 1765, 1700, 1495 cm^{-1}; ^1H NMR δ 7.55 (bd, J=9.8Hz, 1H), 7.38-7.26 (m, 2H), 7.08-6.90 (m, 3H), 5.74 (dd,

J=4.5, 9.8Hz, 1H), 5.35 (d, J=4.5Hz, 1H), 5.02 (bs, 1H), 4.85 (d, J=11.9Hz, 1H), 4.77 (d, J=11.9Hz, 1H), 4.58 (s, 2H), 3.57 (d, J=14.8Hz, 1H), 2.82 (dd, J=0.9, 14.8Hz, 1H), 2.00 (s, 3H). FD/ms 566 [(M+8)$^+$,6%], 564 [(M+4)$^+$,33%], 562 [(M+4)$^+$,80%], 560 [(M+2)$^+$,100%], 558 [M$^+$,49%], 478 [(M-HBr)$^+$,36%]. $[\alpha]_D^{20}$=-5.6°C (c 0.98 in $CHCl_3$).

From the reaction promoted by $Mn(OAc)_3$/LiI, disulphide **14** was isolated in almost 75% yield as a 93/7 mixture of conjugated and non-conjugated double bond derivatives. White solid. ^{1}H NMR of the non-conjugated double bond derivatives δ 7.49 (d, J=8.1Hz, 2H), 7.35-7.22 (m, 4H), 7.06-6.87 (m, 6H), 5.36 (dd, J=4.8, 8.1Hz, 2H), 5.26-5.18 (m, 4H), 5.09 (s, 2H), 4.96 (s, 2H), 4.72 (d, J=11.9Hz, 2H), 4.63 (d, J=11.9Hz, 2H), 4.57 (d, J=15.1Hz, 2H), 4.48 (d, J=15.1Hz, 2H), (s, 6H). The typical signals of the conjugated double bond derivative are the two singlet δ 2.33 and 2.17. FD/ms 96 [(M+10)$^+$, 8%), 966 [(M+8)$^+$, 23%), 964 [(M+6)$^+$, 52%), 962 [(M+4)$^+$, 81%), 960 [(M+2)$^+$ 100 %), 958 (M$^+$,40%), 478 (88%), 447 (52%).

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