

Lewis Acid-Mediated Displacements of
Alkoxydioxolanes: Synthesis of a
1,2-Dioxolane Natural Product

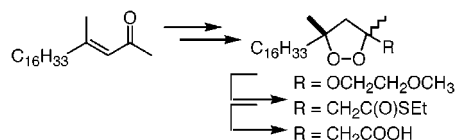
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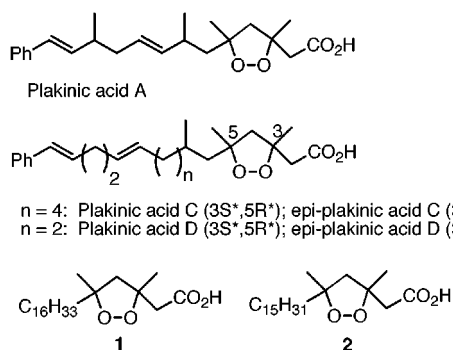
ABSTRACT



Addition of electron-rich alkenes to the peroxycarbenium ions derived from Lewis acid-mediated ionization of 3-alkoxy-1,2-dioxolanes provides an efficient route for the synthesis of substituted 1,2-dioxolanes. The methodology is illustrated with a rapid synthesis of a 1,2-dioxolane natural product related to the plakinic acids.

A number of bioactive molecules containing a 1,2-dioxolane subunit have been isolated from marine sponges (Scheme 1).¹ Plakinic acid A, the first member of the family to be

Scheme 1. 1,2-Dioxolane Natural Products



discovered, is an active antifungal agent and has been reported to inhibit growth of L1210 leukemia cells.² Plakinic

and epiplakinic acids C and D have been reported to inhibit growth of KB and LoVo human cancer cell lines while the saturated dioxolanes **1** and **2** were reported to inhibit growth of HCT-8 tumor cell lines.³

To date, the only synthetic approach to the family has been a racemic synthesis of **2** in which installation of the 1,2-dioxolane was achieved through sequential inter- and intramolecular peroxymercuration.⁴ Unfortunately, peroxymercuration is unlikely to be compatible with the unsaturated side chains of the other plakinic or epiplakinic acids, a drawback also shared by most reported methods for dioxolane synthesis.⁵

Our lab has been exploring the synthesis of functionalized peroxides based upon Lewis acid-mediated reactions of peroxyacetals.⁶ We now report the successful application of this method to the synthesis of functionalized 1,2-dioxolanes

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based upon the ionization of 3-alkoxy-1,2-dioxolanes, followed by trapping of the intermediate peroxy-carbenium ions with allylsilanes, silyl enol ethers, and silyl ketene acetals to install a functionalized headgroup (Figure 1). The utility

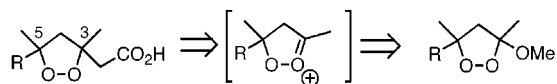
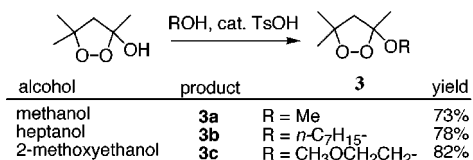


Figure 1. Retrosynthetic approach.

of the method is illustrated with a synthesis of the dioxolane natural product **1**.

Initial substrates **3a–3c** were prepared through acid-catalyzed etherification of 3-hydroxy-3,3,5-trimethyl-1,2-dioxolane (Scheme 2), itself available from base-mediated

Scheme 2. Synthesis of Model Alkoxydioxolanes

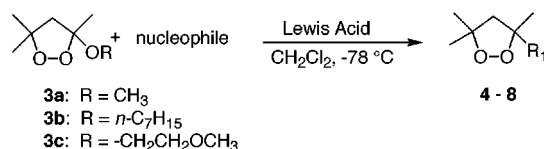


reaction of hydrogen peroxide with 4-methyl-3-penten-2-one.⁷ The choice of the methoxy acetal (**3a**) was based upon our previous experience with methoxy peroxyacetals. However, the volatility of **3a** led us to prepare a higher molecular weight analogue, **3b**. Furthermore, given the excellent performance of the 2-methoxyethoxy group as a leaving group in peroxy-carbenium-mediated reactions, we prepared acetal **3c** through reaction with 2-methoxyethanol⁸.

Initial investigations of alkoxydioxolane displacement were conducted using allyltrimethylsilane as the trapping nucleophile. We were particularly interested in whether the increased strain in 1,2-dioxolanes relative to 1,2-dioxanes or acyclic peroxides would translate into a reduced barrier to ionization. In fact, addition of SnCl₄ to a chilled solution of **3a** followed by addition of allyltrimethylsilane resulted in rapid reaction even at -78 °C to produce a moderate yield of allylated dioxolane **4** (Scheme 3). An improved yield was obtained from heptyloxy analogue **3b** and an even better yield from the 2-methoxyethoxy acetal **3c**. Comparison of Lewis acids revealed SnCl₄ to be superior to TiCl₄, and the combination of SnCl₄ with the 2-methoxyethoxy leaving group was employed for the remainder of these studies.

Displacement with the hindered silyl enol ether derived from 3,3-dimethyl-2-butanone proceeded readily but furnished the dioxolane ketone **5** in much lower yield, accompanied by significant amounts (42%) of the dioxinol. Presumably the bulky nucleophile is less effective in capturing

Scheme 3. Displacements of Alkoxydioxolanes **3a–3c**



s. mat.	nucleophile	Lewis acid	dioxolane	R ₁	yield (%)
3a		SnCl ₄	4	CH ₂ CH=CH ₂	42
3b	" "	SnCl ₄	4	CH ₂ CH=CH ₂	54
3c	" "	SnCl ₄	4	CH ₂ CH=CH ₂	62
3c	" "	TiCl ₄	4	CH ₂ CH=CH ₂	53
3c		SnCl ₄	5	CH ₂ C(O) <i>t</i> -Bu	25
3c		SnCl ₄	6	CH ₂ C(O)Ph	53
3c		TiCl ₄	7	CH ₂ C(O)SEt	57
3c		SnCl ₄	8		74

the cationic intermediate, leading to trapping by water upon workup. This was supported by the improved yields of dioxolanes **6** and **8** obtained upon reaction with the less hindered silyl enol ethers derived from acetophenone and cyclohexanone. Finally, installation of an acetate headgroup was achieved through Lewis acid-mediated reaction of alkoxydioxolane **3c** with the silyl enol ether of ethyl thioacetate to form thioester **7**. The choice of thioester as an acetate synthon was based upon recent investigations demonstrating the superiority of thioacetate silyl ketene acetals as nucleophiles in reactions with simple peroxyacetals.⁹

Given the success of the Lewis acid-mediated displacements, the only remaining concern was the ability to convert the homologated dioxolane into the 1,2-dioxolane acetic acid moiety present in all of the natural products. Hydrolysis of 1,2-dioxolane acetic acid thioester (**7**) in the presence of lithium hydroxide/hydrogen peroxide¹⁰ proceeded rapidly and in good yield to afford the corresponding carboxylic acid **7a** (Figure 2).

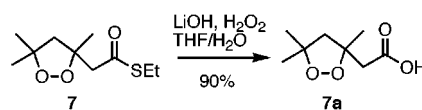


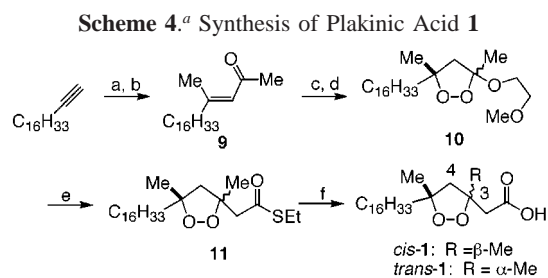
Figure 2. Hydrolysis of thioester.

On the basis of the outcome of the model studies, the new methodology was next applied to a short synthesis of 1,2-

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dioxolane **1**, an analogue of the plakinic acids isolated from *Halichondriidae* sponges. The requisite enone (**9**) was rapidly assembled (Scheme 4). Carboalumination of octadecyne,



^a (a) Me_3Al , Cp_2ZrCl_2 , then acetaldehyde (70%); (b) PDC, DMF (91%); (c) H_2O_2 , LiOH (19%); (d) 2-methoxyethanol, TsOH (79%); (e) $\text{CH}_2=\text{C}(\text{OTMS})\text{SEt}$, TiCl_4 (54%); (f) LiOH, THF, H_2O , H_2O_2 (90%).

followed by trapping of the intermediate alkenylaluminum with acetaldehyde, furnished an allylic alcohol which was oxidized to provide **9**. Conjugate addition of hydrogen peroxide could be achieved in the presence of lithium hydroxide, albeit in low yield, to furnish a mixture of diastereomeric dioxinols. Acid-catalyzed etherification with 2-methoxyethanol furnished alkoxydioxolane **10** as a 1:1 mixture of *cis* and *trans* isomers. Although separable by chromatography, the diastereomeric alkoxydioxolanes exhibited identical reactivity in the next step and were therefore carried on as a mixture. Substitution of the methoxyethoxy group was readily achieved using the silyl ketene acetal of ethyl thioacetate in the presence of TiCl_4 to afford thioester

11 as an inseparable 1:1 mixture of diastereomers. Hydrolysis as before proceeded rapidly to furnish an excellent yield of **1** as a 1:1 mixture of *cis* and *trans* diastereomers which could be separated with difficulty. The first eluting diastereomer was determined to be of *cis* configuration on the basis of the relative strength of the NOE enhancements observed at the individual C_4 methylene hydrogens on the dioxolane ring following irradiation of the C_3 and C_5 methyl groups.

In conclusion, we have demonstrated that addition of carbon nucleophiles to peroxy-carbenium ions provides an efficient route for the synthesis of 1,2-dioxolanes, including a plakinic acid. Application of this strategy to other plakinic acids will be reported in due course.^{11,12}

Acknowledgment. We gratefully acknowledge support from the National Institutes of Health (GM 45571) and the assistance of Prof. Richard Shoemaker with NOE studies. NMR spectra were recorded on spectrometers purchased, in part, with NIH support (SIG-1-510-RR06307).

Supporting Information Available: ^1H and ^{13}C spectra for **1**, 3-hydroxy-3,3,5-trimethyl-1,2-dioxolane, and **3–11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) As with any work involving peroxides, the use of standard safety precautions is strongly recommended: (a) Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992. (b) Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2. (c) Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, p 341.

(12) All new compounds were characterized by ^1H , ^{13}C , IR, and either elemental analysis or high-resolution mass spectrometry.