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SYNTHESIS AND IN VITRO ANTIMALARIAL ACTIVITY OF SULFONE ENDOPEROXIDES

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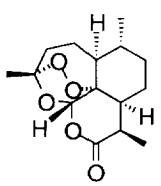
Abstract: A series of 4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes, carrying a variety of substituents at position-8 (**4**) were prepared by a short and efficient method from *R*-(+)-limonene. Key reactions include thiol oxygen cooxidation, and alkylation and acylation of a sterically hindered *tertiary* alcohol compatible with the endoperoxy functionality. Some of compounds **4**, which are structurally related to yingzhaosu A (**2**), were found to exhibit in vitro antimalarial activity comparable to that of artemisinin (**1**) and superior to that of arteflene (**3**).

The devastating consequences of malaria are causing wide international concern.[1] A promising approach for treating malaria deriving from chloroquine-resistant parasites is based on the development of new drugs which incorporate in their molecular structure an endoperoxide functionality.[2–5] Artemisinin (**1**), which is being used as a drug in China, has inspired researchers to design and study various other antimalarial trioxanes.[5–9] A structurally simpler endoperoxide, yingzhaosu A (**2**), was isolated from an antimalarial Chinese folk medicine and was subsequently obtained by total synthesis.[10,11] The synthesis, antimalarial screening and clinical trials of 7-oxo-2,3-dioxabicyclo[3.3.1]nonanes, bearing at C(4) alkyl or alkenyl substituents as represented by arteflene (**3**) were described.[12,13] The expectation that other compounds, like yingzhaosu A and arteflene (**3**), containing the 2,3-dioxabicyclo[3.3.1]nonane system as a central molecular feature may exhibit antimalarial activity led us to design, synthesize and screen sulfur-containing 2,3-dioxabicyclo[3.3.1]nonane derivatives of type **4** (Y = PhS and Z = H, or Y = H and Z = PhS) and **4** (Y = $PhSO_2$ and Z = H, or Y = H and Z = $PhSO_2$). The presence of a sulfonyl group is not alien to antimalarial compounds, and its compatibility with antimalarial activity of 2,3-dioxabicyclo[3.3.1]nonane pharmacophore is reported herein.[14,15]



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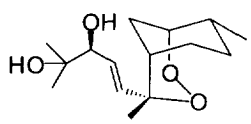

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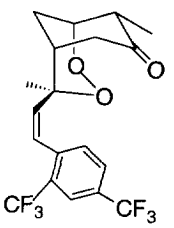

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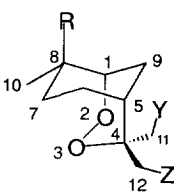

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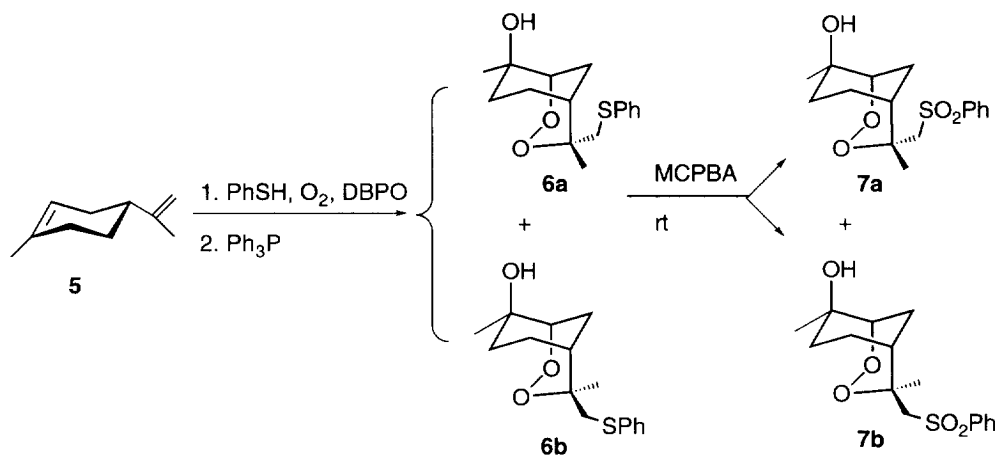
Epimeric sulfide endoperoxides **6a**,**b**, themselves very poor antimalarials, served as starting materials for the preparation of a series of highly active compounds (Table 1).[17] Endoperoxides **6a**,**b** were obtained from *R*-(+)-limonene in a one pot process which involves thiol oxygen cooxidation of the terpene, followed by selective reduction of the resulting endoperoxide-hydroperoxide (Scheme 1).[17] Oxidation of **6a**,**b** with 2.5 equivalents of MCPBA followed by chromatography afforded sulfones **7a** and **7b**.[17] These compounds exhibit significant antimalarial activity indicating that compounds of type **4** in which Y or Z represent a $PhSO_2$ group exhibit higher antimalarial activity than their PhS analogs (Table 1).[18]

Table 1. Antimalarial Activity of 2,3-dioxabicyclo[3.3.1]nonanes **4** Against Chloroquine-Sensitive *P. falciparum* (NF 54) in vitro[a]

Compound	Absolute Configuration	R	Y	Z	IC_{50} (nM)
6a	1*R*, 4*R*, 5*R*, 8*R*	OH	PhS	H	
+					>2500
6b	1*R*, 4*S*, 5*R*, 8*R*	OH	H	PhS	
7a	1*R*, 4*R*, 5*R*, 8*R*	OH	$PhSO_2$	H	55
7b	1*R*, 4*S*, 5*R*, 8*R*	OH	H	$PhSO_2$	89
8a	1*R*, 4*R*, 5*R*, 8*R*	$OCH_2C_6H_4OMe$-*p*	$PhSO_2$	H	14
10a	1*R*, 4*R*, 5*R*, 8*R*	OAc	$PhSO_2$	H	17
10b	1*R*, 4*S*, 5*R*, 8*R*	OAc	H	$PhSO_2$	17
13a	1*R*, 4*R*, 5*R*, 8*R*	OC(O)C(O)OEt	$PhSO_2$	H	170
13b	1*R*, 4*S*, 5*R*, 8*R*	OC(O)C(O)OEt	H	$PhSO_2$	140
14a	1*R*, 4*R*, 5*R*, 8*R*	$OC(O)C(O)NBn_2$	$PhSO_2$	H	21
14b	1*R*, 4*S*, 5*R*, 8*R*	$OC(O)C(O)NBn_2$	H	$PhSO_2$	81
17a	1*R*, 4*R*, 5*R*, 8*R*	$OC(O)CH_2Ac$	$PhSO_2$	H	46
17b	1*R*, 4*S*, 5*R*, 8*R*	$OC(O)CH_2Ac$	H	$PhSO_2$	73
Artemisinin (1)					9.3; 16[b]
Arteflene (3)					71; 110[b]

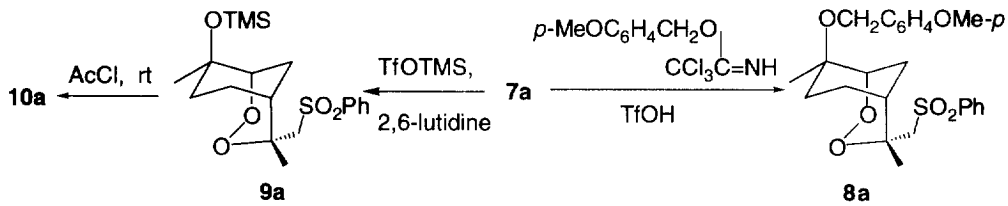
[a]Antimalarial activity was determined by the modified method of Desjardins[26] and Milhous[27] as described in reference 28. The standard deviation for each set of of quadruplets was an average of 9% (≤53%) of the mean. R^2 values for the fitted curves were ≥0.982.
[b]Data taken from reference 13.

Scheme 1



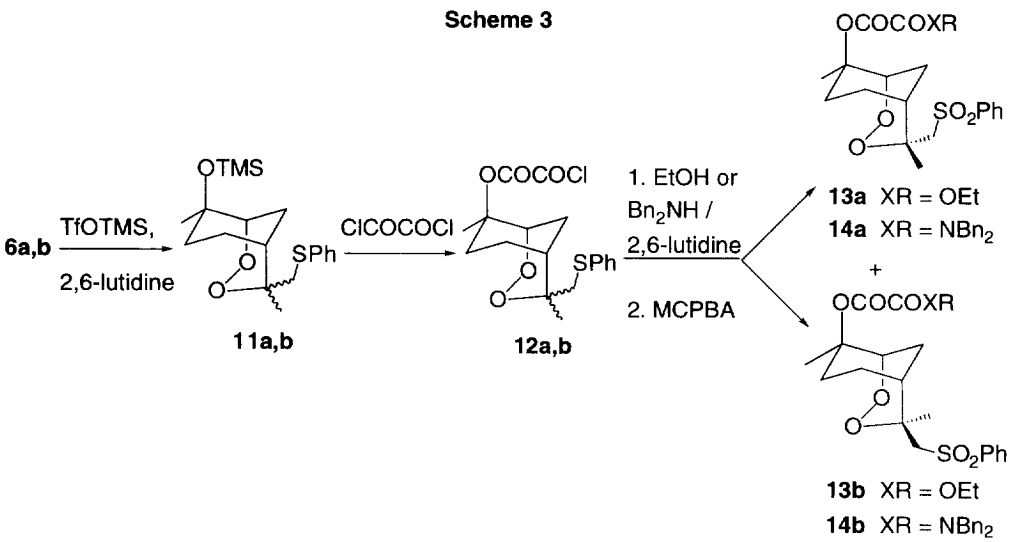
Assuming that decreasing polarity and increasing lipophilicity may be associated with increase of antimalarial activity [8,19–22] derivatives **8a**, **10**, **13–14**, and **17** were prepared.[23,24] Thus, alcohol **7a** (0.85 mmol) in ether (suspension in 3 mL, 0 °C) was treated with *O*-(*p*-methoxybenzyl) trichloroacetimidate[25] (4.2 mmol) in CH_2Cl_2 (1.5 mL) followed by TfOH (0.043 mmol) in ether (0.43 mL) (Scheme 2). After 12 h addition of imidate and TfOH was repeated and the mixture was stirred until consumption of **7a**, to give after standard workup derivative **8a** (46%). Acetyl derivative **10a** was best prepared (95%, from **7a**) by silylation of hydroxysulphone **7a** (0.70 mmol) with TfOTMS (1.5 mmol) and 2,6-lutidine (1.8 mmol) in CH_2Cl_2, followed by treatment of the resulting TMS derivative **9a** with acetyl chloride (3 mL, 45 h, rt) (Scheme 2). This method of

Scheme 2



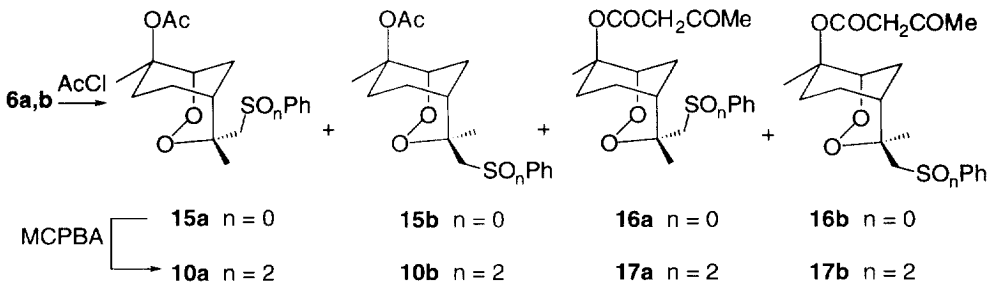
acylation was also applied for the preparation of derivatives **13–14** (Scheme 3). Silylation of epimeric hydroxy sulfides **6a,b** (0.52 mmol) afforded TMS-ethers **11a,b** which were treated with oxalyl chloride (3 mL) to give chlorides **12a,b**. Treatment of **12a,b** with EtOH or Bn_2NH and 2,6-lutidine, followed by oxidation of the sulfide group, afforded respectively the sulfone esters **13a** and **13b** (64%) or sulfone amides **14a** and **14b** (76%).

Scheme 3



Although direct acylation of free *tertiary* alcohols **6a,b** afforded acyl derivatives in lower yields than acylation of the TMS-ethers **9** or **11**, it provided, through a secondary reaction, additional interesting antimalarial endoperoxides (Scheme 4). Thus, addition of AcCl (15.6 mmol) in CH_2Cl_2 (5 mL) to hydroxy sulfides **6a,b** (3.92 mmol), pyridine (19.5 mmol and DMAP (0.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C and then rt (12 h) afforded the sulfide acetates **15a,b** (53%) and sulfide acetoacetates **16a,b** (13%). Oxidation of these acylation products with MCPBA afforded sulfone acetates **10a** and **10b** (97%) and sulfone acetoacetates **17a** and **17b** (67%).

Scheme 4



The data for antimalarial activity in vitro summarized in Table 1 indicates that, except for the case of derivatives **13a** and **13b**, blocking the free hydroxy group in **7** is associated with increase in antimalarial activity. Furthermore, it was found that compounds of the "**a**" series are usually slightly more reactive than their corresponding C-4 epimers of the "**b**" series.[29]

In conclusion, thiol oxygen cooxidation of *R*-(+)-limonene (**5**), followed by alkylation or acylations of a sterically hindered *tertiary* alcohol under conditions compatible with the peroxide function of the 2,3-dioxabicyclo[3.3.1]nonane system, provided a series of readily available and potent antimalarial agents. 4-Phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes **8a**, **10a**, **10b**, and **14a** exhibit in vitro antimalarial activity comparable to that of arteflene (**2**),[12,13] of the drug artemisinin (**1**) and of 1,2,4-trioxanes structurally related to (**1**).[4–9,19–21,30–33]

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17. Reaction mechanism and experimental protocol for the reactions described in Scheme 1 are detailed in: Bachi, M. D.; Korshin, E. E. *Synlett.* **1998**, 122.

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23. All new compounds described in Table 1 were fully characterized by detailed NMR analysis that included NOE difference experiments: 1-D spectra (^{1}H, ^{13}C/DEPT), and 2-D NMR spectra (^{1}H/^{1}H COSY, ^{1}H/^{13}C HMQC), and by elemental microanalysis or CI HRMS.

24. Represantative spectral data for compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.38 (s, 3H, Me^{10}), 1.53 (br.s, 3H, Me^{11}), 1.81 (dddd, 1H, J = 14.0, 14.0, 6.4 and, 3.3 Hz, H_a^6), 1.85 (m, 1H, H_e^6), 1.94 (br.dd, 1H, J = 14.0, 5.0 Hz, H_e^7), 2.11 (ddd, 1H, J = 14.0, 14.0 and 6.4 Hz, H_a^7), 2.17 (m, 2H, $H_e^9 + H_a^9$), 2.27 (br.dddd, 1H, $J \approx 6.4$, 6.4, 3.2 and 3.2 Hz, H_e^5), 3.29 (d, 1H, J = 14.3 Hz, H^{12}), 3.81 (s, 3H, MeO), 3.83 (m, 1H, $J \approx 3.0$ and 3.0 Hz, H_e^1), 4.24 (br.d, 1H, J = 14.3 Hz, H'^{12}), 4.29 and 4.41 (ABq, 2H, J = 10.7 Hz, $CH^{17}H^{17'}O$), 6.88 (ddd, 2H), 7.24 (br.d, 2H), 7.58 (dddd, 2H), 7.66 (dddd, 1H), 7.95 (br.d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 22.16 (Me^{10}), 22.92 (Me^{11}), 23.53 (C^6), 24.57 (C^9), 29.86 (C^5), 30.76 (C^7), 61.10 (C^{12}), 62.91 (C^{17}), 75.94 (C^8), 80.84 (C^1), 82.71 (C^4), 113.78, 127.55 , 128.72 , 129.33 , 131.26 , 133.68, 141.17 , 158.92. CI HRMS: obsd 447.18690, calcd for $C_{24}H_{31}O_6S$ (M + 1) 447.18414.

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