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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3029–3032

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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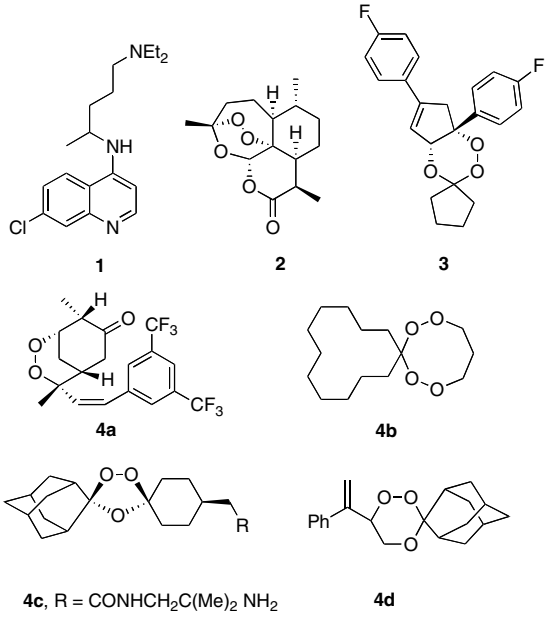
Received 18 January 2005; revised 25 January 2005; accepted 3 March 2005

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

Keywords: Artemisinin; Endoperoxide; Antimalarial.
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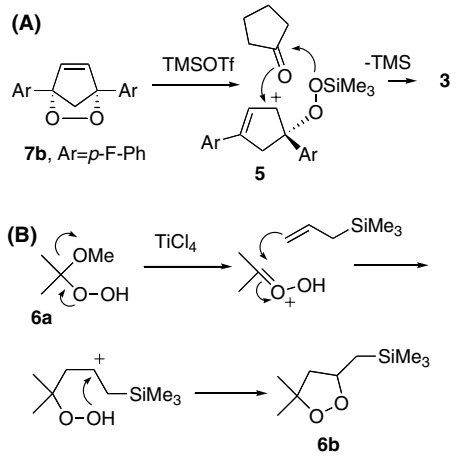
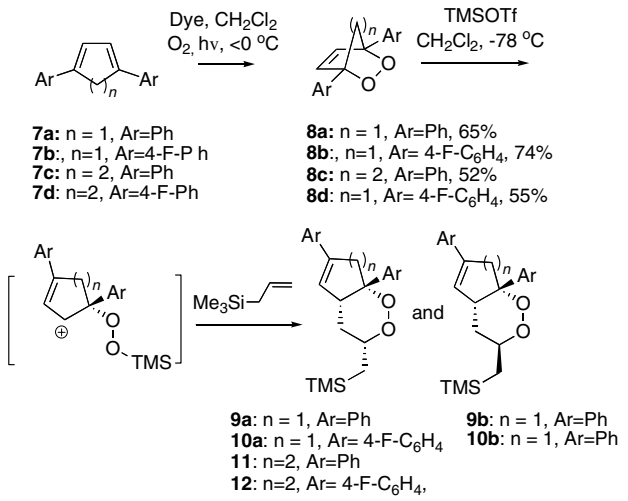
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.03.022



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.

higher fluorinated homologue **12** (Fig. 1) in which this stereochemistry was observed. Figure 1 shows that the unsaturated cyclohexene ring and peroxide-containing ring are *cis* fused with the aromatic substituent adopting a pseudoequatorial position.

We propose the mechanism depicted in Scheme 3 to account for the stereochemical outcome for endoperoxide **12**. TMSOTf-promoted cleavage of the endoperoxide bridge of **12** produces a carbocation that is attacked by the allylsilane in a chair-like transition state. Cyclisation of the peroxysilyl function onto the β-stabilised carbocation provides the product **12**, as shown, with the large $-CH_2SiMe_3$ substituent in the equatorial position.

In order to probe the scope of this reaction, we selected ascaridole **13** and the endoperoxide **14** derived from 1,4-dimethylnaphthalene. Exposure of **13** to allyltrimethylsilane and TMSOTf (1 equiv) led to no reaction, even after 24 h at −30 °C (Scheme 4). This is in sharp contrast to the reaction carried out in the presence of cyclopentanone, where the regioisomeric *cis*-fused 1,2,4-trioxanes are produced in good yield.[12]

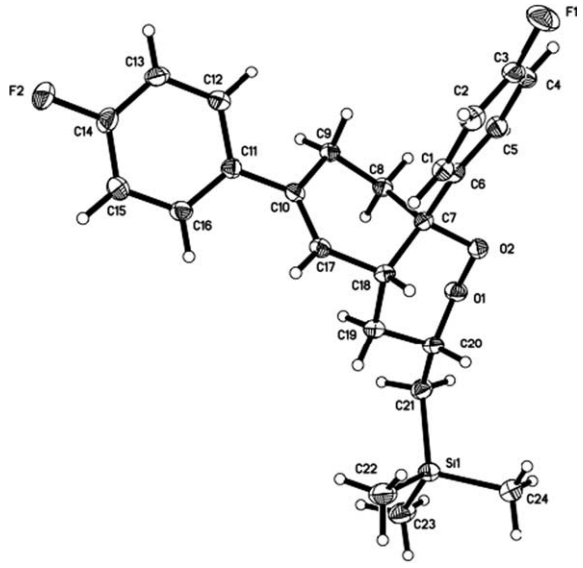
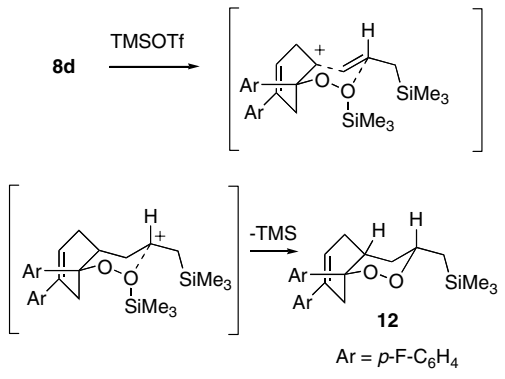
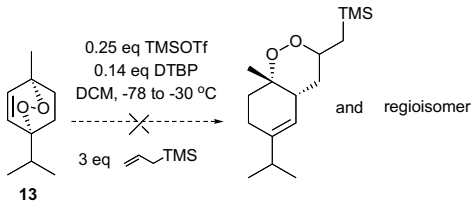


Figure 1. ORTEP view of **12** taken from its crystal structure.[10]



Scheme 3. Proposed mechanism for the transformation of **8d** into silyl endoperoxide **12**.

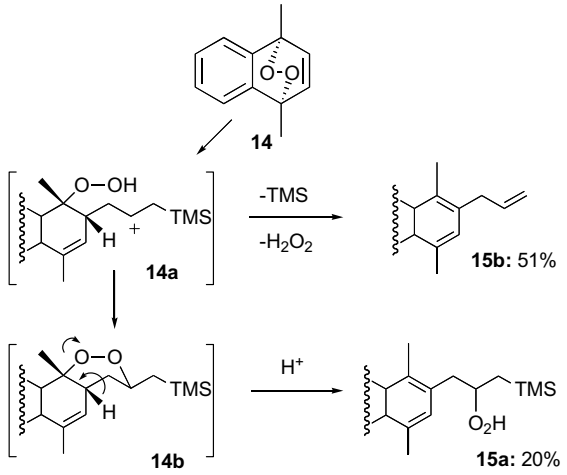


Scheme 4. Attempted rearrangement of ascaridole (**13**).

The reaction of endoperoxide **14** also gave unexpected results. Treatment of **14** with 3 equiv of allyltrimethylsilane gave compounds **15a** and **15b** as the major products in 71% isolated yield. A plausible mechanism for this outcome is depicted in Scheme 5. Heterolytic cleavage of the endoperoxide **14** provides the allyl cation, which reacts to produce the intermediate **14a**. Cyclisation of peroxysilyl group onto the β-stabilised cation provides the product **14b**, which subsequently loses a proton to provide the aromatised hydroperoxy product **15a**.

The other product **15b** is presumably obtained by loss of hydrogen peroxide and the trimethylsilyl group from **14a**. The results clearly demonstrate that the outcomes of these reactions are dictated by the nature of the endoperoxide substrate. For endoperoxides **8a**–**d**, the intermediate cation is doubly stabilised by the alkene and aromatic substituents and this permits a favourable reaction. In contrast, ascaridole is unreactive under these conditions and as we have seen, the pathway followed by the endoperoxide **14** is driven by the thermodynamically favourable aromatisation of the naphthalene ring.

The compounds **9a**–**12**, described above, were evaluated for their antimalarial activity against the most lethal and chloroquine-resistant K1 strain of the *P. falciparum* malaria parasite; the results are shown in Table 2. Disappointingly, these endoperoxide derivatives are poor



Scheme 5. Rearrangement of **14** to **15a** and **15b**.

Table 2. Antimalarial activities of **8c**–**12**

Entry	Compound	IC_{50}/nM
1	**8c**	195
2	**8d**[9]	82
3	**9a**	684
4	**9b**	733
5	**10a**	545
6	**10b**	788
7	**11**	>1000
8	**12**	>1000
9	Artemisinin **2**	12.3
10	Fenozan **3**	5.1

antimalarials when compared with both Fenozan and artemisinin with IC_{50} values exceeding 500 nM in most cases. The endoperoxide precursors **8c** and **8d** were also assayed and shown to have relatively good antimalarial activity.

Summary

We have shown for the first time that unsaturated bicyclic [2.2.*n*] endoperoxides can be transformed into silyl substituted endoperoxides in the presence of allyltrimethylsilane and TMSOTf. By the use of catalytic quantities of Lewis acid, this reaction has been shown to proceed with a high degree of diastereoselectivity. The endoperoxides were shown to have relatively poor antimalarial activity, which may be the result of the high lipophilicity imparted by the presence of the TMS function (C$\log P > 7.25$ for compounds **9a**–**12**, artemisinin C$\log P = 2.84$). Use of an allylsilane that produces a product with a silyl group that can be removed under oxidative conditions will be the focus of future work in this area.

Acknowledgements

The authors thank the EPSRC and Knoll (BASF) for a studentship to S.R.

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9. Posner, G. H.; Tao, X. L.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 7225–7228.
10. Crystal data for **12**: $C_{24}H_{28}F_2O_2Si$, $M = 414.56$, monoclinic, $a = 12.4944(9)$, $b = 10.5879(8)$, $c = 17.2697(13)$ Å, $U = 2245.6(3)$ Å^3, $T = 100(2)$ K, space group $P21/n$, $Z = 4$, absorption co-efficient = 0.137 mm^{-1}. Reflections collected = 12,793, independent reflections = 5092 [R(int) = 0.0339]. Final R indices [$I > 2\sigma(I)$]$R1 = 0.0388$, $wR2 = 0.1070R$; indices (all data) $R1 = 0.0460$, $wR2 = 0.1108$. Additional crystallographic data (excluding structure factors) for the structure **12** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 256341. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ca.uk).
11. For **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (4H, m, Ar), 7.32 (4H, m, Ar), 7.18 (2H, m, Ar), 6.13 (1H, d, $J = 2.0$ Hz, H-5), 4.00 (1H, m, H-3), 3.58 (1H, m, H-4a), 3.26 (1H, d, $J_{7-7} = 17.1$ Hz, H-7), 2.95 (1H, d, $J_{7-7} = 17.1$ Hz, H-7), 2.27 (1H, m, H-4), 1.38 (1H, m, H-4), 1.16 (1H, dd, $J_{2-3} = 6.1$ Hz, $J_{2-2} = 14.1$ Hz, H-2), 0.87 (1H, dd, $J_{2-3} = 8.2$ Hz, $J_{2-2} = 14.1$ Hz, H-2), 0.01 (9H, s, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 139.8, 136.8, 129.1, 129.0 (C_5), 128.7, 128.1, 127.0, 126.5, 125.2, 93.0 (C_{7a}), 77.7 (C_3) 60.7 (C_{4a}), 51.7 (C_7), 42.5 (C_4), 25.2 (C_2), 0.0 (C_1). IR ν_{max} (neat)/cm^{-1} 3032, 2957, 1601, 1494, 1447, 1248, 1086, 1074, 860, 837, 752, 699; EIMS m/z = 364 (M^+, 0.5), 307 (7), 218 (86), 156 (52), 141 (19), 128 (27), 115 (66), 91 (38), 77 (Ph, 70), 73 (TMS, 100); HRMS (M^+) calcd, for $C_{23}H_{28}O_2Si$ 364.18585. Found: 364.18632.
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