

Synthesis of novel polar derivatives of the antimalarial endoperoxides ascaridole and dihydroascaridole

Emmanuel Hatzakis,^a Igor Opsenica,^b Bogdan A. Solaja,^b and Manolis Stratakis^{*a}

^aDepartment of Chemistry, University of Crete, Voutes, 71003 Iraklion, Greece

^bFaculty of Chemistry, University of Belgrade, POB 158, 11000 Belgrade, Serbia

E-mail: stratakis@chemistry.uoc.gr

Dedicated to Professor Waldemar Adam on the occasion of his 70th birthdate, and for his remarkable contribution in the chemistry of peroxides

Abstract

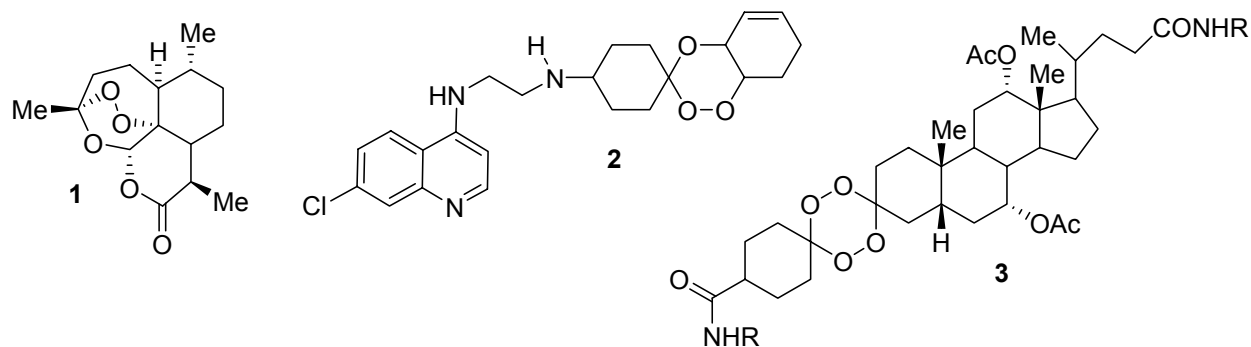
Novel polar derivatives of the antimalarial endoperoxide ascaridole were synthesized based on the zeolite NaY-promoted isomerization of perillyl and nopol derivatives to conjugated cyclohexadienes, followed by reaction with singlet oxygen. Several unsaturated endoperoxides were *in situ* reduced with diimide to form dihydroascaridole derivatives, as well.

Keywords: Isomerization, zeolites, singlet oxygen, endoperoxides, ascaridole

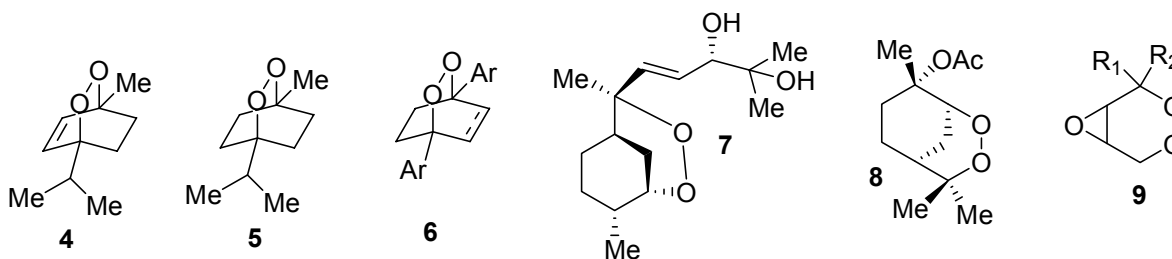
Introduction

Terpene peroxides constitute an interesting category of organic compounds that have received a considerable attention for the past two decades because of their often remarkable antimalarial activity at the nanomolar concentration scale.¹ Generally, it is believed that scission of the peroxide O-O bond by Fe(II) species in the erythrocytes generates radicals which are fatal to the parasite. Among them, artemisinin (**1**),² a naturally occurring antimalarial sesquiterpene peroxide possessing an 1,2,4-trioxane group, is considered as one of the most important antimalarial drugs currently in use, with high activity against multidrug-resistant forms of parasite *Plasmodium falciparum*.³ The enhanced pharmacological activity of **1** has triggered the interest of the organic chemists towards the synthesis of novel artemisinin-based derivatives,⁴ such as dihydroartemisinin, artemisone, artemether and artesunate, with even better pharmacological properties. In addition, novel methodologies were developed⁵ for the synthesis of peroxo compounds bearing the antimalarial active 1,2,4-trioxane carbon skeleton, and this topic continues to be highly active, from the synthetic point of view.

Meunier and co-workers have synthesized⁶ a novel class of compounds termed trioxaquinines (such as compound **2**) with high antimalarial activity, by combining the 1,2,4-trioxane pharmacophore, covalently bound with another well known antimalarial pharmacophore moiety, the aminoquinolines. Apart of trioxanes, the 1,2,4,5-tetraoxanes,⁷ such as the stereoisomers of compound **3**, have emerged recently as a promising category of active antimalarial peroxy compounds. The mechanism of antimalarial action for tetraoxanes⁸ seems to be different compared to the 1,2,4-trioxanes, involving O-centred radicals as the probable active species being fatal to the parasites.



Bicyclic endoperoxides, such as the monoterpenes ascaridole (**4**) and dihydroascaridole (**5**), have been reported to exhibit moderate antimalarial properties.⁹ However, the assay may underestimate the potency of these volatile compounds. In addition, the highly lipophilic character of **4** and **5** might be a drawback for an enhanced antimalarial activity. Posner and co-workers have synthesized⁹ a series of diaryl substituted ascaridole-type endoperoxides (for example, compound **6**), which showed higher activity compared to ascaridole or dihydroascaridole. Apart of the ascaridole-type compounds **4-6**, a naturally occurring bicyclic endoperoxide, namely yingzhaosu A (**7**),¹⁰ was found to be a potent antimalarial. A Japanese group reported recently that bicyclic peroxide **8**¹¹ which possesses the peroxy core skeleton of yingzhaosu A exhibits antimalarial activity comparable to artemisinin (**1**). On the other hand, monocyclic peroxides (1,2-dioxanes) bearing an epoxide functionality, such as compounds possessing the motif of **9**,¹² display weak to moderate antimalarial properties.

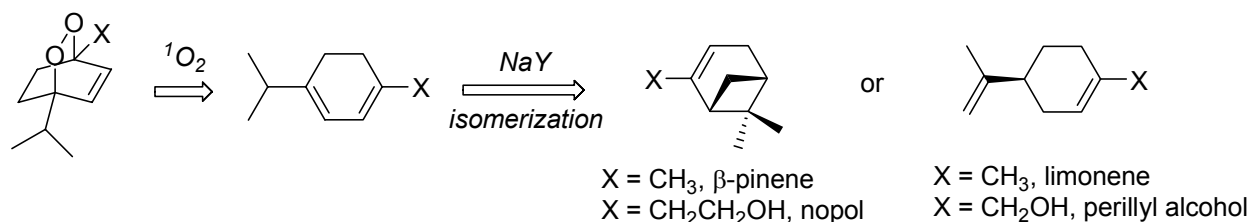


Generally, however, bicyclic endoperoxides have received a limited attention as possible potent antimalarial compounds. It is possible that the low activity of the volatiles **4** and **5** might

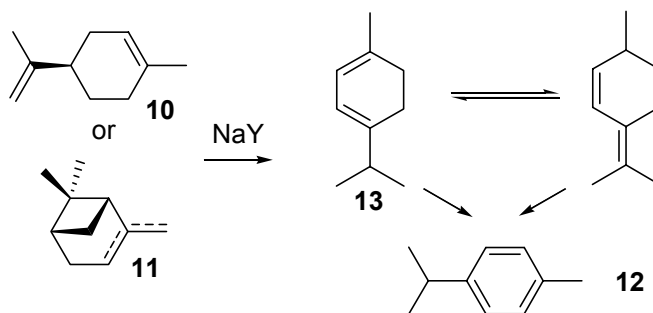
be misleading and even discouraging for further examination of compounds bearing an endoperoxide moiety. For this purpose, we attempted the synthesis of less volatile, and polar as well, derivatives of ascaridole and dihydroascaridole with the aim of studying their antimalarial properties.

Results and Discussion

In this paper we describe a methodology for the synthesis of polar derivatives of ascaridole (**4**) and dihydroascaridole (**5**) using as starting materials commercially available terpenoids such as derivatives of nopol and perillyl alcohol. The retrosynthetic analysis, presented in Scheme 1, was triggered by our observation¹³ that several monoterpenes like limonene (**10**) and α - or β -pinene (**11**) undergo transformation to the aromatic p-cymene (**12**) via intermediate formation of the conjugated cyclohexadiene α -terpinene (**13**), in a sequence promoted by zeolite NaY (Scheme 2). Under certain reaction conditions (temperature, time, and substrate/zeolite loading level) the reaction mixture might be enriched for the desired intermediate conjugated cyclohexadiene, which upon reaction with singlet oxygen in a [4+2] fashion generates an endoperoxide (ascaridole, **4**, in the case of α -terpinene, **13**). We envisioned formation of the appropriately substituted cyclohexadienes, structurally related to α -terpinene (**13**), by the zeolite NaY-promoted isomerization of nopol a terpenoid with a structure similar to β -pinene, and from derivatives of perillyl alcohol, a terpene structurally similar to limonene.



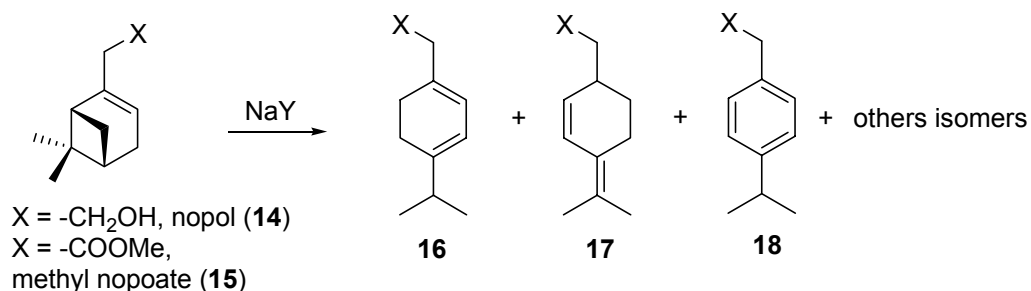
Scheme 1. Retrosynthetic analysis for the synthesis of ascaridole-type endoperoxides.



Scheme 2. Transformation of monoterpenes to p-cymene (**12**) via intermediate formation of **13**.

Endoperoxides from nopol (14) and methyl nopoate (15)

By using 2.5 mmoles of nopol (14) or methyl nopoate (15) per 1 gr of dry NaY suspended in 10 mL of hexane, and heating to 70 °C for 8 hours, an inseparable mixture of products was formed in 75% combined yield (Scheme 3). Analysis by GC and GC-MS revealed that the total ratio of the mainly formed (16+17+18) relative to other isomeric byproducts was ~ 4/1. From the crude ¹H NMR spectrum it was obvious the presence of the desired diene 16 in ~25% relative yield, the isomeric diene 17 in comparable amounts, while 18 was the major one (~30%). Prolonged reaction times increase the relative percentage of the dehydrogenation product 18.



Scheme 3. Isomerization of nopol and methyl nopoate promoted by zeolite NaY.

Direct photooxygenation of the crude mixture, accompanied by chromatographic purification afforded the endoperoxides 19 (X = -CH₂OH, Figure 1) and 20 (X = -COOMe) as viscous colorless oils, yet in low isolated yield (5-8%) relative to the starting materials, nopol or methyl nopoate, respectively.

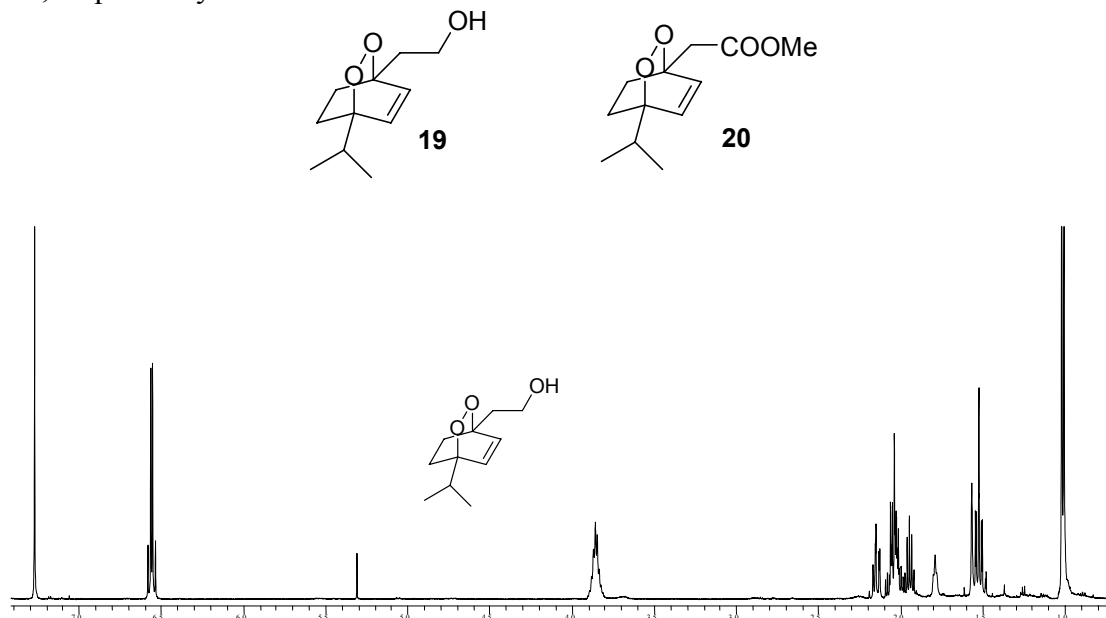
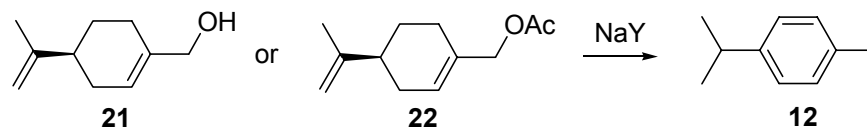


Figure 1. ¹H NMR spectrum of endoperoxide 19.

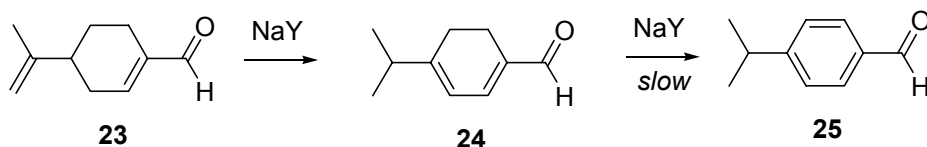
Endoperoxides from perillyl alcohol (21) and its derivatives

As a next step, following the discouraging low yield formation of the ascaridole derivatives **19** and **20** from nopol, we examined the possibility of forming the appropriate conjugated cyclohexadienes via isomerization of perillyl alcohol (**21**) or its derivatives. Disappointingly, upon treatment with NaY, **21** or its acetate (**22**) were transformed to p-cymene (**12**), via dehydration or acetic acid elimination, respectively, under the acidic zeolite conditions (Scheme 4).



Scheme 4. Formation of p-cymene (**12**) from perillyl alcohol (**21**) or its acetate (**22**) within NaY.

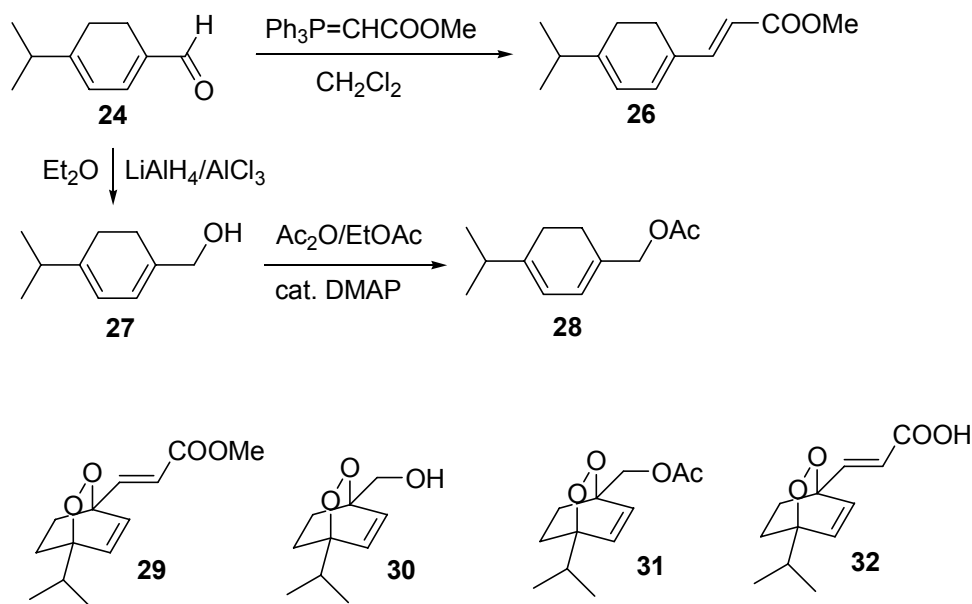
Yet, perillyl aldehyde (**23**) under certain reaction conditions transforms cleanly to the isomeric conjugated dienal **24** (p-mentha-1,3-dien-7-al) in 77% yield, and without formation of the aromatic aldehyde **25** (Scheme 5). We found that the optimum reaction conditions require 1.1 mmoles of perillyl aldehyde per 1 g of dry NaY, and heating to 70 °C for 24 hours. Prolonged reaction time results to the gradual formation of **25**. Formation of dienal **24** has been reported¹⁴ to result in excellent yield by heating perillyl aldehyde with excess of concentrated H₂SO₄ at 120-130 °C. In our hands, this experimental procedure proceeds in 80% combined product yield, however, generates in addition to **24**, the aromatic aldehyde **25** in ~15-20% product ratio, and approximately 10% of unidentified byproducts (GC analysis).



Scheme 5. Isomerization of perillyl aldehyde (**23**) to the conjugated dienal **24**.

Having in our hands the dienal **24** we easily accomplished its further functionalization (Scheme 6) to form triene **26**, and dienes **27-28**, suitable for transformation to endoperoxides by reaction with singlet oxygen. Thus, **24** reacted with the stabilized ylide Ph₃P=CHCOOMe to form triene **26** in 50% isolated yield. Furthermore, selective carbonyl reduction of **24** with LiAlH₄/AlCl₃¹⁵ yielded alcohol **27**¹⁶ (79% yield), while acetylation of **27** with acetic anhydride formed **28**¹⁷ in >90% yield. Photooxygenation of **26-28** afforded the corresponding endoperoxides **29-31** in almost quantitative yield. It is notable that in the case of triene **26**, the cycloaddition occurs exclusively on the diene system within the 6-membered ring, most probably due to the electron-deficiency of the double bond next to the ester functionality. Furthermore,

endoperoxide **29**, which was isolated as a white crystalline solid, was hydrolyzed quantitatively by LiOH in THF/H₂O = 10/1 to the corresponding acid **32**, also isolated as white solid.



Scheme 6. Syntheses of **26-28** from dienal **24**, and the endoperoxides **29-32** derived from them.

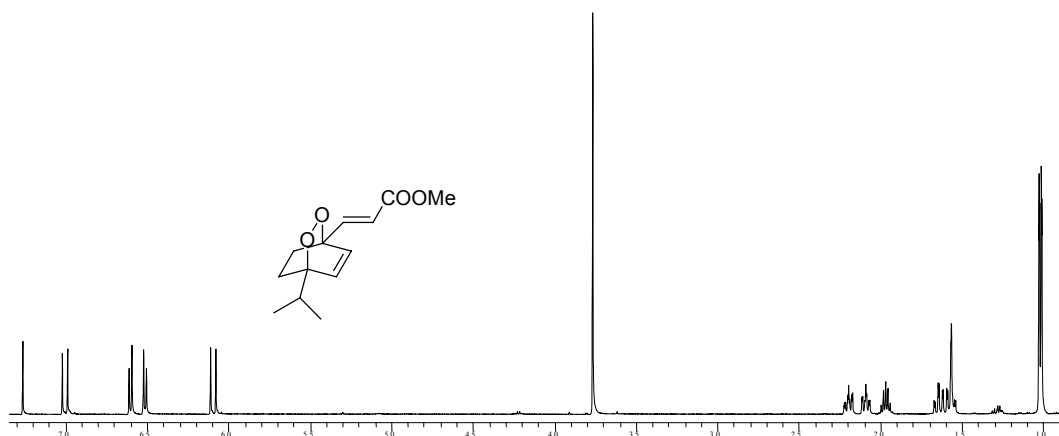
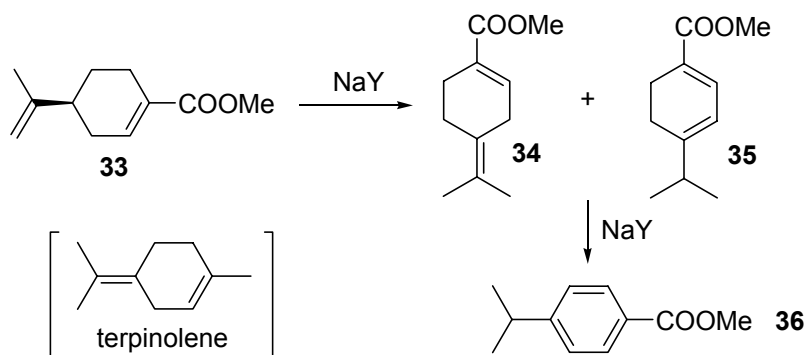


Figure 2. ¹H NMR spectrum of endoperoxide **29**.

Endoperoxides from methyl perillate (**33**)

The facile formation of endoperoxides **29-32** using perillyl aldehyde as starting material, urged us to examine the synthesis of analogous ascaridole-type endoperoxides from methyl perillate (**33**). Surprisingly, the isomerization of methyl perillate to the desired diene **35** was very slow

with the intermediate non-conjugated diene **34** to predominate under identical reaction conditions applied to the intrazeolite isomerization of perillyl aldehyde. After 6 hour of zeolite treatment, methyl perillate was consumed and ^1H NMR analysis of the crude reaction mixture revealed that diene **34** was the predominant product (>80% product ratio). The structure determination of **34** was tentative, and was mainly based on several spectral similarities to the known terpene terpinolene^{13a} (see Scheme 7). On prolonged reaction time, **34** isomerizes slowly to the desired conjugated diene **35**,¹⁶ however, the aromatic ester **36** is gradually formed. The optimum reaction time was 60 hours, after which, a mixture of **34/35/36** appeared in a relative yield of 25/50/25, and in 65% isolated yield (Scheme 7). It is quite surprising the stability of non-conjugated **34** towards isomerization to **35** under NaY treatment, taking into account that, terpinolene (Scheme 7) a non-conjugated monoterpene structurally similar to **34** is an intermediate product in the isomerization of several monoterpenes (such as limonene or pinenes), however, it does not persist under zeolite treatment¹³ and undergoes fast isomerization.



Scheme 7. Isomerization of methyl perillate (**33**) promoted by zeolite NaY.

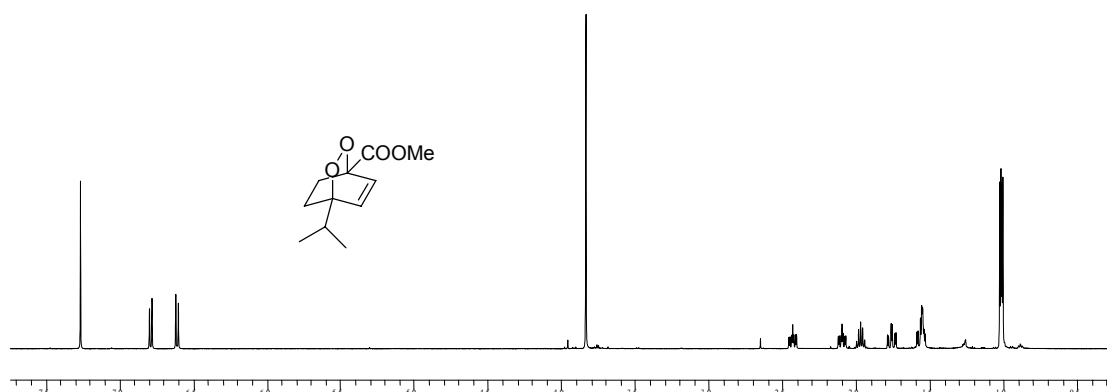
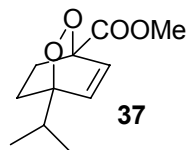


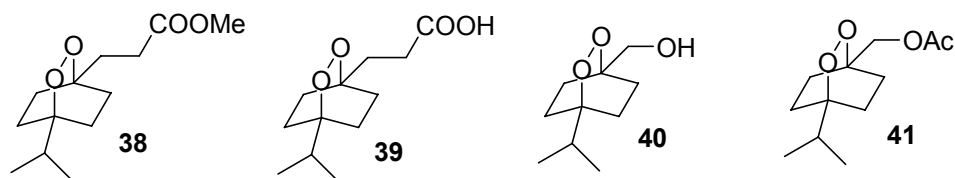
Figure 3. ^1H NMR spectrum of endoperoxide **37**.

Photooxygenation of the crude reaction mixture followed by careful flash chromatography allowed the isolation of the endoperoxide **37** (Figure 3) in pure form, however, in relatively low yield (~15%) from methyl perillate.



Dihydroascaridole derivatives

The observation that saturated bicyclic endoperoxides are more potent antimalarials relative to their unsaturated counterparts,⁹ urged us to reduce the endoperoxides **29-32** with *in situ* generated diimide (HN=NH).¹⁸ The reaction was very clean without affecting the peroxide O-O bond, and the novel saturated endoperoxides **38-41** were isolated in almost quantitative yield. In our hands, approximately 30 equivalents of the diimide precursor (KOOC-N=N-COOK) per alkene double bond are necessary to achieve complete reduction.



Conclusions

In conclusion, we have developed a novel methodology for the synthesis of polar derivatives of the endoperoxides ascaridole and dihydroascaridole using as starting materials readily available terpenoids. The key reaction is the isomerization of the terpenoids to conjugated cyclohexadienes promoted by zeolite NaY. While the yield of the endoperoxides arising from nopol and methyl perillate are very low (5-15%), in the case of perillyl aldehyde due to the very clean isomerization to its conjugated dienal, the overall yield of the endoperoxides **29-32** is relatively good (~30-40% from perillyl aldehyde). The antimalarial potency of these compounds is currently under investigation.

Experimental Section

General Procedures. Nuclear magnetic resonance spectra were recorded on a 500 MHz spectrometer in CDCl₃. Isomeric purities were determined by ¹H NMR spectroscopy, by

analytical gas chromatography on an SP-5 capillary column, and by GC-MS. Photooxygenation reaction were carried out using a 300 W Xenon lamp.

Starting materials. Nopol (**14**) and perillyl aldehyde (**23**) are commercially available. Methyl nopoate (**15**) was prepared by Jones oxidation of nopol to nopoic acid (in 10 mmoles scale) followed by esterification of the resulting acid with CH_2N_2 (65% yield over the two steps). ^1H NMR: 5.38 (m, 1H), 3.67 (s, 3H), 3.01 (d, 1H, $J = 15.0$ Hz), 2.98 (d, 1H $J = 15.0$ Hz), 2.05-2.41 (m, 5H), 1.25 (s, 3H), 1.17 (d, 1H, $J = 9.0$ Hz), 0.81 (s, 3H). Methyl perillate (**33**)¹⁹ was synthesized by esterification of the commercially available perillic acid (in 5.5 mmoles scale) with CH_2N_2 in quantitative yield. ^1H NMR: 6.97 (m, 1H), 4.73 (br s, 1H), 4.70 (br s, 1H), 3.71 (s, 3H), 1.82-2.50 (m, 5H), 1.72 (s, 3H), 1.45 (m, 2H).

Transformation of nopol (14) and methyl nopoate (15) promoted by zeolite NaY and the synthesis of 19 and 20. In a 50 mL flask were placed 1 g of zeolite NaY, which had been previously dried at 120-130 °C under vacuum (10^{-4} torr) for at least 6 hours prior to use, 10 ml of hexane and then 0.4 gr of nopol (**14**) or methyl nopoate (**15**). The slurry was refluxed to 70 °C for 8 hours. The reaction mixture was cooled to room temperature and then filtered. The filtrate was kept and the solid material was further treated with 2 x 10 mL of methanol for 30 minutes each time, and then filtered again. The combined solvent extracts were evaporated to afford 0.3 gr of a mixture of products (mainly **16**, **17** and **18**). Characteristic absorptions of the desired cyclohexadienes **16**, from the crude reaction mixture: 5.70 (d, 1H, $J = 5.5$ Hz), 5.60 (d, 1H, $J = 5.5$ Hz).

Photooxygenation of the crude reaction mixture (methylene blue, 10^{-4} M, as sensitizer) in dichloromethane, followed by flash column chromatography using hexane/ethyl acetate = 5/1 as eluant afforded 22 mg of endoperoxide **19** and 19 mg of endoperoxide **20** as colourless oils. ^1H NMR of **19**: 6.57 (d, 1H, $J = 8.5$ Hz), 6.54 (d, 1H, $J = 8.5$ Hz), 3.83-3.87 (m, 2H), 1.94-2.16 (m, 5H), 1.79 (m, 1H), 1.56 (br. s, 1H), 1.52 (m, 2H), 1.01 (d, $J = 7.0$ Hz, 6H). ^{13}C NMR of **19**: 134.8, 133.5, 80.1, 76.8, 58.4, 38.2, 32.1, 28.2, 24.9, 17.2, 17.1. ^1H NMR of **20**: 6.68 (d, 1H, $J = 8.5$ Hz), 6.52 (d, 1H, $J = 8.5$ Hz), 3.70 (s, 3H), 2.73 (d, 1H, $J = 14.5$ Hz), 2.64 (d, 1H, $J = 14.5$ Hz), 2.01-2.13 (m, 2H), 1.94 (septet, 1H, $J = 7.0$ Hz), 1.70 (dt, 1H, $J_1 = 12.5$ Hz, $J_2 = 3.0$ Hz), 1.55 (dt, 1H, $J_1 = 12.0$ Hz, $J_2 = 3.0$ Hz) 0.99 (d, 6H, $J = 7.0$ Hz).

Synthesis of conjugated dienal 24, and its derivatives 26, 27 and 28. In a 100 ml one-necked flask were suspended 8 gr of dry NaY, 1.5 mL of perillyl aldehyde (**23**) and 50 mL of hexane. After refluxing for 24 hours and methanol treatment as described above, the dienal **24** was isolated in 77% yield and was used in the next steps without purification. ^1H NMR of **24**: 9.45 (s, 1H), 6.77 (d, 1H, $J = 5.5$ Hz), 5.95 (d, 1H, $J = 5.5$ Hz), 2.41 (m, 3H), 2.20 (t, $J = 9.0$ Hz, 2H), 1.02 (d, 6H, $J = 6.5$ Hz). ^{13}C NMR of **24**: 192.3, 158.4, 144.3, 135.5, 116.5, 35.2, 25.1, 20.6, 18.6.

In a 100 ml one-necked flask were placed 0.7 ml (4.5 mmoles) of aldehyde **24**, 2.4 gr (50% excess) of the stabilized ylide $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$, and 30 ml CH_2Cl_2 . After 6 hours at room temperature most of the solvent was removed and the residue was washed with 4 x 15 mL of

hexane. The combined hexane extracts were evaporated and the oily residue was chromatographed (hexane/ethyl acetate = 10/1) to yield ester **26** in 50% yield. ^1H NMR of **26**: 7.34 (d, 1H, $J = 15.5$ Hz) 6.22 (d, 1H, $J = 5.5$ Hz), 5.80 (d, 1H, $J = 15.5$ Hz), 5.79 (d, 1H, $J = 5.5$ Hz), 3.73 (s, 3H), 2.20-2.37 (m, 5H), 1.07 (d, 6H, $J = 6.5$ Hz).

In a 50 ml two-necked dry flask were placed under inert atmosphere 5 mL of dry ether, and 1.5 mmoles LiAlH_4 . Subsequently, 1.3 mmoles of AlCl_3 were slowly added over a period of 5 minutes at 0°C , and the resulting white slurry was stirred for 15 additional minutes. Then 1 mmol of dienal **24** was slowly added, and let reacting for 6 hours at ambient temperature. The reaction mixture was quenched with H_2O and the aqueous layer was washed with diethyl ether. The organic layer was dried with MgSO_4 , the solvent was removed under vacuum to yield alcohol **27** in 79% yield. ^1H NMR of **27**: 5.84 (d, 1H, $J = 5.5$ Hz), 5.64 (d, 1H, $J = 5.5$ Hz), 4.09 (s, 2H), 2.37-2.15 (m, 5H), 1.02 (d, 6H, $J = 5.5$ Hz).

Half part of the isolated alcohol **27** was acetylated with acetic anhydride in ethyl acetate as solvent using equimolar to the anhydride amount of K_2CO_3 , and catalytic amount of DMAP. The acetate **28** was isolated in 92% yield. ^1H NMR of **28**: 5.88 (d, 1H, $J = 5.5$ Hz), 5.63 (d, 1H, $J = 5.5$ Hz), 4.53 (s, 2H), 2.20 (s, 3H), 1.16-1.27 (m, 5H), 1.01 (d, 6H, $J = 8.0$ Hz).

Synthesis of endoperoxides 29-31 via photooxygenation of 26-28. Photooxygenation of **26-28** in dichloromethane led to the isolation of endoperoxides **29-31**, which were purified for analytical purposes by flash column chromatography, using hexane/ethyl acetate = 8/1 as eluant. ^1H NMR of **29**: 6.99 (d, 1H, $J = 16.0$ Hz), 6.60 (d, 1H, $J = 8.5$ Hz), 6.51 (d, 1H, $J = 8.5$ Hz), 6.09 (d, 1H, $J = 16.0$ Hz), 3.76 (s, 3H), 2.06-2.22 (m, 2H), 1.96 (septet, 1H, $J = 7.0$ Hz), 1.53-1.67 (m, 2H), 1.02 (d, 6H, $J = 7$ Hz). ^{13}C NMR of **29**: 166.3, 144.4, 133.9, 133.6, 122.2, 80.6, 75.5, 51.8, 32.1, 28.8, 24.9, 17.1, 17.1. ^1H NMR of **30**: 6.63 (d, 1H, $J = 8.5$ Hz), 6.55 (d, 1H, $J = 8.5$ Hz), 3.80 (d, 1H, $J = 5.5$ Hz), 3.76 (d, 1H, $J = 5.5$ Hz), 1.37-2.12 (m, 5H), 1.00 (d, 3H, $J = 7.0$ Hz), 0.98 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR of **30**: 133.6, 133.5, 80.4, 77.7, 64.4, 31.9, 24.6, 24.6, 17.0. ^1H NMR of **31**: 6.57 (d, 1H, $J = 10.0$ Hz), 6.50 (d, 1H, $J = 10.0$ Hz), 4.31 (d, 1H, $J = 12.0$ Hz), 4.19 (d, 1H, $J = 12.3$ Hz), 2.12-1.90 (m, 2H), 2.06 (s, 3H), 1.43-1.55 (m, 2H), 1.22 (d, 1H, $J = 7.0$ Hz), 0.99 (d, 6H, $J = 7.0$ Hz). ^{13}C NMR of **31**: 170.6, 133.8, 131.6, 80.2, 75.6, 64.5, 31.9, 24.9, 24.4, 21.0, 17.0, 16.9.

Synthesis of endoperoxide 32. The endoperoxide **29** (10 mg) was hydrolyzed for 30 minutes with 4 mg of LiOH , in $\text{THF}/\text{H}_2\text{O} = 10/1$ to form the corresponding acid **32** as a white solid in 95% yield. ^1H NMR of **32**: 7.07 (d, 1H, $J = 16.0$ Hz), 6.60 (d, 1H, $J = 8.5$ Hz), 6.51 (d, 1H, $J = 8.5$ Hz), 6.07 (d, 1H, $J = 16.0$ Hz), 1.96-2.21 (m, 4H), 1.57-1.66 (m, 1H), 1.02 (d, 6H, $J = 5.5$ Hz). ^{13}C NMR of **32**: 170.0, 146.6, 133.8, 133.2, 121.4, 80.6, 75.4, 31.9, 28.6, 24.7, 17.0.

Isomerization of methyl perillate (33) promoted by zeolite NaY, and synthesis of endoperoxide 37. Methyl perillate (**33**) was treated with dry NaY under the conditions (temperature, loading level) described above for perillyl aldehyde. After 6 hours the non-conjugated diene ester **34** was mainly formed, while the conjugated diene **35** was the major product after 60 hours. Characteristic ^1H NMR absorptions of **35** from the crude reaction

mixture: 6.99 (d, 1H, J = 5.5 Hz), 5.79 (d, 1H, J = 5.5 Hz), 3.72 (s, 3H), 2.45 (m, 2H), 2.14 (m, 2H), 1.04 (d, 6H, J = 7.0 Hz).

Photooxygenation of the crude reaction mixture followed by column chromatography (hexane/ethyl acetate = 6/1) afforded endoperoxide **37** in 14% yield from methyl perillate. ¹H NMR of **43**: 6.78 (d, 1H, J = 8.5 Hz), 6.60 (d, 1H, J = 8.5 Hz), 3.83 (s, 3H), 2.40-2.45 (m, 1H), 2.07-2.12 (m, 1H), 1.94-1.99 (m, 1H), 1.73-1.78 (m, 1H), 1.53-1.59 (m, 1H), 1.02 (d, 3H, J = 7.5 Hz), 1.00 (d, 3H, J = 7.5 Hz). ¹³C NMR of **43**: 169.7, 134.0, 132.1, 80.6, 52.9, 31.9, 27.17, 24.4, 17.2, 17.1.

Reduction of endoperoxides 29-32 to 38-41 with diimide. The diimide reductions were carried out as described in the literature.¹⁵ In our hands, 30 equivalents of the diimide precursor (KOOC-N=N-COOK) per alkene double bond are necessary to achieve complete reduction of the unsaturated endoperoxides, after 6 hours of reaction. The saturated endoperoxides **38-41** were isolated in near quantitative yields. ¹H NMR of **38**: 3.66 (s, 3H), 2.34-2.38 (t, 2H), 1.89-1.94 (m, 4H), 1.76-1.79 (m, 2H), 1.59-1.69 (m, 5H), 0.86 (d, 6H, J = 7.0 Hz). ¹³C NMR of **38**: 173.8, 79.4, 75.7, 51.7, 34.2, 32.5, 28.7, 28.0, 25.7, 16.8. ¹H NMR of **39**: 2.37-2.42 (m, 2H), 1.89-1.93 (m, 4H), 1.76-1.79 (m, 2H), 1.61-1.68 (m, 5H), 0.85 (d, 6H, J = 7.0 Hz). ¹³C NMR of **39**: 130.6, 79.3, 75.4, 34.0, 32.1, 28.5, 27.5, 25.6, 16.6. ¹H NMR of **40**: 3.48 (d, 2H, J = 6.5 Hz), 2.06-1.54 (m, 8H), 1.25 (s, 1H), 0.88 (d, 6H, J = 9.0 Hz). ¹H NMR of **41**: 3.97 (s, 2H), 2.06 (s, 3H), 1.65-2.03 (m, 9H), 0.86 (d, 6H, J = 9.0 Hz). ¹³C NMR of **41**: 170.8, 79.8, 75.7, 66.5, 34.1, 26.2, 25.3, 20.7, 16.8.

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