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LETTERS

Ferric Chloride, an Efficient Promoter of Cationic Polyene Cyclizations

Stephanie E. Sen,* Steven L. Roach, Sarah M. Smith, and Yan zhi Zhang

Department of Chemistry, Indiana University-Purdue University at Indianapolis
402 North Blackford Street, Indianapolis, IN 46202, USA

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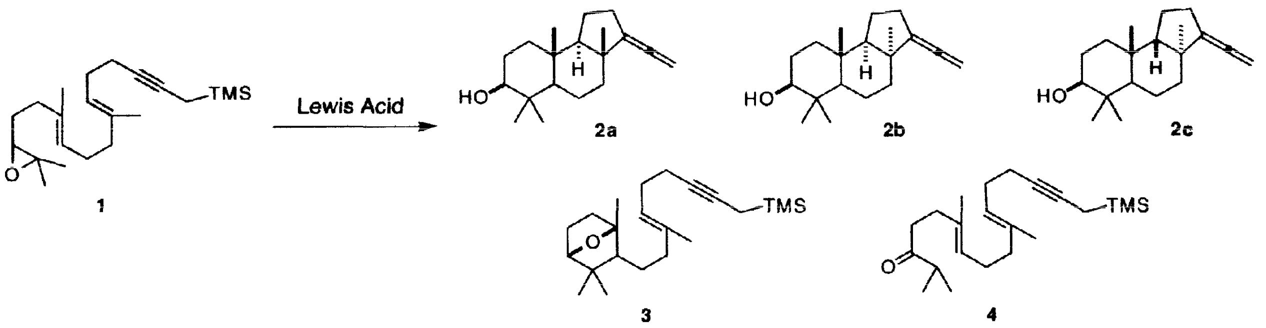
Abstract: The ability of ferric chloride to function as a promoter in biomimetic polyene cyclizations was evaluated using epoxy-polyene **1** as substrate. Reaction of **1** with either $FeCl_3 \cdot 6H_2O$ or anhydrous $FeCl_3$ yielded tricyclic alcohols **2a-c** in excellent yield, with comparable efficiency to $MeAlCl_2$ and Ti(*i*-OPr)Cl_3. This method can be extended to the cyclization of other polyene substrates, as seen in the conversion of **7** to decalol derivative **8**. © 1998 Elsevier Science Ltd. All rights reserved.

Cationic polyene cyclization methodology provides a valuable means of constructing a variety of natural products, including steroids and diterpenoids.[1] The ability of the epoxide functionality to serve as a cyclization initiator is quite attractive since its use leads to the direct generation of lanostane-type A ring structures.[2] Unfortunately, problems with such a biomimetic approach are numerous and epoxide rearrangement, partial cyclization, polymerization, as well as acid promoter incompatibility typically result in lower yields for epoxy-ene cyclizations.[3] We now report our initial studies utilizing ferric chloride as an alternative promoter in biomimetic polyene cyclizations. This reagent is convenient and highly effective in the cyclization of **1** (Scheme 1), comparing favorably with commonly-utilized titanium and aluminum based Lewis acids.



Scheme 1. Major Products Generated from the Lewis Acid-Promoted Cyclization of **1**.

To compare the efficiency of ferric chloride in biomimetic polyene cyclizations, the known epoxide **1**[4] was reacted with several Lewis acids (Table).[5] $BF_3 \cdot OEt_2$ was the least effective of the cyclization promoters tested,[6] providing only a 34% (combined) yield of tricycles **2a-c**, along with significant amounts of bicyclic ether (**3**) and ketone (**4**) which form *via* acid-catalyzed epoxide rearrangement chemistry. The mixed titanium reagent, Ti(*i*-OPr)Cl_3, was previously shown to be an effective cyclization promoter of **1**;[7] similarly, we found that reaction of **1** with Ti(*i*-OPr)Cl_3 yielded 68% of **2a-c** as a 4:1:1 isomeric mixture. We also examined the ability $MeAlCl_2$ to cyclize **1**; this Lewis acid which is widely used in epoxide polyene cyclizations was the

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most effective promoter studied,[8] producing tricyclic alcohols **2a-c** in 84% yield with only trace amounts of bicyclic ether **3**.

Although there are limited examples of epoxide cyclizations utilizing ferric chloride as a cyclization promoter,[9] recent studies from our laboratory demonstrating the ability of $FeCl_3 \cdot 6H_2O$ to function as a tandem deprotection/cyclization agent[10] prompted us to examine its ability to cyclize **1**. To our surprise, this Lewis acid, in either the anhydrous or hexahydrate form, was a highly effective cyclization promoter, providing tricycles **2a-c** in 74% and 82% yield, respectively. As noted in the $MeAlCl_2$ cyclization of **1**, byproduct formation was substantially suppressed. A general procedure follows:[11]

General cyclization procedure using $FeCl_3 \cdot 6H_2O$: To a solution of epoxide **1** (57 mg, 0.16 mmol) in CH_2Cl_2 (25 mL) at rt was added $FeCl_3 \cdot 6H_2O$ (133 mg, 3 equiv). The resulting yellow suspension was stirred for 15 min, then poured into a separatory funnel containing 25 mL of sat'd aq $NaHCO_3$. The layers were partitioned and the aqueous layer was extracted with ether (2 x 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a dark yellow oil. Flash chromatography using 2% EtOAc/hexane provided tricyclic alcohols **2a-c** (34 mg, 76%) as a white solid.

Promoter	Equiv	Temp °C	% Yield[a] **2a-c**[b]	 **3**	 **4**	Tricycle Ratio **2a / 2b / 2c**
$BF_3 \cdot OEt_2$	3.0	-78	34	7	10[c]	3.6 / 1 / 1
$Ti(i\text{-}OPr)Cl_3$	3.0	-78	68	16	2	4 / 1 / 1
$MeAlCl_2$	0.5	-78	84	4	0	5.6 / 1 / 1
$FeCl_3$	3.0	23	74	9	0	6 / 1 / 1
$FeCl_3 \cdot 6H_2O$	3.0	23	82	2	0	5.6 / 1 / 1

[a] GLC yield. [b] Structure determination of **2a** was performed by single crystal X-ray analysis of the corresponding *p*-bromobenzoate derivative. [c] Remainder: 45% unidentified.

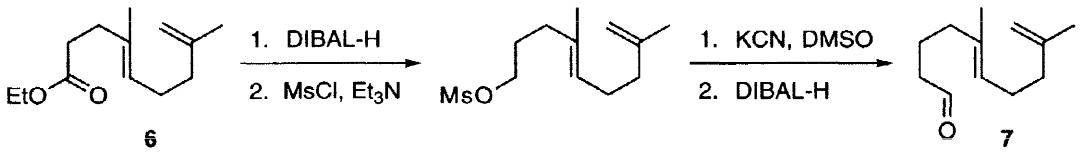
Table. Results from Lewis acid Promoted Cyclizations of Epoxide **1**.

Because consistently higher yields were obtained when *hydrated* $FeCl_3$ was used as promoter, it appeared that the presence of water facilitated the cyclization of **1**. The fact that $FeCl_3 \cdot 6H_2O$ displays modest protic acidity[12] and shows ligand coordination of $[Fe(H_2O)_4Cl_2]Cl \cdot 2H_2O$ in the solid state,[13] suggests that its mode of cyclization is different from traditional Lewis acid promoters. To investigate the role of water further, we attempted to prepare $FeCl_3 \cdot 6H_2O$ *in situ* by the addition of 6-10 equiv H_2O to a partially dissolved solution of anhydrous $FeCl_3$. This material proved to be an inferior cyclization promoter, increasing the quantity of both bicyclic ether **3** and monocyclized materials. This result suggests that the presence of unbound water increases the protic acidity of the solution (leading to undesired acid catalyzed epoxide rearrangement chemistry) and facilitates partial cyclization by premature trapping of the monocyclic cationic intermediate. Based on these results and previous acetal deprotection and epoxide ring opening studies,[14] we propose that anhydrous $FeCl_3$

effects the cyclization of **1** by traditional Lewis acid coordination of the epoxide oxygen, while $FeCl_3{\cdot}6H_2O$ promotes the cyclization of **1** *via* a combination of metal coordination and metal-mediated epoxide protonation.

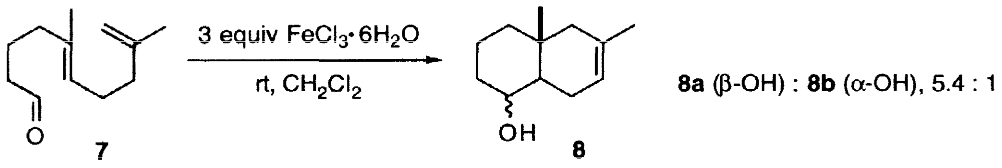
There are several advantages seen in the $FeCl_3{\cdot}6H_2O$ promoted cyclization of **1** which indicate that this acid can serve as a useful alternative to more traditional promoters. In contrast to $BF_3{\cdot}OEt_2$ and both the Ti- and Al-based Lewis acids, reactions involving $FeCl_3{\cdot}6H_2O$ can be carried out at room temperature, without the need for anhydrous and inert atmosphere conditions. Despite its protic acidity, $FeCl_3{\cdot}6H_2O$ did not cause premature protodesilylation of **1**; thus, it appears that this Lewis acid will have reasonable compatibility with acid sensitive functionalities which are frequently present in polyene cyclization substrates.

To determine the scope of $FeCl_3{\cdot}6H_2O$ as a cyclization promoter, we extended our studies to include the cyclization of polyene **7**; this compound was synthesized from ester **6**[15] (4 steps, 73%) *via* nitrile displacement of the corresponding mesylate followed by DIBAL-H reduction (Scheme 2).



Scheme 2. Synthesis of Aldehyde **7**.

Aldehyde **7** was subjected to the analogous conditions utilized for the cyclization of epoxide **1** (3.0 equiv $FeCl_3{\cdot}6H_2O$, rt, CH_2Cl_2, 15 min) and bicyclic alcohols **8a-b** were generated in 91% yield.[16,17] The excellent yield of alcohol **8**, derived from the weaker isopropenyl cyclization terminator, suggests that ferric chloride may serve as an effective promoter for higher-order polyene cyclizations.



Scheme 3. Ferric Chloride Promoted Cyclization of **7**.

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17. The ratio of α and β-OH isomers is consistent with a previous aldehyde-initiated polyene cyclization (see reference 4).