Journal of Enzyme Inhibition and Medicinal Chemistry, 2002 Vol. 17 (6), pp. 431–437

Synthesis and Antimalarial Activity of Some New 1,2-Dioxolane Derivatives

JEAN-JACQUES HELESBEUX[a], DAMIEN PEYRONNET[a], MEHDI LABAïED[b], PHILIPPE GRELLIER[b], FRANÇOIS FRAPPIER[c], DENIS SERAPHIN[a], PASCAL RICHOMME[a] and OLIVIER DUVAL[a,*]

[a]*SONAS, UFR des Sciences Pharmaceutiques et Ingénierie de la Santé, 16 Bd Daviers, 49100 Angers, France;* [b]*Laboratoire de Chimie, ESA 8041 CNRS, Museum National d'Histoire Naturelle, 63 rue Buffon 75005 Paris, France;* [c]*Laboratoire de Biologie Parasitaire, Protistologie, Helminthologie, Muséum National d'Histoire Naturelle, FR CNRS 63, 61 rue Buffon 75231 Paris Cedex 05, France*

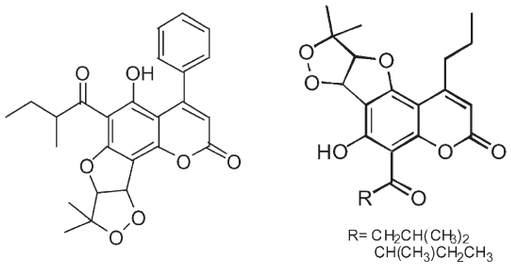
(Received 20 March 2002)

The synthesis of 1,2-dioxolane derivatives in two different acetophenone series, as simplified models of natural coumarins is described. 2-Acetyl-3-acetoxy-4-(3-hydroperoxy-3-methylbut-1-enyl)phenyl acetate and 2-acetyl-5-acetoxy-4-(3-hydroperoxy-3-methylbut-1-enyl) phenyl acetate synthons are used as precursors to these structures. *In vitro* antimalarial activity of the 1,2-dioxolane derivatives has been investigated.

Keywords: 1,2-Dioxolane; Tertiary allylic hydroperoxide; Antimalarial activity; Photochemistry; Natural product models

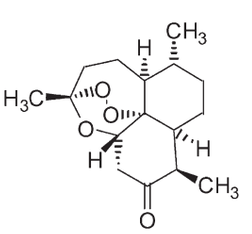
INTRODUCTION

As part of our work on natural products isolation, diverse coumarins were isolated from *Calophyllum dispar*. Among these derivatives, **1**, a new dioxolano[3″,4″:4′,5′]furo[2′,3′:5,6]benzo[1,2-*b*]pyran-2-one was characterized.[1] This compound could be related to the1,2-dioxolane **2**, previously isolated from the seeds of *Mammea americana*.[2] In the last decade, cyclic natural endoperoxides, such as artemisinin or arteflene, showed biological activities in the antimalarial drugs field.[3] We thus decided to explore new synthetic pathways leading to dioxolano[3″,4″:4′,5′]furo[2′,3′:5,6]benzo[1,2-*b*]pyran-2-ones as a potentially new pharmacophore. Principal methods for synthesizing the 1,2-dioxolane structure involved autooxidation, photooxidation, nucleophilic displacement with hydrogen peroxide, peroxymercuration or photolysis of extended π-systems.[4–8]

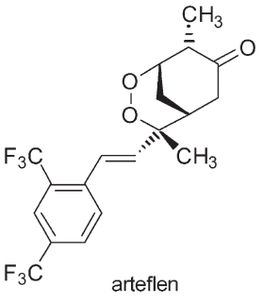


1

2



artemisinin



arteflen

We recently described photooxygenation as a straightforward means of access to *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols without the need for any phenolic protecting group.[9] In that

*Corresponding author. Fax: +33-241731548. E-mail: olivier.duval@univ-angers.fr

ISSN 1475-6366 print/ISSN 1475-6374 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/1475636021000005677

work, we demonstrated that, contrary to the secondary allylic hydroperoxide, tertiary allylic hydroperoxide readily decomposed at room temperature. Protected *ortho*-phenolic tertiary allylic peroxides have already been used as intermediates in the synthesis of natural products.[10,11] With all these results in mind, we thought that a protected 2-(3-hydroxy-3-methylbut-1-enyl)phenol could represent a key intermediate for the synthesis of the 1,2-dioxolane derivative **1**. Therefore, we first decided to focus our work towards an improved pathway leading to this type of compound by using a previously studied acetophenone model.[9]

MATERIALS AND METHODS

Chemistry

Instrumentation

Melting points were determined on an Electrothermal 8100 melting point apparatus and are uncorrected. ^{1}H, ^{13}C NMR spectra experiments were recorded on a Jeol GSX WB 270 MHz and a Bruker Avance DRX 500 MHz instruments using tetramethylsilane as the internal standard. IR spectra were recorded on a Bruker FT IR vector 22 using potassium bromide disc for solids or neat liquid films for liquids. HREIMS (70 eV) were recorded on a Varian MAT 311 spectrometer; HRFABMS and HRAPCIMS were recorded on a JEOL JMS-700 spectrometer. X-ray diffraction data were collected at 293 K on a Enraf Nonius MACH3 four circles diffractometer equipped with a graphite monochromator utilizing Mo Kα radiation $\lambda = 0.71073$ Å. The structure was solved by direct methods (SIR) using MolEN package programs and refined on F by full matrix least-squares method. For **9**, all non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were calculated from the Hydro program. An empirical absorption correction using ψ scans of seven reflections was applied. For **11**, bromine and oxygen atoms were refined anisotropically, carbon atoms isotropically. Some hydrogen atoms were located by Fourier difference synthesis (H01, H02) and the remaining hydrogen atoms were calculated from the Hydro program. Additional information can be obtained by writing to the corresponding author.

Synthesis

We describe below each typical procedure used to obtain the described compounds.

PRENYLATION: to a dioxane solution (25 ml) of dihydroxyacetophenone (3 g), purchased commercially, was added 0.75 ml (0.3 eq.) of boron trifluoride etherate. Then, a solution of 2-methylbut-3-en-2-ol 2.47 ml (1.2 eq.) was added dropwise over a period of 50 min. The mixture was stirred for 2 days. An aqueous solution (15%, 20 ml) of sodium acetate was then added and the reaction mixture was concentrated with removal of dioxane. 50 ml of ethyl acetate was added and the organic phase was washed four times with a sodium acetate solution in water (15%, 50 ml), dried over sodium sulfate and filtered. A viscous crude oil was obtained after solvent removal. The mixture was then separated using liquid chromatography (silica, cyclohexane/AcOEt: 85/15).

1-[2,6-Dihydroxy-3-(3-methylbut-2-enyl)phenyl] Ethanone ***4*** Yield: 44% (yellow powder). Mp = 113–114°C. IR (cm^{-1}): 3348, 1616, 1598, 1257. ^{1}H NMR($CDCl_3$), δ (ppm): 1.78 (s, CH_3), 1.79 (s, CH_3), 2.73 (s, $COCH_3$), 3.29 (d, 7.5 Hz, CH_2), 5.29 (t, 7.5 Hz, CH), 6.33 (d, 8.5 Hz, H arom.), 7.13 (d, 8.5 Hz, H arom.), 9.24 (b, OH), 9.87 (b, OH). ^{13}C NMR($CDCl_3$), δ (ppm): 17.85 (CH_3), 25.81 (CH_3), 28.79 (CH_2), 33.57 (CH_3), 107.36 (CH arom.), 110.23, 119.16, 121.60 (CH), 135.12, 136.18 (CH arom.), 159.37, 159.60, 205.32 ($COCH_3$). HRMS (EI +): $M^+ = 220.1080$ (theoret. 220.1099)

1-[2,4-Dihydroxy-5-(3-methylbut-2-enyl)phenyl]ethanone ***13*** Yield: 21%. Mp = 139–140°C. IR (cm^{-1}): 3285, 1637, 1379, 1235. ^{1}H NMR($CDCl_3$), δ (ppm): 1.80 (s, 6H, CH_3), 2.56 (s, $COCH_3$), 3.31 (d, 7 Hz, CH_2), 5.30 (t, 7 Hz, CH), 5.85 (b, OH), 6.37 (s, H arom.), 7.45 (s, H arom.), 12.53 (s, OH). ^{13}C NMR($CDCl_3$), δ (ppm): 17.80 (CH_3), 25.71 (CH_3), 26.19 ($COCH_3$), 28.93 (CH_2), 103.81 (CH arom.), 114.16, 118.84, 121.48 (CH), 132.33 (CH arom.), 135.61, 161.68, 163.75, 202.84 ($COCH_3$). HRMS (EI +): $M^+ = 220.1101$ (theoret. 220.1099)

PHENOLIC PROTECTION: 2.54 ml of triethylamine (4 eq) and 1.30 ml (4 eq) of acetyl chloride were successively added to a solution of the diphenolic compound (4.55 mmol) in dichloromethane (50 ml) at 25°C. After complete consumption of the starting material, followed by TLC (Cyclohexane/AcOEt: 70/30), the mixture was washed successively with a 1 M HCl solution of in water (2 × 25 ml) and water (25 ml). The organic layer was then dried over sodium sulfate, filtered and evaporated.

3-Acetoxy-2-acetyl-4-(3-methylbut-2-enyl)phenyl Acetate ***5*** Yield: 97% (brown oil). ^{1}H NMR($CDCl_3$), δ (ppm): 1.69 (s, CH_3), 1.75 (s, CH_3), 2.27 (s, $OCOCH_3$), 2.28 (s, $OCOCH_3$), 2.45 (s, $COCH_3$), 3.21 (d, 7 Hz, CH_2), 5.20 (t, 7 Hz, CH), 7.01 (d, 8.5 Hz, H arom.), 7.29 (d, 8.5 Hz, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 17.81 (CH_3), 20.63 (CH_3), 20.98 (CH_3), 25.66 (CH_3), 28.43 (CH_2), 30.82 (CH_3), 120.33 (CH arom.), 120.69 (CH), 128.00, 131.37 (CH arom.), 132.31, 134.06, 145.42, 145.69, 168.71 ($OCOCH_3$), 198.95 ($COCH_3$). HRMS (CI +): $[M + H]^+ = 305.1365$ (theoret. 305.1389)

5-Acetoxy-2-acetyl-4-(3-methylbut-2-enyl)phenyl Acetate ***16*** Yield: 98%. IR (cm^{-1}): 1770, 1742, 1688, 1197. ^1H NMR($CDCl_3$), δ (ppm): 1.71 (s, CH_3), 1.76 (s, CH_3), 2.32 (s, $OCOCH_3$), 2.34 (s, $OCOCH_3$), 2.54 (s, $COCH_3$), 3.26 (d, 7.5 Hz, CH_2), 5.21 (t, 7.5 Hz, CH), 6.91 (s, H arom.), 7.68 (s, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 17.87 (CH_3), 20.82 (CH_3), 21.11 (CH_3), 25.69 (CH_3), 28.38 (CH_2), 29.45 ($COCH_3$), 117.93 (CH arom.), 120.59 (CH), 128.31, 131.53, 131.69 (CH arom.), 134.16, 147.79, 151.90, 168.39 ($OCOCH_3$), 169.21 ($OCOCH_3$), 196.64 ($COCH_3$).

TERTIARY HYDROPEROXIDE SYNTHESIS: Dried air was bubbled through a solution of diacetate (764 mg, 2.51 mmol) in dichloromethane (150 ml) containing (10 mg, 0.017 mmol). The reaction mixture was water-cooled at 15°C and irradiated with a halogen lamp (500 W) for 3 h. After evaporation, the residue was chromatographed over silica gel, eluted with cyclohexane/AcOEt (70/30), to give the tertiary hydroperoxide **6** and the ketone **8**.

3-Acetoxy-2-acetyl-4-(3-hydroperoxy-3-methylbut-1-enyl)phenyl Acetate ***6*** Yield: 46% (yellow powder). Mp = 82–83°C. IR (cm^{-1}): 3440, 1770, 1702, 1188. ^1H NMR($CDCl_3$), δ (ppm): 1.42 (s, 6H, CH_3), 2.29 (s, $OCOCH_3$), 2.30 (s, $OCOCH_3$), 2.46 (s, $COCH_3$), 6.26 (d, 16.5 Hz, CH), 6.53 (d, 16.5 Hz, CH), 7.07 (d, 8.5 Hz, H arom.), 7.58 (d, 8.5 Hz, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 20.37 (CH_3), 20.72 (CH_3), 24.06 (CH_3), 30.92 (CH_3), 81.96, 120.74 (CH arom.), 122.39 (CH), 128.20, 128.49 (CH arom.), 128.61, 137.38 (CH), 144.70, 146.81, 168.79 ($OCOCH_3$), 168.88 ($OCOCH_3$), 198.89 ($COCH_3$).

2-Acetyl-3-hydroxy-4-(3-methyl-2-oxobut-3-enyl)phenyl Acetate ***8*** Yield: 28% (bright yellow powder). Mp = 68–69°C. IR (cm^{-1}): 3449, 1763, 1677, 1622, 1603, 1200. ^1H NMR($CDCl_3$), δ (ppm): 1.91 (s, CH_3), 2.38 (s, $OCOCH_3$), 2.62 (s, $COCH_3$), 4.03 (s, CH_2), 5.86 (s, 1H, CH_2), 6.18 (s, 1H, CH_2), 6.60 (d, 8 Hz, H arom.), 7.32 (d, 8 Hz, H arom.), 13.07 (s, OH). ^{13}C NMR($CDCl_3$), δ (ppm): 17.70 (CH_3), 21.58 ($OCOCH_3$), 32.12 ($COCH_3$), 37.81 (CH_2), 113.35 (CH), 113.87, 122.56, 125.56 (CH_2), 136.76 (CH), 144.09, 150.10, 161.41, 168.79 ($OCOCH_3$), 198.84 (CH_2CO), 203.24 ($COCH_3$).

5-Acetoxy-2-acetyl-4-(3-hydroperoxy-3-methylbut-1-enyl)phenyl Acetate ***17*** Yield: 43% (white powder). Mp = 84–85°C. IR (cm^{-1}): 3442, 1770, 1688, 1191. ^1H NMR($CDCl_3$), δ (ppm): 1.45 (s, 6H, CH_3), 2.35 (s, 6H, $OCOCH_3$), 2.57 (s, $COCH_3$), 6.33 (d, 16.5 Hz, CH), 6.53 (d, 16.5 Hz, CH), 6.96 (s, H arom.), 7.96 (s, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 20.85 (CH_3), 21.12 (CH_3), 24.35 (CH_3), 29.56 ($COCH_3$), 82.24, 118.26 (CH), 122.41 (CH), 127.61, 128.69, 128.78 (CH), 137.13 (CH), 148.80, 150.85, 168.34 ($OCOCH_3$), 168.98 ($OCOCH_3$), 196.50 ($COCH_3$).

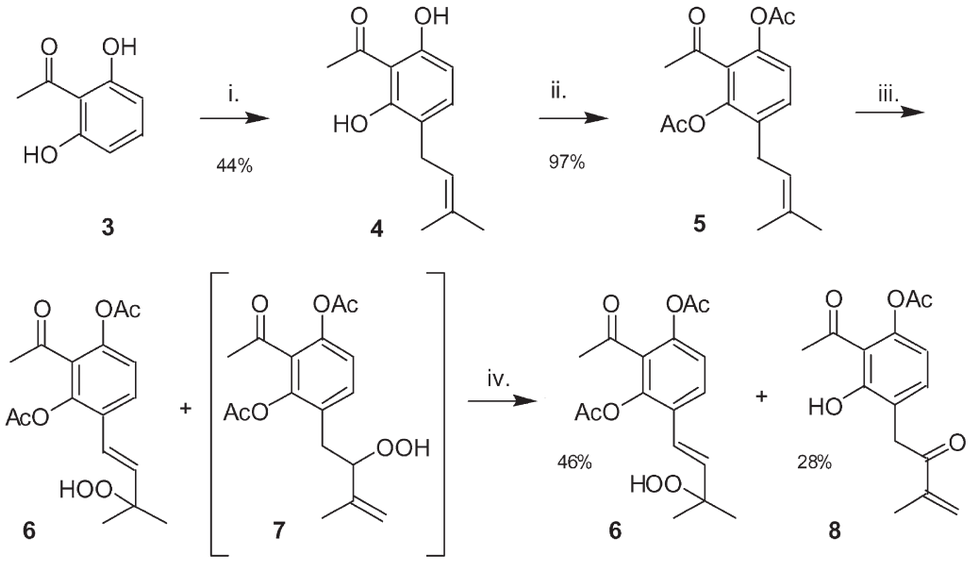
2-Acetyl-5-hydroxy-4-(3-methyl-2-oxobut-3-enyl)phenyl Acetate ***18*** Yield: 30% (white powder). Mp = 77–78°C. IR (cm^{-1}): 3443, 1763, 1676, 1610, 1205. ^1H NMR ($CDCl_3$), δ (ppm): 1.91 (s, CH_3), 2.34 (s, $OCOCH_3$), 2.49 (s, $COCH_3$), 4.01 (s, CH_2), 5.99 (s, 1H, CH_2), 6.29 (s, 1H, CH_2), 6.56 (s, H arom.), 7.62 (s, H arom.), 8.87 (b, OOH). ^{13}C NMR($CDCl_3$), δ (ppm): 17.45 (CH_3), 21.20 ($OCOCH_3$), 29.19 ($COCH_3$), 39.42 (CH_2), 112.27 (CH), 119.37, 122.52, 128.25 (CH), 133.76 (CH), 143.77, 150.47, 160.43, 169.73 ($OCOCH_3$), 195.80 (CH_2CO), 202.00 ($COCH_3$).

1,2-DIOXOLANE SYNTHESIS: 4 Eq. of mercury (II) nitrate monohydrate were added to 1 eq. of tertiary hydroperoxyde in dichloromethane (80 ml). The solution was stirred for 16 h at room temperature, filtered on Kieselguhr and 1.4 eq. of potassium bromide, in 50 ml of water, was added to the filtrate. The reaction mixture was stirred for 1.5 h. The organic layer was separated, dried over sodium sulfate and evaporated at 15°C.

2-Acetyl-3-acetoxy-4-(4-bromomercuri-5,5-dimethyl-1,2-dioxolan-3-yl)phenyl Acetate ***9*** Yield: 71% (yellow powder). Mp = 145–146°C. IR (cm^{-1}): 1770, 1701, 1188. ^1H NMR($CDCl_3$), δ (ppm): 1.52 (s, CH_3), 1.56 (s, CH_3), 2.32 (s, $OCOCH_3$), 2.38 (s, $OCOCH_3$), 2.46 (s, $COCH_3$), 2.95 (d, 9 Hz, CHHgBr), 5.52 (d, 9 Hz, CH), 7.17 (d, 8.5 Hz, H arom.), 7.74 (d, 8.5 Hz, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 20.98 (CH_3), 21.24 (CH_3), 24.87 (CH_3), 29.49 (CH_3), 31.08 (CH_3), 76.40 (CHHgBr), 79.40 (CH), 86.87 (CMe_2), 121.53 (CH arom.), 127.77, 129.03 (CH arom.), 130.57, 144.51, 147.52, 168.45 ($OCOCH_3$), 169.61 ($OCOCH_3$), 198.38 ($COCH_3$).

2-Acetyl-5-acetoxy-4-(4-bromomercuri-5,5-dimethyl-1,2-dioxolan-3-yl)phenyl Acetate ***19*** Yield: 70% (yellow powder). Mp = 68–69°C. IR (cm^{-1}): 1773, 1687, 1369, 1193. ^1H NMR($CDCl_3$), δ (ppm): 1.46 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.34 (s, $OCOCH_3$), 2.38 (s, $OCOCH_3$), 2.56 (s, $COCH_3$), 2.78 (d, 9 Hz, CHHgBr), 5.55 (d, 9 Hz, CH), 6.96 (s, H arom.), 8.04 (s, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 21.08 (CH_3), 21.53 (CH_3), 24.85 (CH_3), 29.34 (CH_3), 29.43 (CH_3), 76.28 (CHHgBr), 79.20 (CH), 86.95 (CMe_2), 118.30 (CH arom.), 128.81 (CH arom.), 129.04, 129.46, 149.11, 150.24, 168.40 ($OCOCH_3$), 169.47 ($OCOCH_3$), 196.37 ($COCH_3$).

BROMODEMERCURIATION: 1.2 Eq of bromine was added to a cooled solution (0°C) of 0.32 mmol of bromomercuri-1,2-dioxolane in dichloromethane (40 ml). The solution was first stirred on ice in darkness and then at room temperature overnight. The solvent was removed under reduced pressure at 15°C, diethylether (10 ml) was added to the residue and the solution filtered on Kieselguhr. After evaporation of the solvent under reduced pressure at 15°C, 10 ml of dichloromethane were added.



SCHEME 1 i. 2-methylbut-3-en-2-ol, BF_3 etherate, dioxane ii. CH_3COCl, $(C_2H_5)_3$ N iii. hν, CH_2Cl_2, TPP iv. SiO_2: cyclohexane / ethyl acetate mixture (70/30).

The organic layer was washed with 2 M hydrochloric acid solution, dried over sodium sulfate and evaporated under reduced pressure at 15°C.

3-Acetoxy-2-acetyl-4-(4-bromo-5,5-dimethyl-1,2-dioxolan-3-yl)phenyl Acetate ***11*** Yield: 95%. IR (cm^{-1}): 1773, 1702, 1185. ^{1}H NMR($CDCl_3$), δ (ppm): 1.41 (s, CH_3), 1.58 (s, CH_3), 2.31 (s, $OCOCH_3$), 2.32 (s, $OCOCH_3$), 2.46 (s, $COCH_3$), 4.27 (d, 5.5 Hz, CHBr), 5.41 (d, 5.5 Hz, CH), 7.14 (d, 8.5 Hz, H arom.), 7.67 (d, 8.5 Hz, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 21.06 (CH_3), 21.27 (CH_3), 23.00 (CH_3), 23.81 (CH_3), 30.82 (CH_3), 63.61 (CHBr), 85.48 (CH), 86.17 (CMe_2), 120.94 (CH arom.), 128.49, 128.84, 129.15 (CH arom.), 145.18, 147.85, 168.33 ($OCOCH_3$), 169.02 ($OCOCH_3$), 198.46 ($COCH_3$).

5-Acetoxy-2-acetyl-4-(4-bromo-5,5-dimethyl-1,2-dioxolan-3-yl)phenyl Acetate ***21*** Yield: 94%. IR (cm^{-1}): 1774, 1690, 1430, 1191. ^{1}H NMR($CDCl_3$), δ (ppm): 1.43 (s, CH_3), 1.59 (s, CH_3), 2.34 (s, $OCOCH_3$), 2.37 (s, $OCOCH_3$), 2.56 (s, $COCH_3$), 4.25 (d, 6 Hz, CHBr), 5.47 (d, 6 Hz, CH), 7.03 (s, H arom.), 8.04 (s, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 21.03 (CH_3), 21.30 (CH_3), 23.03 (CH_3), 23.70 (CH_3), 29.33 (CH_3), 63.52 (CHBr), 84.93 (CH), 86.23 (CMe_2), 118.78 (CH arom.), 127.71, 128.63, 129.22 (CH arom.), 149.53, 151.18, 168.22 ($OCOCH_3$), 168.95 ($OCOCH_3$), 196.23 ($COCH_3$).

HYDRIDODEMERCURIATION: A bromomercuri-1,2-dioxolane solution (0.16 mmol) in dichloromethane (7 ml) and an aqueous sodium borohydride (4 eq.) solution containing sodium hydroxyde (2 M) were prepared and cooled between −5 and 0°C. Then, 1.5 ml of an aqueous sodium hydroxide (2 M) was poured into the dioxolane solution. The obtained mixture was introduced very quickly into the sodium borohydride solution with vigorous stirring. The mixture was stirred for 15 min at − 5°C and for another 15 minutes at room temperature. The organic solution was isolated and the aqueous phase extracted with dichloromethane (3 × 5 ml). The combined organic solutions were dried over sodium sulfate, filtered and evaporated under reduced pressure at 15°C.

2-Acetyl-3-acetoxy-4-(5,5-dimethyl-1,2-dioxolan-3-yl)phenyl Acetate ***10*** Yield : 45%. IR (cm^1): 1772, 1701, 1187. ^{1}H NMR($CDCl_3$), δ (ppm): 1.38 (s, CH_3), 1.43 (s, CH_3), 2.29 (s, $OCOCH_3$), 2.31 (s, $OCOCH_3$), 2.33 (dd, 6.5 Hz, 12 Hz, 1H, CH_2), 2.46 (s, $COCH_3$), 2.81 (dd, 8.5 Hz, 12 Hz, 1H, CH_2), 5.35 (dd, 6.5 Hz, 8.5 Hz, CH), 7.12 (d, 8.5 Hz, H arom.), 7.74 (d, 8.5 Hz, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 20.75 (CH_3), 21.05 (CH_3), 25.28 (CH_3), 26.09 (CH_3), 30.98 (CH_3), 54.02 (CH_2), 77.34 (CH), 83.81 (CMe_2), 120.87 (CH arom.), 127.96, 128.37 (CH arom.), 132.07, 144.31, 147.07, 168.47 ($OCOCH_3$), 168.65 ($OCOCH_3$), 198.57 ($COCH_3$).

2-Acetyl-5-acetoxy-4-(5,5-dimethyl-1,2-dioxolan-3-yl)phenyl Acetate ***20*** Yield = 45%. IR (cm^{-1}): 1773, 1689, 1369, 1192. ^{1}H NMR($CDCl_3$), δ (ppm): 1.39 (s, CH_3), 1.45 (s, CH_3), 2.32 (dd, 6 Hz, 12 Hz, 1H, CH_2), 2.34 (s, 6H, $OCOCH_3$), 2.58 (s, $COCH_3$), 2.86 (dd, 8.5 Hz, 12 Hz, 1H, CH_2), 5.41 (dd, 6 Hz, 8 Hz, CH), 6.97 (s, H arom.), 8.10 (s, H arom.). ^{13}C NMR($CDCl_3$), δ (ppm): 20.95 (CH_3), 21.06 (CH_3), 25.25 (CH_3), 26.13 (CH_3), 29.27 (CH_3), 53.88 (CH_2), 77.17 (CH), 83.85 (CMe_2), 118.19 (CH arom.), 128.45, 128.51 (CH arom.), 130.97, 148.86, 150.40,

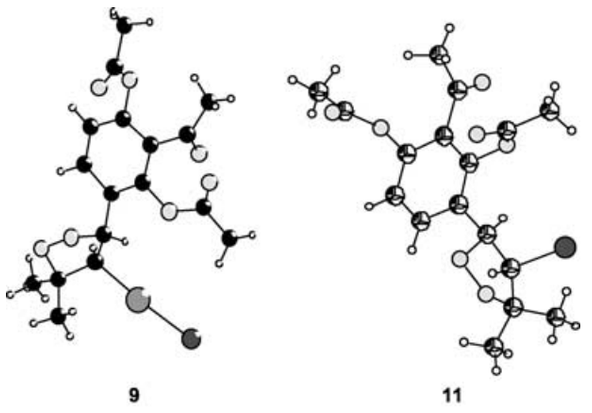


FIGURE 1 Perspective views of the crystal structures of 1,2-dioxolanes **9** and **11**.

167.98 ($OCOCH_3$), 169.18 ($OCOCH_3$), 196.61 ($COCH_3$).

Pharmacology

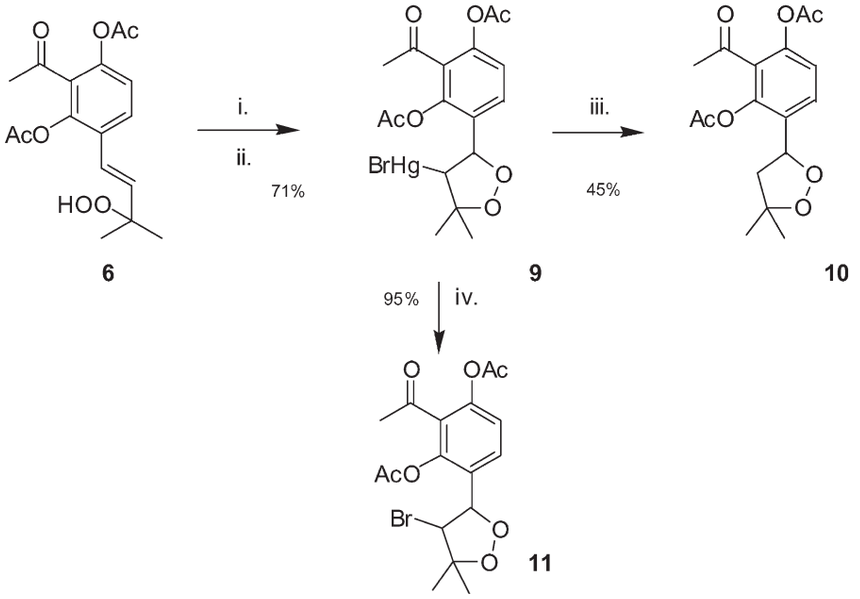
In Vitro P. Falciparum Culture and Drug Assays

P. falciparum strain FcB1/colombia was maintained continuously in culture on human erythrocytes as described by Trager and Jensen.[12] *In vitro* antiplasmodial activity was determined using a modification of the semi-automated microdilution technique of Desjardins *et al*.[13] Stock solutions of chloroquine diphosphate and test compounds were prepared in sterile, distilled water and DMSO, respectively. Drug solutions were serially diluted with culture medium and added to asynchronous parasite cultures (1% parasitemia and 1% final hematocrite) in 96-well plates for 24 h, at 37°C, prior to the addition of 0.5 μCi of [^{3}H]hypoxanthine (1 to 5 Ci/mmol; Amersham, Les Ulis, France) *per* well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentration causing 50% inhibition (IC_{50}) was obtained from the drug concentration-response curve and the results were expressed as the mean ± the standard deviations determined from several independent experiments. The DMSO concentration, which never exceeded 0.1%, did not inhibit parasitic growth.

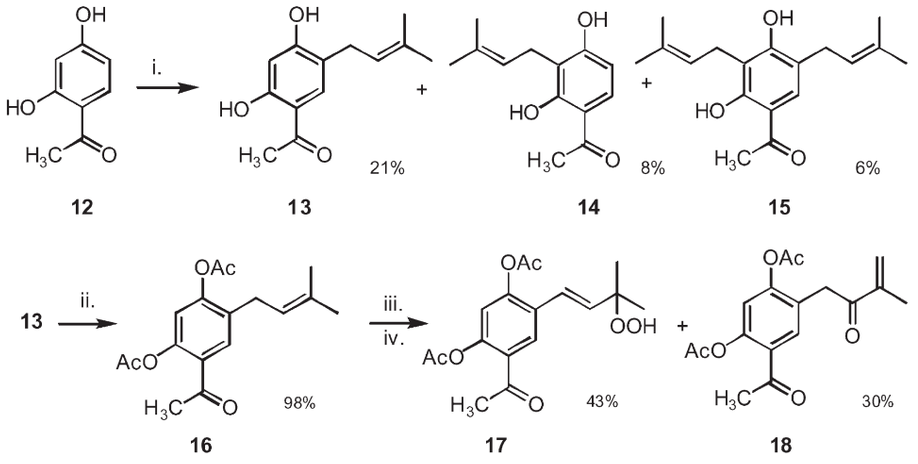
RESULTS AND DISCUSSION

Chemistry

The diphenolic tertiary allylic hydroperoxide diacetate derivative **6** is obtained from the commercial diphenol **3** through isoprenylation (**4**),[14] protection of the phenolic groups (**5**) and photooxygenation, using tetraphenylporphine as sensitiser in dichloromethane at 15°C (Scheme 1). The last step reaction yielded a 2:1 ratio in favour of the tertiary hydroperoxide. The result was in contrast with the non protected-diphenolic compound.[4–8] Compound **6** was separated from the mixture by silica gel chromatography and obtained in a 46% overall yield. During this purification step, the ketone **8**, resulting from dehydration of the secondary hydroperoxide **7** in acidic medium, was isolated in 28% yield.



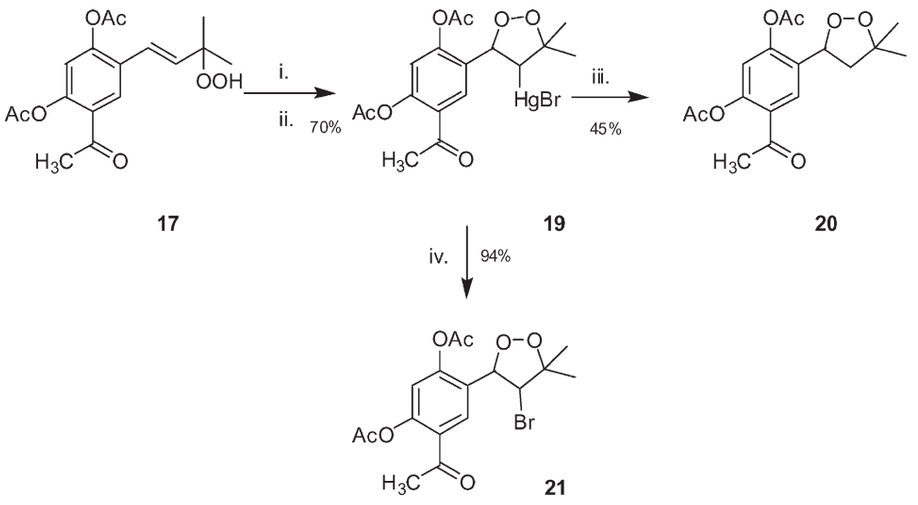
SCHEME 2 i. $Hg(NO_3)_2$, CH_2Cl_2, ii. KBr, H_2O iii. $NaBH_4$, 2 M NaOH, CH_2Cl_2, −5°C iv. Br_2, CH_2Cl_2, −5°C to RT, dark.



SCHEME 3 i. 2-methylbut-3-en-2-ol, BF_3 etherate, dioxane ii. CH_3COCl, $(C_2H_5)_3$ N iii. hν, CH_2Cl_2, TPP iv. SiO_2: cyclohexane / ethyl acetate mixture (70/30).

The 1,2-dioxolane skeleton was synthesized by peroxymercuriation. The allylic tertiary hydroperoxide **6** reacted with an excess of mercuric nitrate monohydrate in dry dichloromethane at room temperature to furnish the somewhat unstable organomercuric nitrate. After treatment of the crude reaction mixture with aqueous potassium bromide, the organomercury (II) bromide **9** was more satisfactorily characterized. The value of the coupling constant (9 Hz) between the benzylic proton and its vicinal neighbour in **9** was not sufficient enough to ascertain the stereochemistry of this unusual five-endo ring closure product.[15] Apart from confirming the structure of **9**, an X-ray diffraction study showed a *trans* relationship between the two early mentioned protons (Figure 1) and we also confirmed the anti-addition in oxymercuriations.[8] Following this cyclisation step and aiming at conducting further cyclisation towards the synthesis of analogues of **1**, we attempted to modify the structure of **9**. Thus, we first proceeded to a bromodemercuration using bromine in dichloromethane leading to the bromo substituted derivative **11**. X-ray analysis showed a retention of configuration confirming a SE_2 mechanism under our reaction conditions (Fig. 1). **10** was obtained by reduction of **9** in presence of an aqueous 2 M sodium hydroxide solution of sodium borohydride (Scheme 2) at −5°C. Our attempts to introduce a hydroxy group in the same position under Ganem reaction conditions failed.[16]

In order to improve the scope of our work, the 2,4-dihydroxyacetophenone series was used for further



SCHEME 4 i. $Hg(NO_3)_2$, CH_2Cl_2, ii. KBr, H_2O iii. $NaBH_4$, 2 M NaOH, CH_2Cl_2, −5°C iv. Br_2, CH_2Cl_2, −5°C to RT, dark.

TABLE I *In vitro* sensitivity of the *P. falciparum* FcB1/colombia strain towards the antimalarial 1,2-dioxolanes **10**, **11**, **20** and **21** and chloroquine

	P. falciparum
Compound	FcB1/colombia strain IC_{50} (μmol/ml)
10	0.98 ± 0.11
11	1.06 ± 0.08
20	1.98 ± 0.17
21	1.76 ± 0.11
Chloroquine	0.126 ± 0.03

synthesis. The isoprenylation step led to a three product mixture **13**, **14** and **15** which was separated using silica gel chromatography (cyclohexane / ethyl acetate: 85/15). The hydroperoxide **17** was obtained from **16**, under the same conditions described above, along with the ketone **18** (Scheme 3). Peroxymercuriation was carried out to furnish **19** which gave **20** under reductive conditions and **21** in the presence of bromine (Scheme 4).

Biology

In this work, the antimalarial activities of our 1,2-dioxolanes **10**, **11**, **20** and **21** were evaluated against a *P. falciparum* chloroquine-resistant clone (Table I). It was found that all the compounds had a weak activity by comparison with chloroquine. A slightly better activity in the 2,6-acetophenone series was also seen.

In conclusion, four 1,2- dioxolane derivatives **10**, **11**, **20** and **21** have been synthesized in the 2,6- and 2,4-dihydroxyacetophenonic series from tertiary allylic hydroperoxide intermediates **7** and **16**. We have demonstrated that the secondary allylic hydroperoxides are unstable under our separation conditions and are transformed into the corresponding ketone. These structures have also showed some activity against a resistant line on *P. falciparum* and are likely useful models on the way to synthesizing the dioxolano[3″,4″:4′,5′]furo[2′,3′:5,6]benzo[1,2-*b*] pyranone **1**. Further studies towards synthesis of simplified skeletons from **9** or **19**, involving deprotection of the phenolic functions and nucleophilic displacement of the bromine moiety or other groups are currently under investigation in our laboratory.

Acknowledgements

This research was supported by a grant from Département du Maine et Loire.

References

[1] Guilet, D. (2000) "Etude phytochimique d'une clusiaceae malaise", *le Calophyllum dispar* Thèse de l'université d'Angers, 291.

[2] Crombie, L., Games, D.E., Haskins, N.J., Reed, G.F., Finnegan, R.A. and Merkel, K.E. (1970) "Identification of nine new 5,6-annulated relatives of the *mammea* coumarins B/BA, B/BB and B/BC", *Tetrahedron Letters* **11**, 3975–3978.

[3] Meshnick, S.R., Jefford, C.W., Postner, G.H., Avery, M.A. and Peters, W. (1996) "Second-generation antimalarial endoperoxides", *Parasitology Today* **12**, 79–82.

[4] Bloodworth, A.J. and Loweit, M.E. (1978) "Oxymetallation. Part 11. Synthesis of secondary alkyl peroxides via the peroxymercuration of α,ω-dienes", *Journal of Chemical Society, Perkin, I*, 522–530.

[5] Zimmerman, H.E. and Lamers, P.H. (1989) "Photochemistry of some extended π-systems: Type A and aryl rearrangements of systems with extended conjugation related to cyclohexadienones and cyclohexenones. Mechanistic and exploratory organic photochemistry", *Journal Organic Chemistry* **54**, 5788–5804.

[6] Porter, N.A. and Zuraw, P.J. (1984) "Stereochemistry of hydroperoxide cyclization reactions", *Journal of Organic Chemistry* **49**, 1345–1348.

[7] Bascetta, E. and Gunstone, F.D. (1984) "Synthesis of cyclic peroxides from methyl oleate", *Journal of Chemical Society, Perkin, I*, 2207–2216.

[8] Courtneidge, J.L., Bush, M. and Lay See, L. (1992) "5-Endo ring closure of allylic hydroperoxides: useful routes to 1,2-dioxolanes involving strongly stereoselective free radical and polar reactions", *Tetrahedron* **48**, 3835–3856.

[9] Helesbeux, J.J., Guilet, D., Seraphin, D., Duval, O., Richomme, P. and Bruneton, J. (2000) "*ortho*-Prenylphenol photooxygenation as a straighforward access to *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols", *Tetrahedron Letters* **41**, 4559–4562.

[10] Ito, C., Fujiwara, K., Kajita, M., Ju-Ichi, M., Takemura, Y., Suzuki, Y., Tanaka, K., Omura, M. and Furukawa, H. (1991) "New coumarins from *citrus* plants", *Chemical Pharmaceutical Bulletin* **39**, 2509–2513.

[11] Murray, R.D.H. and Zeghdi, S. (1989) "Synthesis of the natural coumarins, murraol (CM-c_2), *trans*-dehydroosthol and swietenocoumarin G", *Phytochemistry* **28**, 227–230.

[12] Trager, W. and Jensen, J.B. (1976) "Human malarial parasites in continuous culture", *Science* **193**, 673–677.

[13] Desjardins, R.E., Canfield, C.J., Haynes, J.D. and Chulay, J.D. (1979) "Quantitative assessment of antimalarial activity *in vitro* by a semiautomated microdilution technique", *Antimicrobial Agents Chemotherapy* **16**, 710–718.

[14] Jain, A.C., Lal, P. and Seshadri, T.R. (1970) "A study of nuclear prenylation of β-resacetophenone—II Synthesis of bavachalcone, 4′-*O*-methylbavachalcone and bavachin", *Tetrahedron* **26**, 2631–2635.

[15] Baldwin, J.E. (1976) "Rules for ring closure", *Journal of Chemical Society, Chemical Communications*, 734–736.

[16] Bernotas, R.C. and Ganem, B. (1985) "Efficient preparation of enantiomerically pure cyclic aminoalditols; total synthesis of 1-deoxynojirimycin and 1-deoxymannojirimycin", *Tetrahedron Letters* **26**, 1123–1126.