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ACETAL ELIMINATION REACTION ACCOMPANIED WITH REGIOSELECTIVE RING OPENING OF 1,4-BISACETAL-1,4-EPOXY-1,4-DIHYDRONAPHTHALENES

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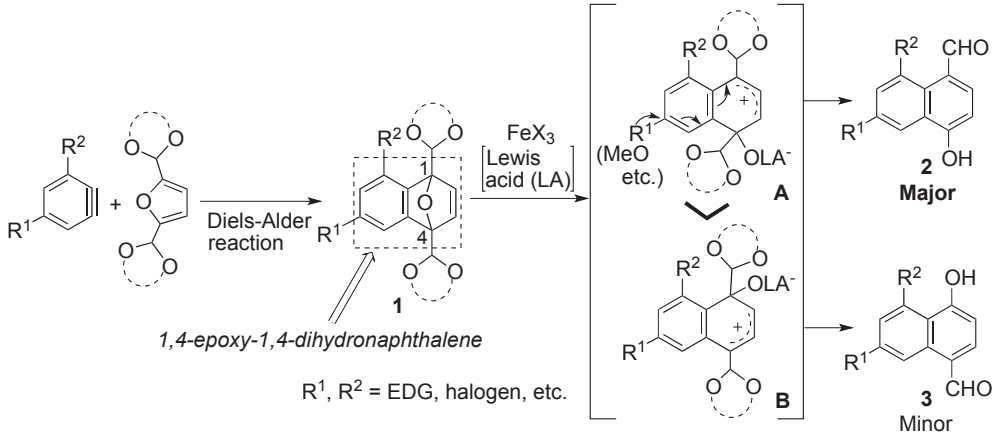
This paper is dedicated to Dr. Tohru Fukuyama, Specially Appointed Professor of Nagoya University and Professor Emeritus of the University of Tokyo for the occasion of his 70th birthday.

Abstract – 1,4-Epoxy-1,4-dihydronaphthalenes are useful precursors to synthesize 1-naphthols by an acid-catalyzed ring opening of their 1,4-epoxy moieties. 1-Acetal-substituted 1,4-epoxy-1,4-dihydronaphthalene was also converted to 1-naphthol via the unique iron-catalyzed ring opening of the 1,4-epoxy moiety followed by the elimination of the acetal moiety. The present method could be applied to the regioselective syntheses of highly-functionalized 4-formyl-1-naphthols from the unsymmetrical 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes.

1,4-Epoxy-1,4-dihydronaphthalenes (the basic skeleton of **1** in Scheme 1), easily prepared by the Diels-Alder reaction between benzynes and furans, are useful synthetic precursors of 1-naphthols via the acid-catalyzed ring opening of the 1,4-epoxy moieties.[1,2] The unsymmetrical substrates bearing the functional groups (R^1 and R^2) on the aromatic moiety are transformed into two cation intermediates (like **A** and **B**) resulted by the different acid-catalyzed ring opening paths of the 1,4-epoxy moiety. The regioselective ring opening can be controlled by the electronic effect of the R^1 and/or R^2 groups to selectively synthesize the 1-naphthol derivatives.[2] We have continuously investigated these regioselective ring opening reactions using various 1,4-epoxy-1,4-dihydronaphthalene derivatives followed by the further functionalizations in the presence of an Lewis acidic iron catalyst.[3] Both substituents on the 1 and

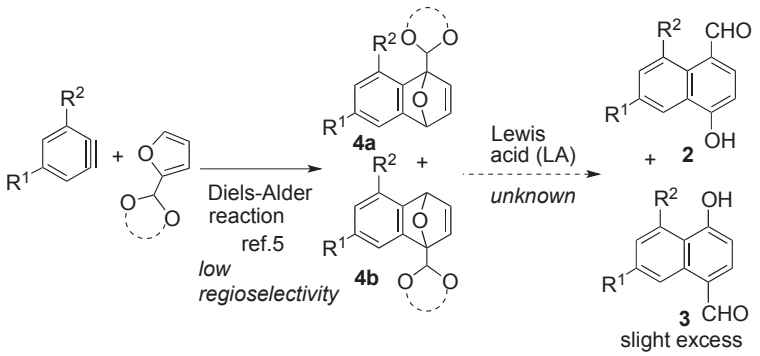
4 bridge-head positions play an important role in the stabilization of the resulting cation intermediates (like **A** and **B**) to achieve these desirable reactions. We now report the unique reaction of the 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes **1** as substrates to form 4-formy-1-naphthols **2** by the iron-catalyzed ring opening of the 1,4-epoxy moiety of **1** accompanied with the elimination of one acetal unit (Scheme 1). The regioselective ring opening of the unsymmetrical substrates bearing an electron-donating methoxy group or halogen as the R^1 or R^2 group on the aromatic nucleus could be accomplished to selectively prepare the functionalized 4-formy-1-naphthols **2** as major isomers.



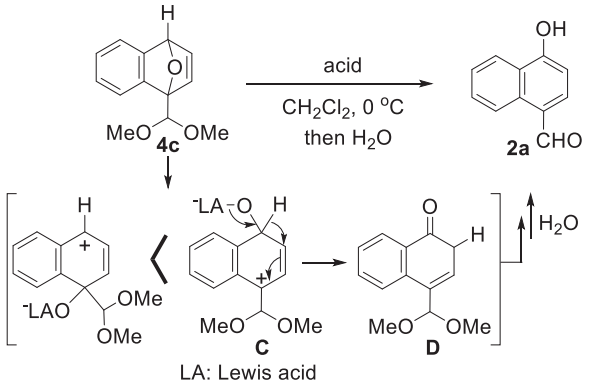
Scheme 1. Regioselective ring opening of 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes accompanied by the elimination of one acetal moiety to 4-formyl-1-naphthols (EDG: electron-donating group)

4-Formyl-1-naphthols **2** and **3**, which are important precursors to synthesize the bioactive compounds,[4] were assumed to be constructed from the 1-acetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes **4a** and **4b**, prepared by the Diels-Alder reaction between the corresponding benzyne and 1-acetal-substituted furan derivatives,[5] by the acid-catalyzed ring opening of the 1,4-epoxy moieties and the aqueous deprotection of the acetal to the aldehyde (Scheme 2). However, the regioselective coupling of the unsymmetrical benzyne and furan derivatives could not be controlled, and the mixture of **4a** and **4b** was obtained with a slight excess amount of **4b**.[5] Meanwhile, the ring opening reaction of **4a** and **4b** is unreported. If the assumed ring opening of **4a** and **4b** was accomplished, the mixture of two isomers **2** and **3** could be obtained with a slight excess amount of **3**. Unexpectedly, the 4-formyl-1-naphthol **2a** could not be efficiently synthesized from 1-dimethoxymethyl-substituted 1,4-epoxy-1,4-dihydronaphthalene **4c** as a simple substrate (Scheme 3). The use of 5 mol% $FeCl_3$ or $FeBr_3$[6] gave trace amounts of **2a**, and the activation of $FeCl_3$ by the addition of trimethylsilyl chloride (TMSCl)[7] gave a complex mixture. Only 36% of **2a** could be obtained by using 50 mol% of $FeBr_3$ via the regioselective ring opening (C-O bond cleavage) to form a more stable tertiary carbocation intermediate

C followed by the hydride shift[1,2] and the aqueous deprotection of the acetal to aldehyde. The use of 1 equivalent of $FeBr_3$ was required to complete the reaction. Trifluoroacetic acid (TFA: 200 mol%) as a Brønsted acid was also ineffective.



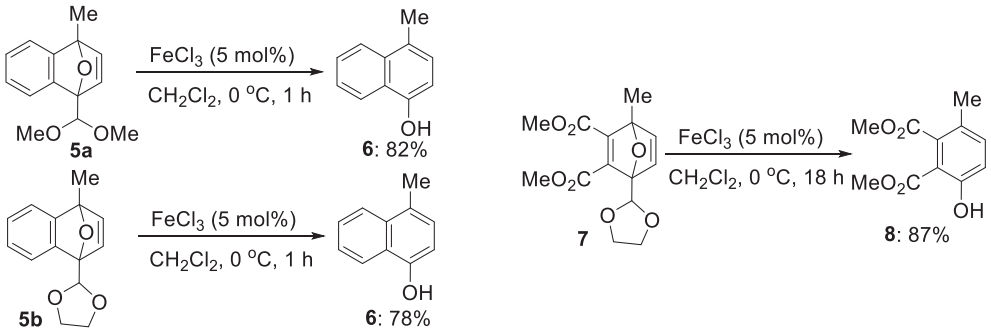
Scheme 2. Problem in the case of a 1-acetal-substituted substrate



acid	yield of **2a**
$FeCl_3$ (5 mol%)	trace
$FeCl_3$ (5 mol%) + TMSCl (1 equiv.)	complex mixture
$FeBr_3$ (5 mol%)	trace
$FeBr_3$ (50 mol%)	36% (6 h) (44% of **4c** was recovered)
$FeBr_3$ (1 equiv.)	93% (6 h)
TFA (200 mol%)	no reaction

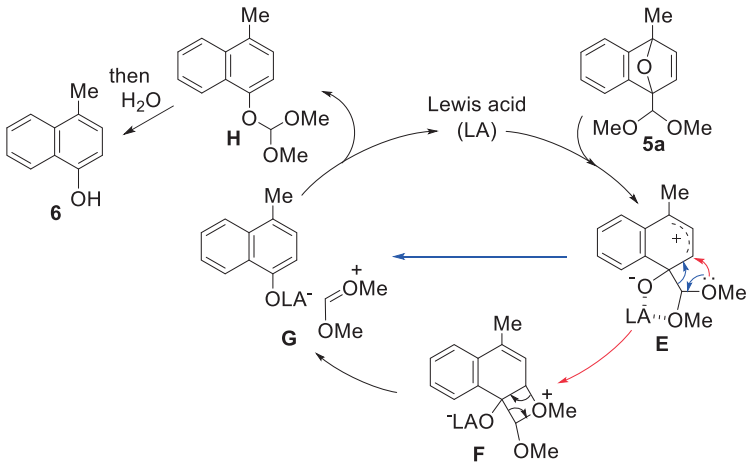
Scheme 3. Acid-catalyzed ring opening of 1-dimethoxymethyl-substituted 1,4-epoxy-1,4-dihydronaphthalene

As mentioned in the Introduction, the various iron-catalyzed ring opening functionalizations of 1,4-epoxy-1,4-dihydronaphthalenes based on the effect of both bridge-head substituents were accomplished.[3] We newly investigated the reaction using a substrate bearing an acetal unit and an alkyl group at each bridge-head carbon of 1,4-epoxy-1,4-dihydronaphthalene. 1-Dimethoxymethyl-4-methyl-1,4-epoxy-1,4-dihydronaphthalene **5a** was transformed in the presence of $FeCl_3$ (5 mol%) in CH_2Cl_2 at 0 °C for 1 h to 4-methyl-1-naphthol **6** in a high isolated yield (82%) accompanied by the elimination of the acetal unit (Scheme 4). Similarly, 1-(1,3-dioxolan-2-yl) substitute **5b** was converted into **6** in 78% yield. A monocyclic 1-phenol derivative **8** was also produced from 1-(1,3-dioxolan-2-yl)-4-methyl-oxanorbornadiene substrate **7** in a similar manner.



Scheme 4. Reactions of 1-acetal-substitued 4-methyl-oxanorbornadiene derivatives

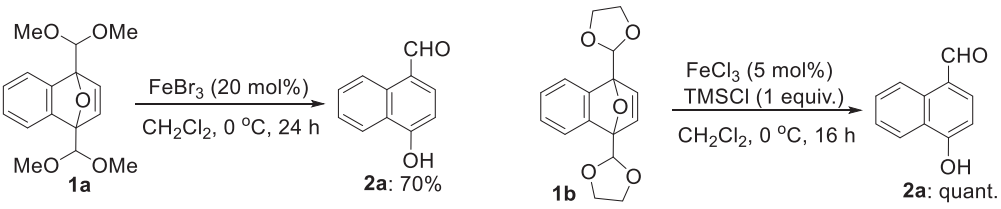
The proposed reaction mechanism for the reaction of **5a** to **6** is shown in Scheme 5. The cleavage of the C-O bond of **5a** is site-selectively carried out via the formation of the five-membered coordination state between the two oxygen atoms of the 1,4-epoxy moiety and a methoxy group of the acetal in **5a** and a Lewis acid (LA) to construct the zwitter-ionic intermediate **E**. The subsequent elimination of the acetal unit via the direct path (blue arrow) or formation of the oxetane intermediate **F** (red arrow) and the coupling between the corresponding naphthol and an oxonium ion intermediate **G** produce the orthoester intermediate **H**. Finally, the hydrolysis of **H** gives the 1-naphthol derivative **6**. The trap of the cation intermediates using various nucleophiles (allylTMS, $TMSN_3$, arenes, MeMgBr, PhMgBr, etc.) failed to give any positive result.



Scheme 5. Proposed reaction mechanism

The iron-catalyzed ring opening accompanied by the elimination of the acetal unit could be applied to the reaction using 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes **1a** and **1b** (Scheme 6). 1,4-Bis(dimethoxymethyl)- or 1,4-(1,3-dioxolan-2-yl)-1,4-epoxy-1,4-dihydronaphthalene **1a** or **1b** was each efficiently transformed to 4-formyl-1-naphthol **2a** in good or excellent yield after the aqueous

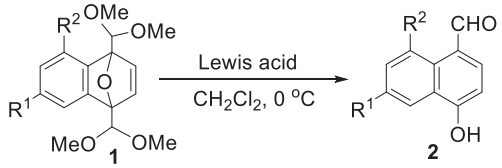
deprotection of the remaining acetal moiety to the corresponding aldehyde, while **2a** could not be efficiently constructed from the 1-dimethoxylmethyl-substituted derivative **4c** as a simple substrate as shown in Scheme 1. Although the screening of the optimal catalyst was required in each reaction including the results shown in Table 1, $FeCl_3$ or $FeBr_3$ indicated a better catalyst activity (the catalyst efficiency for the reaction of **1a** is described in the Supporting Information).[8]

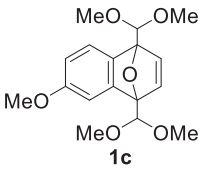
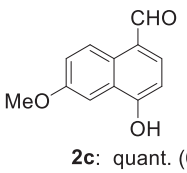
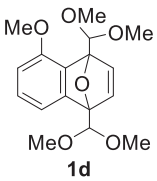
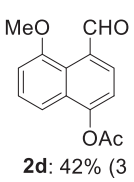
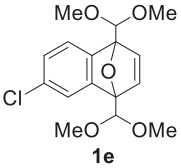
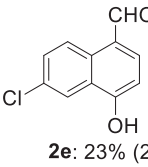


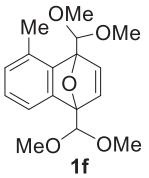
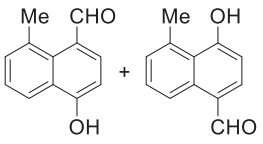
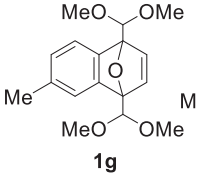
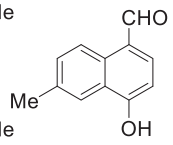
Scheme 6. Ring opening of 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes

Encouraged by the 4-formyl-1-naphthol **2a** synthesis from 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes **1a** and **1b**, the regioselective reaction using unsymmetrical substrates bearing a functional group on the aromatic nucleus was next investigated (Table 1).

Table 1. Regioselective synthesis of 4-formyl-1-naphthols from unsymmetrical bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes



Substrate	Product
 **1c**	 **2c**: quant. (6 h)[a]
 **1d**	 **2d**: 42% (3 h)[a,b] (Recovered **1d**: 35%)
 **1e**	 **2e**: 23% (20 h)[c] (Recovered **1e**: 50%)

Substrate	Product
 **1f**	 **2fa**: 20%, **2fb**: 2% (20 h)[d] (Recovered **1f**: 68%)
 **1g**	 **2g**: 22% (20 h)[e] (Recovered **1g**: 49%)

[a] $FeCl_3$ (5 mol%) and TMSCl (1 equiv.) were used.
[b] Isolated after acetylation, because the inseparable byproducts were contaminated.
[c] $FeCl_3$ (10 mol%) and TMSCl (1 equiv.) were used.
[d] $FeBr_3$ (10 mol%) was used.
[e] $FeBr_3$ (5 mol%) was used.

The reactivity of 1,4-(1,3-dioxolan-2-yl) derivative **1b** was higher than that of substrate **1a** as shown in Scheme 6 and the Supporting Information. Substrates possessing bisdimethoxymethyl functionalities **1c-1g** were used in Table 1 due to the easy preparation. The unsymmetrical substrate **1c** bearing an electron-donating methoxy group on the distal[9] position (R^1) of the aromatic nucleus was transformed into the naphthol product **2c** in quantitative yield with a perfect regioselectivity by the site-selective C-O bond cleavage of **1c** to stabilize the cation intermediate (like **A** in Scheme 1). Compound **1d** possessing a methoxy group on the proximal position (R^2) underwent the perfect regioselective ring opening to produce **2d** in 42% yield, and 35% of **1d** was recovered. Although the chloro- and methyl-substituted substrates **1e**-**1g** were also regioselectively transformed to the corresponding 4-formyl-1-naphthol derivatives **1f**, **2fa** and **2g**, the reactions were imcomplete. The use of other catalysts, increasing usage of the catalyst and elongation of the reaction time were all ineffective for the yield improvement. These poor reactivities are not clearly explained.

In conclusion, the unprecedented Lewis acid-catalyzed ring opening accompanied by the elimination of an acetal unit by using the acetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes as substrates was accomplished. The unsymmetrical 1,4-bisacetal-substituted 1,4-epoxy-1,4-dihydronaphthalenes bearing a methoxy, chloro, or methyl group on the aromatic nucleus underwent the regioselective ring opening to produce the corresponding 4-formyl-1-naphthol derivatives in moderate to good yields based on the consumed starting material. The present method is expected to be applied to the syntheses of materially useful naphthalene derivatives.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, 1H and 13C NMR, MS etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/25784/99/1.

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6. Iron catalysts, such as $FeCl_3$ and $FeBr_3$, were suitable to activate the benzylic C-O bonds in various functionalizations, see; (a) Y. Sawama, S. Nagata, Y. Yabe, K. Morita, Y. Monguchi, and H. Sajiki, *Chem. Eur. J.*, 2012, **18**, 16608; (b) Y. Sawama, K. Shibata, Y. Sawama, M. Takubo, Y. Monguchi,

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7. TMSCl can increase the Lewis acidity of $FeCl_3$ by the formation of a combined Lewis acid between $FeCl_3$ and TMSCl, see the references 3d, 5b and 5c. The formation of a combined Lewis acid derived from TMSCl and $InCl_3$ was also suggested in the literature. See; Y. Onishi, Y. Nishimoto, M. Yasuda, and A. Baba, *Org. Lett.*, 2011, **13**, 2762.
8. For experimental details and spectral data of new compounds, see the supporting information.
9. R^1 and R^2 groups of substrates **1c-g** were respectively expressed as distal and proximal substituents on the basis of the distance from the dihydrobenzene ring as depicted in reference 3b.