Tetrahedron 74 (2018) 3358–3369

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and study of the antimalarial cardamom peroxide

Xirui Hu [a], Pharath Lim [b, c, 1], Rick M. Fairhurst [b], Thomas J. Maimone [a, *]

[a] Department of Chemistry, University of California–Berkeley, Berkeley, CA 94720, USA
[b] Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, USA
[c] National Center for Parasitology, Entomology, and Malaria Control, Phnom Penh, Cambodia

ARTICLE INFO

Article history:
Received 4 February 2018
Received in revised form
15 March 2018
Accepted 20 March 2018
Available online 26 March 2018

Keywords:
Malaria
Endoperoxide
Total synthesis
Natural product

ABSTRACT

A full account of our previously disclosed synthesis of the monoterpene dimer cardamom peroxide is reported. Inspired by hypotheses regarding the potential biosynthetic origins of this natural product, several unproductive routes are also reported. The chemical reactivity of this structurally unique metabolite in the presence of iron (II) sources is also reported as is its antimalarial activity against *Plasmodium falciparum* clinical isolates from several Cambodian provinces.

1. Introduction

Malaria, a parasitic disease transmitted by *Anopheles* mosquitoes, is prevalent in over 99 countries. More than 3 billion people are at risk of acquiring this disease worldwide, and an estimated 445,000 deaths occurred as a result of malaria in 2016.[1] Among the five known Plasmodium parasites that cause malaria in humans, *Plasmodium falciparum* is associated with the greatest mortality. Humanity's fight against malaria dates back to the 1600s, when Peruvian Indians were observed chewing on Cinchona bark to stop shivering.[2] The Cinchona bark, from which the early antimalarial drug quinine was isolated, was introduced into Europe as a treatment for malaria in the early 17th century.[3] Driven by the needs of the military and the colonial powers, antimalarial drug development grew rapidly in the 20th century. Due to this demand, chloroquine was developed in 1934 and quickly became the front-line antimalarial drug after approval in 1946; however, a development of chloroquine resistance in parasites was observed.[4] Sulfadoxine-pyrimethamine (SP), a combination of antifolates, served briefly as the successor of chloroquine, but widespread resistance to this substance also emerged after a period of only 5 years. In 1972, Tu and coworkers discovered the terpenoid peroxide artemisinin (**2**) from the leaves of *Artemisia annua*,[5] a plant used for at least 2000 years for the treatment of fever by Chinese herbal medicine practitioners. Since then, artemisinin derivatives and artemisinin combination therapies (ACTs) have served as the front-line treatment for uncomplicated and severe *P. falciparum* infections. In the past decade however, continually growing reports detailing resistance to derivatives of **2** have surfaced, observations which severely threaten global malaria control.[6]

Since the isolation of **2** in the 1970's, a large number of endoperoxide-containing natural products of both terpenoid and polyketide origin have been discovered (Fig. 1A).[7] While far from approaching the remarkable low nM potency of **2** and its congeners, many of these compounds possess significant antimalarial activity and have thus proven to be attractive targets for chemical synthesis and the development of peroxidation methodology.[8,9] Moreover, these naturally occurring O–O bond-containing molecules have also inspired the development of new synthetic antimalarials such as the ozonide arterolane and the endoperoxide arteflene which is based on the yingzhaosu A scaffold (Fig. 1B).[10,11]

Cardamom peroxide (**1**), a structurally interesting terpene endoperoxide, was isolated in 1995 by Clardy and coworkers from *Amomum krevanh* fruit (Siam cardamom) (Fig. 1).[12] Initial *in vitro* assays indicated that **1** exhibited strong inhibition of *P. falciparum* ($EC_{50} = 170$ nM), a potency similar to the synthetic antimalarial arteflene. Cardamom peroxide contains a rare seven-membered endoperoxide motif (1,2-dioxepane) thus making it an

* Corresponding author.
E-mail address: maimone@berkeley.edu (T.J. Maimone).
[1] Current address: Medical Care Development International, Silver Spring, MD, USA.

https://doi.org/10.1016/j.tet.2018.03.045
0040-4020/

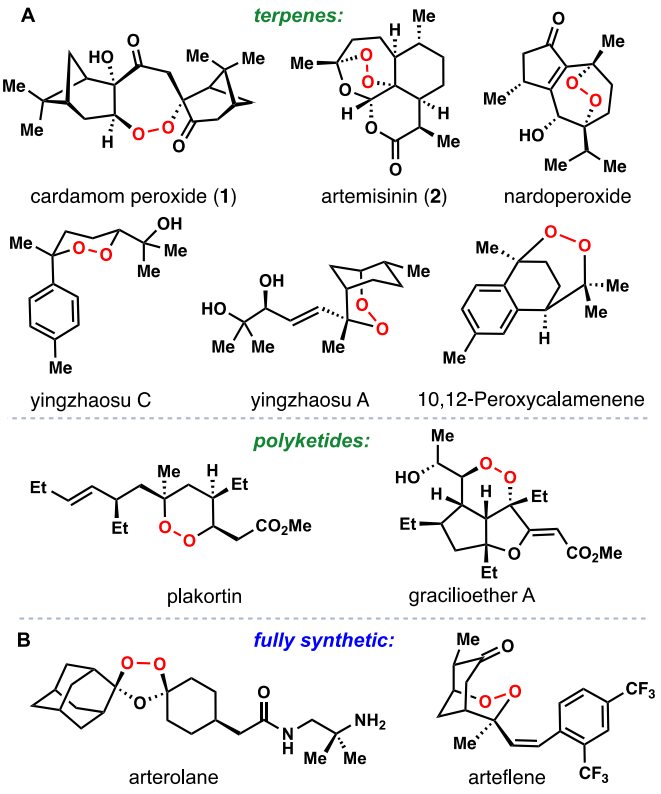

Fig. 1. Antimalarials containing an oxygen-oxygen bond. **A**) selected endoperoxide-containing natural products. **B**) fully synthetic molecules inspired by natural products.

architecturally and biologically intriguing synthetic target. This feature combined with interest over its possible biosynthetic origins led us to target **1** for chemical synthesis. In 2014, we reported a 4-step synthesis of this natural product using oxygen as the sole sources of all of the oxygen atoms.[13] Herein we provide a full account of our synthetic studies and further antimalarial evaluation of **1** against *P. falciparum* clinical isolates from several regions of Cambodia.

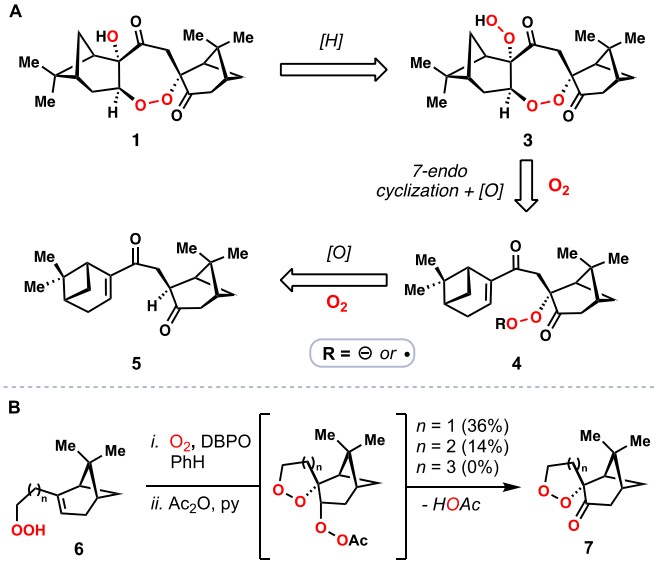

Fig. 2. Synthetic approaches to **1**. **A**) initial retrosynthesis. **B**) studies by Mayrargue and co-workers demonstrates the challenge in forming the 1,2-dioxepane unit found in **1**. (DBPO = Di-*tert*-butyl peroxyoxalate).

Retrosynthetically, we envisioned that **1** might be produced first in nature as diperoxide **3** and then chemoselectively reduced (Fig. 2A). We viewed **3** as the result of a *7-endo-trig* cyclization of either a peroxy radical or peroxide precursor (see **4**) followed by oxygenation of the resulting α-keto radical or enolate respectively. Enone **4** in turn could come from an air oxidation process of diketone **5**, which appears to be the product of a pinane-type monoterpene dimerization. We suspected that from **5**, the ketone α-oxygenation event and the 7-*endo* cyclization/oxygenation cascade would occur diastereoselectively as a result of the steric constraints placed by the pinane units. Thus it was our belief that enzymatic assistance would not be needed to dictate the stereochemical course of this reaction. Given that various monterpenes were isolated alongside **1**, and the observation that the peroxide-forming step in the biosynthesis of **2** is non-enzymatic give credence to these ideas.[12,14] Nevertheless literature precedent suggested that the *7-endo* cyclization would be challenging and we were congnizant that Mayrargue and coworkers could not forge the 1,2-dioxepane unit (see **7**) from pinene-derived model peroxide **6** via a radical cyclization that was competent in forging 1,2-dioxolane and 1,2-dioxane structures (Fig. 2B).[15]

2. Results and discussion

2.1. First generation attempt towards the synthesis of (+)-cardamom peroxide

Initial forays into the construction of the cardamom peroxide began with attempts to construct dimeric pinane-derived diketone **5** from the terpene chiral pool (Scheme 1).[16] A Stetter-type coupling between enone **9**, prepared from pinene via intermediate peroxide **8**,[17] and (−)-myrtenal proved unsuccessful under the mediation of thiazolium salt **10** and base. Also examined, but found to be unworkable, were the coupling of **9** and (−)-myrtenal either by Rh-catalyzed hydroacylation or SmI_2-mediated reductive coupling (Scheme 1A).[18,19] While bromopinene **11** could be dimerized under reductive, titanocene-mediated conditions to give **12** (a plausible biogenetic precursor to **1**),[20] achieving the desired oxidation patterns found in **5** proved challenging (Scheme 1B). Initial success in forging **5** was eventually found via the pathway shown in Scheme 1C. First, a Cu(I)-mediated addition of the Grignard reagent prepared from **11** to enone **9** delivered 1,4-addition product **13** in 48% yield and as a single isomer after acidic work-up.[21] Next, this material underwent allylic oxidation using selenium dioxide to form an allylic alcohol which was immediately oxidized with DMP. While this route provided the first glimpse of **5**, the very low yield encountered in the SeO_2 oxidation (12%, unoptimized) was a bottleneck for material throughput.

Concurrent with these studies, however, we discovered a superior route to **5** based on the chemistry shown in Scheme 1D. We opted to immediately dimerize (−)-myrtenal under reductive coupling conditions, a maneuver which produced triene **14** with more appropriately placed “handles” for further synthetic manipulation. While ultimately capable of providing gram quantities of material, this transformation required significant optimization under rigorously air- and moisture-free conditions (Table 1). While reductive coupling methods based on aluminum[22] and chromium[23] failed to produce triene **14** (entries 1 and 2), several titanium reagents were applicable to this coupling. Conditions employing titanium powder as reductant produced a small amount of **14** with a variety of inseparable non-polar side products (entry 3).[24] Employing stoichiometric quantities of titanocene dichloride with added reducing agent successfully produced **14** as a single isomer (entries 4 and 5); however the catalytic version of this system failed