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Lewis acid catalysed rearrangements of unsaturated bicyclic [2.2.*n*] endoperoxides in the presence of vinyl silanes; access to novel Fenozan BO-7 analogues

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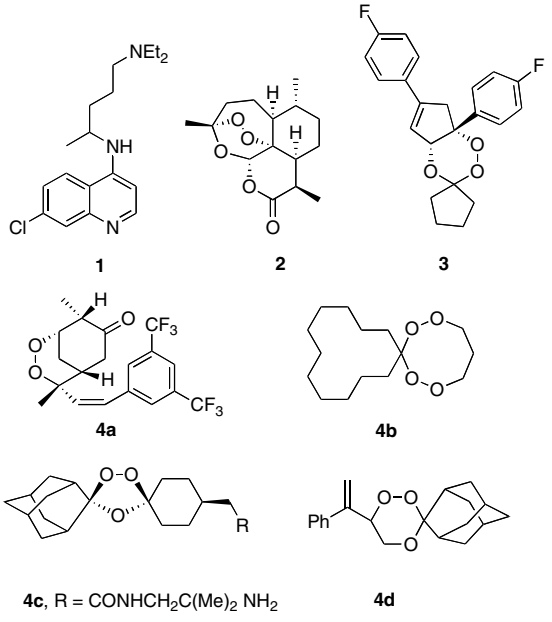
Abstract—Reactions of a series of unsaturated bicyclic [2.2.*n*] endoperoxides with allyltrimethylsilane in the presence TMSOTf or $SnCl_4$ provides the *cis*-configured endoperoxides **9a**–**12**. It is proposed that this novel reaction proceeds via attack of the allylsilane on the carbocation derived from heterolytic cleavage of the endoperoxide bridge. The reaction proceeds with a high degree of diastereoselectivity and we propose that the bulky $-CH_2SiMe_3$ substituent adopts an equatorial position in a product-like transition state. In contrast to Fenozan B0-7, these compounds displayed poor antimalarial activity versus chloroquine-resistant parasites in vitro.

The increasing resistance of many strains of the *Plasmodium falciparum* malaria parasite to traditional quinoline antimalarial drugs such as chloroquine **1** has rendered these treatments useless in many parts of the world. The search for new therapies has established that artemisinin **2** is a potent antimalarial and several derivatives are currently used to treat resistant malaria.[1] However, artemisinin and its semi-synthetic derivatives are expensive replacements for chloroquine and alternatives are being sought. The antimalarial activity of artemisinin stems from its peroxide bond and currently several groups around the world are involved in the search for new synthetic endoperoxide-containing antimalarials, which to date has resulted in several promising leads, including Fenozan **3**,[2] arteflene[3] **4a**, tetraoxanes such as **4b**[4] and Vennerstrom's dispiro 1,2,4-trioxolane **4c**.[5] Recently, Singh et al.[6] have also made significant progress in the design and synthesis of potent endoperoxides including the simple dispiro 1,2,4-trioxanes **4d**.



As noted above, one of the most promising classes of synthetic antimalarials to have been prepared to date are the 1,2,4-trioxane derivatives such as **3** (this

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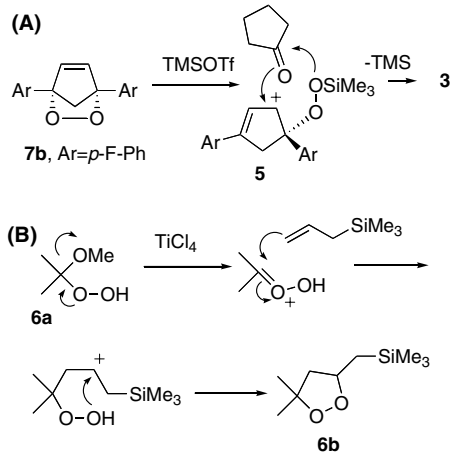
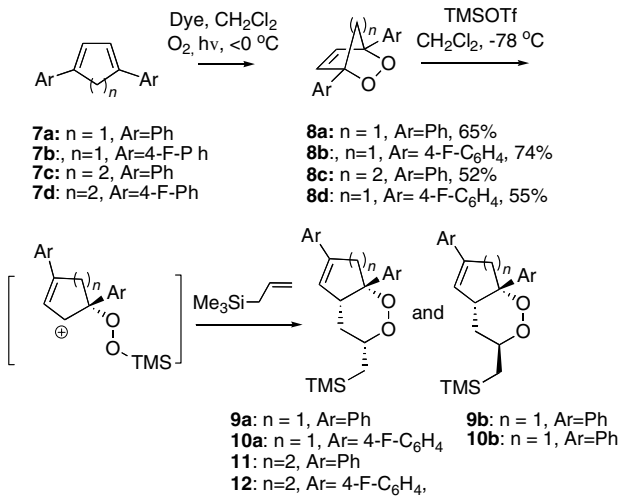


Scheme 1. (A) Lewis acid catalysed synthesis of Fenozan **3** and (B) synthesis of endoperoxide **6b** from peroxy acetal **6a**.



Scheme 2. Synthesis of endoperoxides **9a**–**10b**.

compound is also known as Fenozan B0-7). These compounds are prepared by the Lewis acid catalysed reaction of the endoperoxide **7b** in the presence of cyclopentanone.[7]

The mechanism of this transformation is depicted in Scheme 1A and involves reaction of the peroxycation **5** with cyclopentanone to provide the *cis*-fused 1,2,4-trioxane **3**. We reasoned that the intermediate cation **5** could be trapped with an allylsilane such that the hydroperoxysilyl group could cyclise onto the β-silicon-stabilised carbocation intermediate. A close precedent for the proposed reaction was recently reported by Dussault et al.[8] whereby the peroxy acetal **6a** was transformed into the cyclic 1,2-dioxolane **6b** by treatment with allyltrimethylsilane as shown in Scheme 1B.

The requisite endoperoxides **8a**–**d** were prepared by photooxygenation of the corresponding 1,3-dienes, **7a**–**d**, according to the literature methods of Jefford et al.[7] and Posner et al.[9] in good overall yield (Scheme 2). Treatment of **8a** with a catalytic amount of TMSOTf in the presence of allyltrimethylsilane led to a rapid reaction in which the desired endoperoxide **9a** was obtained as a single diastereomer in 54% yield. Increasing the concentration of TMSOTf to 1.1 equiv provided the product in 48% yield as a mixture of diastereomers (1:0.7). Similar results were observed when $SnCl_4$ was employed as Lewis acid.

For endoperoxide **8b**, we also observed the formation of two diastereomeric products in ratios approaching 1:1 when TMSOTf was employed in slight excess. A single or predominant diastereomer was produced when a catalytic quantity of TMSOTf was used. Further investigations allowed us to conclude that only the stoichiometry of the Lewis acid governed the diastereomeric outcome of these reactions even when reaction times were extended.

In contrast, for the higher homologues **8c** and **8d** a single diastereomer was observed even when excess TMSOTf was employed (Table 1).

We were unable to crystallise **9a** or **10a** although the proton NMR spectra for both appeared as a single set of well-defined peaks that were unchanged at low temperature indicating that there was only one conformation in solution.

Based on NMR analysis alone, we were unable to determine unambiguously the relative stereochemistry of each diastereoisomer. The crystal structures of Fenozan and related 1,2,4-trioxanes have been reported and the cyclopentene and peroxide-containing rings have been shown to be *cis* fused with an aromatic substituent in a pseudoequatorial position.[7]

We suggest that **9a**[11]**/b** and **10a/b** will adopt a similar geometry and tentatively propose that the diastereomer, which predominated when catalytic Lewis acid was employed was that in which the bulkier silyl group adopted an equatorial position in a product-like transition state leading to the diastereomer in which this group was equatorial and on the same face as the pseudoequatorial aromatic substituent. This assumption seems reasonable since we were able to obtain a crystal structure of the

Table 1. Reaction conditions employed for the synthesis of **9a**–**10b**

endo-Peroxide	Equivalents of TMSOTf (or $SnCl_4$)	Reaction time/min	Product/ diastereomeric ratio[a]	Total yield (%)
8a	0.033	15	**9a/b**, 1:0	54
8a	1.1	15	**9a/b**, 1:0.7	48
8a	1.0 $SnCl_4$	30	**9a/b**, 1:1	53
8b	0.033	15	**10a/b**, 1:0.2	60
8b	0.033	<10	**10a/b**, 1:0.2	—[b]
8b	0.033	20	**10a/b**, 1:0.2	—[b]
8b	0.033	45	**6a/b**, 1:0.2	—[b]
8b	1.1	15	**10a/b**, 1:0.8	60
8c	1.1	40	**11**, 1:0	10
8d	1.1	40	**12**, 1:0	48
8d	0.1	60	**12**, 1:0	27

[a] Determined from the proton NMR of the crude products.
[b] Purified together and isolated in 31% overall yield.