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Applications of triphenylpyrylium salt-sensitized electron-transfer photo-oxygenation reactions to the synthesis of benzo-fused 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes as new antimalarial cyclic peroxides

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Abstract Benzo-fused 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes **4a–d** (**4a**: Ar = C_6H_5, **4b**: Ar = *p*-FC_6H_4, **4c**: Ar = *p*-MeC_6H_4, **4d**: Ar = *p*-$MeOC_6H_4$) were synthesized by 2,4,6-triphenylpyrylium tetrafluoroborate ($TPPBF_4$)-sensitized photoinduced electron-transfer (PET)-promoted oxygenation reactions, and their in-vitro antimalarial activity was evaluated. The results showed that these substances have sufficiently high activity to enable them to serve as antimalarial lead compounds. In addition, $TPPBF_4$-biphenyl-cosensitized PET oxygenation was shown to be an efficient method for introduction of an O–O moiety in the construction of antimalarial cyclic peroxides.

Keywords Photoinduced electron transfer · Single electron transfer · Photo-oxygenation · Triphenylpyrylium salt · Cyclic peroxide · Antimalarial activity

Introduction

Because malaria parasites rapidly develop resistance to antimalarial alkaloids, for example chloroquine and mefloquine, the discovery that non-alkaloidal endoperoxides, for example artemisinin and related compounds can act as antimalarial agents stimulated several synthetic and mechanistic studies [1–9]. In particular, much effort has been devoted to the preparation and evaluation of structurally

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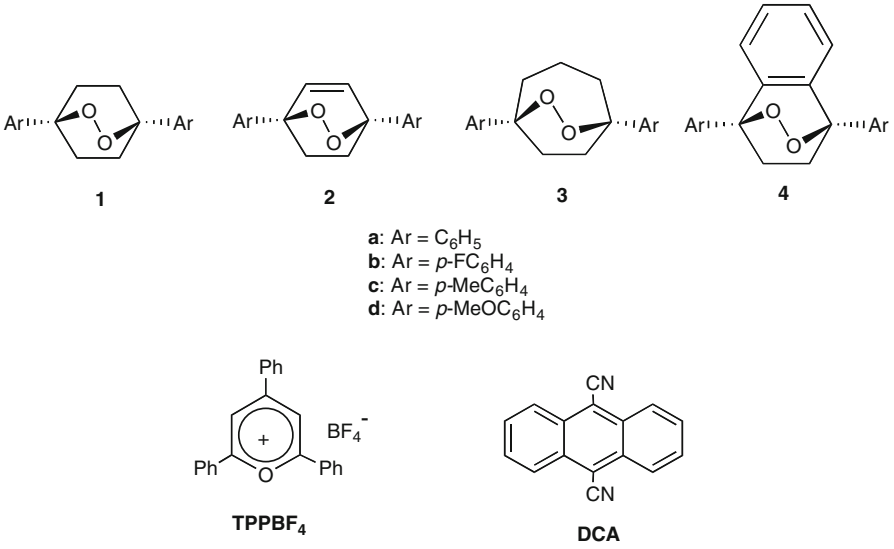
simple, more potent antimalarial cyclic peroxides. Posner reported that 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes **1a–b** [10], 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-enes **2a–c** [10], and 1,5-diaryl-6,7-dioxabicyclo[3.2.2]nonane **3d** [11, 12] are potent antimalarials (Scheme 1). Later, we also described the synthesis, mechanism of degradation, and antimalarial activity of endoperoxides **1a–d** [13], **2a–d** [14–16], and **3a–d** [17].

During the course of ongoing investigation of the use of single-electron-transfer (SET)-promoted reactions in synthetic organic chemistry [18–26] and the development of new antimalarial cyclic peroxides [13, 14, 17], we became interested in benzo-fused 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octane targets **4a–d** with a similar framework to **1** and **2**. Although it has been reported that **4a** can be synthesized by 9,10-dicyanoanthracene (DCA)-sensitized PET oxygenation of 1,2-bis(1-phenylethenyl)benzene **5a** via a cyclization and oxygenation process that is similar to that for the preparations of **1** and **3** [27, 28], the yield of the reaction was relatively low (<50 %). In addition, synthesis of other derivatives **4b–d** and assessment of the antimalarial activity of **4a–d** have not been investigated. In previous work we demonstrated that **3a–c** can be efficiently prepared by 2,4,6-triphenylpyrylium tetrafluoroborate ($TPPBF_4$)-sensitized PET oxygenation of the corresponding 2,6-diaryl-1,6-heptadienes and that these substances can be readily separated by chromatography as a consequence of the ionic character of $TPPBF_4$ [17]. These observations stimulated our interest in the application of $TPPBF_4$-sensitized PET oxygenation reactions to conversion of 1,2-bis(1-arylethenyl)benzenes **5a–d** to the corresponding bicyclic peroxides **4a–d**. Below, we describe the results of a recent study that has led to concise syntheses of bicyclic peroxides **4a–d** by $TPPBF_4$-sensitized PET oxygenation reactions, and evaluation of their antimalarial properties.

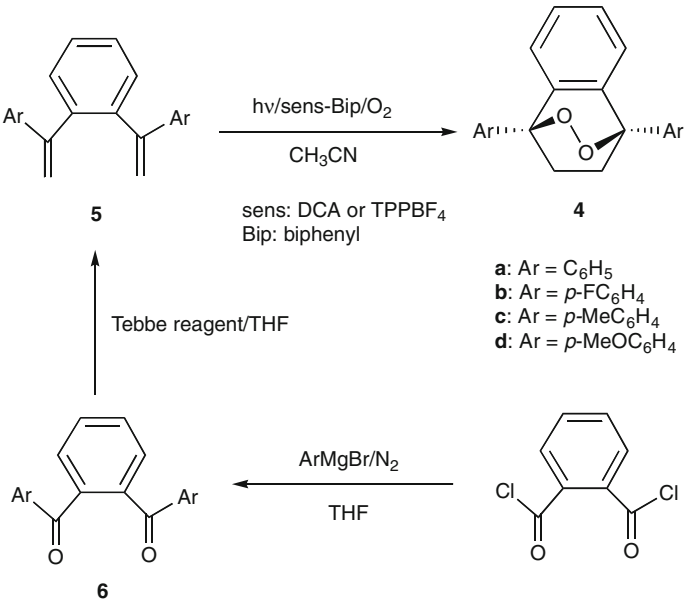


Scheme 1 Synthesis of antimalarial bicyclic peroxides by $TPPBF_4$-sensitized and DCA-sensitized PET oxygenation reactions

Results and discussion

1,2-Bis(1-arylethenyl)benzenes **5a–d** were prepared by methylation of the corresponding *o*-diaroylbenzenes **6a–d** in THF, using the Tebbe reagent (Scheme 2). The *o*-diaroylbenzenes **6a–d** were prepared via Grignard addition of the corresponding arylmagnesium bromides with phthaloyl chloride in THF [29]. The oxidation potentials of **5a–d** in CH_3CN containing 0.1 M Et_4NClO_4 were determined, by use of cyclic voltammetry, to be +1.49, +1.44, +1.38, and +1.19 V ($E^{OX}_{1/2}$ vs. SCE), respectively. The estimated reduction potential of the excited singlet state of $TPPBF_4$ ($^*E^{red}_{1/2}$ vs. SCE) is ca +2.50 V [30]. Therefore, the calculated ΔG^o values for SET between **5a–d** and the excited singlet state of $TPPBF_4$ in CH_3CN are −25, −26, −27, and −32 kcal mol^{-1}, respectively [22, 30–34]. Similarly the calculated ΔG^o values for SET between **5a–d** and the excited singlet state of DCA ($^*E^{red}_{1/2} = +1.90$ V vs. SCE) in CH_3CN are −11, −12, −13, and −18 kcal mol^{-1}, respectively. Consequently, SET from **5a–d** to the excited singlet states of $TPPBF_4$ and DCA are highly exothermic.

PET oxygenation reactions were performed in dry CH_3CN solutions of **5a–d** (20 mM) and a sensitizer ($TPPBF_4$: 2 mM or DCA: 0.2 mM) in the presence or absence of biphenyl (Bip: 60 mM). The solutions were irradiated at 20 °C under an oxygen atmosphere using a 2-kW Xe lamp and a Toshiba L-39 filter (>390 nm). The progress of each reaction was monitored by use of thin-layer chromatography and further analyzed by use of 200 MHz ^{1}H NMR spectroscopy ($CDCl_3$). The peroxides **4a–d** were isolated by silica gel chromatography. As the results summarized in Table 1 show, $TPPBF_4$-sensitized PET oxygenation reactions of



Scheme 2 Synthesis of benzo-fused bicyclic peroxides **4a-d**

5a–d produce the corresponding bicyclic peroxides **4a–d** in moderate to good yield (60–71 %, runs 3, 7, 11, and 15), with small amounts of *o*-diaroylbenzenes **6a–d**, whereas processes promoted by DCA as sensitizer are less efficient (36–58 %, runs 1, 5, 9, and 13) and generate appreciable amounts of **6a–d**. On the basis of an observation by Schaap that use of biphenyl (Bip) as cosensitizer leads to dramatic enhancement of the efficiency of DCA-sensitized PET oxygenation reactions of aryl-substituted oxiranes [26, 35–38], Bip was incorporated in the photo-oxygenation mixture to improve the yields of **4a–d**. We observed that $TPPBF_4$–Bip-cosensitized PET oxygenation reactions of **5a–d** occur with significantly improved yields (66–88 %, runs 4, 8, 12, and 16) to form **4a–d**, with diminished production of **6a–d**. Although yields of **4a–d** are similarly improved when DCA–Bip-cosensitization conditions are used (44–68 %, runs 2, 6, 10, and 14), they did not exceed those of the $TPPBF_4$–Bip-cosensitized oxygenation reactions. The combined results indicate that use of $TPPBF_4$–Bip-cosensitization is the best method for synthesis of **4a–d**, especially **4a–c**, which have relatively weaker electron-donating aromatic groups.

On the basis of the results of this and related studies [11–17, 22, 26–28, 30, 39–41], it is possible to propose a mechanism for $TPPBF_4$–Bip-cosensitized PET oxygenation reactions leading to **4** as shown in Scheme 3. SET oxidation of **5** with

Table 1 PET oxygenation reactions of 1,2-bis(1-arylethenyl)benzenes **5**

Run	Substrate[a]	Sensitizer[a]	Irradiation time (min)	Yield of products (%)[b]	
				4	**6**
1	**5a**	DCA	15	36	19
2	**5a**	DCABip	10	49	12
3	**5a**	$TPPBF_4$	10	61	6
4	**5a**	$TPPBF_4$–Bip	5	83	3
5	**5b**	DCA	15	40	11
6	**5b**	DCABip	10	44	11
7	**5b**	$TPPBF_4$	15	60	6
8	**5b**	$TPPBF_4$–Bip	5	66	2
9	**5c**	DCA	15	54	15
10	**5c**	DCABip	10	68	11
11	**5c**	$TPPBF_4$	10	71	7
12	**5c**	$TPPBF_4$–Bip	5	88	4
13	**5d**	DCA	15	58	9
14	**5d**	DCABip	10	58	9
15	**5d**	$TPPBF_4$	3	66	0
16	**5d**	$TPPBF_4$–Bip	3	67	0

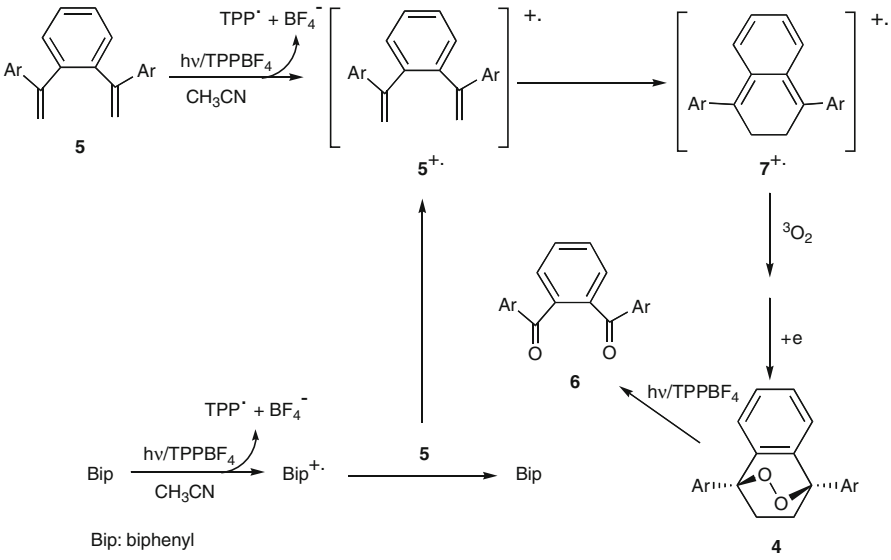
Oxygen-saturated acetonitrile solutions (10 mL) of **5** (0.20 mmol) containing the sensitizer or the sensitizer with Bip were irradiated with a 2-kW Xe lamp ($\lambda > 360$ nm)

[a] [5] = 20 mM; [$TPPBF_4$] = 2.0 mM; [DCA] = 0.2 mM; [Bip] = 60 mM

[b] Isolated yield by silica gel TLC. **5a–d** were completely consumed

the excited singlet state of $TPPBF_4$ leads to the corresponding cation radical $\mathbf{5}^{+\bullet}$, which cyclizes to generate the *o*-xylylene cation radical $\mathbf{7}^{+\bullet}$ [27, 28]. Reaction of $\mathbf{7}^{+\bullet}$ with molecular oxygen ($^3O_2$) followed by back electron transfer from the pyryl radical ($TPP^{\bullet}$) or electron transfer from **5** then affords **4**. Under the irradiation conditions, *o*-diaroylbenzene **6** is produced by SET from **4** to the excited singlet state of $TPPBF_4$ [42]. Our previous result that **4a** was formed in the tris(4-bromophenyl)aminium hexachloroantimonate-catalyzed oxygenation of **5a** under oxygen in the dark supports the participation of $^3O_2$ in this $TPPBF_4$-sensitized PET oxygenation reaction [28]. The possibility of involvement of the oxygen anion radical ($O_2^{-\bullet}$) in the oxygenation process can be ruled out by taking into account the redox properties of the excited $TPPBF_4$ [30, 40, 43–46]. Electron transfer from $TPP^{\bullet}$ to $^3O_2$ is calculated to be endothermic by approximately 20.1 kcal mol^{-1} using the reduction potentials ($E_{1/2}^{OX}$) of −0.43 and −1.30 V (vs. SCE in CH_3CN) respectively for $TPPBF_4$ and $^3O_2$. Thus, generation of $O_2^{-\bullet}$ by this electron-transfer step is unfavorable. On the other hand, participation of singlet oxygen ($^1O_2$) in this oxygenation process is also unfavorable, because generation of $O_2^{-\bullet}$ and $^1O_2$ can be ruled out as reported in the $TPPBF_4$-sensitized PET oxygenation reaction of adamantylideneadamantane [47]. The efficiency enhancement effect of addition of Bip ($E_{1/2}^{OX} = +1.86$ V vs. SCE in CH_3CN) to the reaction mixture, although not yet fully elucidated owing to a lack of spectroscopic data, is likely to be a consequence of the participation of Bip in electron transfer with the excited singlet state of $TPPBF_4$ that occurs in addition to electron transfer from **5** to generate the Bip cation radical ($Bip^{+\bullet}$) [48]. This leads to a greater utilization of the excited state of $TPPBF_4$ in forming cation radical species that eventually produce the key reactive intermediate $\mathbf{5}^{+\bullet}$. Thus, under $TPPBF_4$–Bip-cosensitized conditions $\mathbf{5}^{+\bullet}$ is effectively generated by exothermic electron transfer from **5** to $Bip^{+\bullet}$. Under the DCA-sensitized photoreaction conditions, oxygenation pathways similar to those involved in the $TPPBF_4$–Bip-cosensitized process occur except that $O_2^{-\bullet}$ and $^1O_2$ are also produced as reactive intermediates [48–50].

The in-vitro antimalarial activity of endoperoxides **4a–d** against *Plasmodium falciparum* (*P. falciparum*) and their cytotoxicity against mouse mammary tumor FM3A cells (FM3A cells) were evaluated to clarify relationships that may exist between activity and the nature of aromatic substituents (Table 2) [6, 7, 9]. The results show that EC_{50} of **4a–d** against *P. falciparum* are in the range 1.7×10^{-7} to 8.0×10^{-8} M, values that are higher than those of **1a–d** (1.2×10^{-6}–5.6×10^{-7} M) [13]. The nature of the benzo-substituent in **4a–d** remarkably affects the antimalarial activity of **4a–d**; this may be a consequence of their enhanced lipophilicity compared with **1a–d**. In addition, **4c** and **4d** have fairly high antimalarial activity and selectivity (cytotoxicity against FM3A cells/antimalarial activity against *P. falciparum*: see "Experimental" section). The high antimalarial activity and low toxicity of **4c** and **4d** may be the result of the presence of 1,4-disubstituted electron-donating aromatic groups as compared with **4a** and **4b**. The activity of **4a** and **4b** is somewhat lower and their selectivity is poor, owing to their slightly high toxicity. Although the presence of a fluorine atom in **1** and **2** has been reported to enhance antimalarial activities [10], the activity of **4b** does not reflect this effect. Finally, despite their structural and synthetic simplicity, the new series of



Scheme 3 A mechanism for the PET oxygenation reaction of **5**

Table 2 In vitro antimalarial activity of cyclic peroxides **4** against *P. falciparum* (FCR-3 strain) and cytotoxicity against FM3A cells

Substrate	EC_{50} (M)		Selectivity[c]
	P. falciparum[a]	FM3A cell[b]	
4a	1.3×10^{-7}	1.0×10^{-6}	8
4b	1.7×10^{-7}	3.0×10^{-6}	18
4c	8.0×10^{-8}	1.9×10^{-5} (66 %)[d]	>238
4d	1.1×10^{-7}	1.0×10^{-5}	91
1a[e]	1.0×10^{-6}	3.2×10^{-5}	>32
1b[e]	5.6×10^{-7}	1.8×10^{-5}	>32
1c[e]	5.0×10^{-7}	1.7×10^{-6}	3
1d[e]	1.2×10^{-6}	1.8×10^{-5}	>15
Artemisinin[f]	1.0×10^{-8}	1.0×10^{-5}	1,000

In vitro antimalarial activity and cytotoxicity are described in the "Experimental" section

[a] Chloroquine-sensitive (FCR-strain)

[b] Mouse mammary tumor FM3A cells in culture as a control for mammalian cell cytotoxicity

[c] Selectivity = (mean of EC_{50} value for FM3A)/(mean of EC_{50} value for *P. falciparum)*

[d] Growth percent at the concentration indicated

[e] Ref. [13]

[f] Ref. [7]

benzo-fused bicyclic peroxides **4a–d** should serve as promising lead compounds in efforts targeted at the design and preparation of new antimalarial drugs.

Conclusion

In conclusion, the results of the investigation described above demonstrate that benzo-fused bicyclic peroxides **4a–d** can be efficiently prepared by $TPPBF_4$–Bip-cosensitized PET oxygenation processes. The $TPPBF_4$–Bip-cosensitized PET oxygenation reaction should serve as a convenient method for synthesis of a variety of antimalarial cyclic peroxides via concise sequences, because it enables introduction of an O–O bond simultaneous with C–C bond-formation in some dienes [17] or C–C bond cleavage in some cyclopropanes [51]. We are now investigating further structural modifications of these substances and the Fe(II)-promoted degradation of **4** with the purpose of clarifying the relationship that might exist between reaction intermediates and antimalarial activity.

Experimental

General experimental procedures

All melting points are uncorrected. Elemental analysis was performed at the Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer (operating at 200 MHz for ^1H and 50 MHz for ^{13}C), with $CDCl_3$ as solvent. Half-wave oxidation potentials were measured on a BAS cyclic voltammograph CV-1B. CH_3CN (Wako, special grade) for electrochemical measurements and photoreactions was distilled twice over phosphorus(V) oxide and once over calcium hydride. Triphenyl pyrilium tetrafluoroborate ($TPPBF_4$) was prepared by a method reported elsewhere [52] and recrystallized twice from CH_3CN. 9,10-Dicyanoanthracene (DCA, Wako) was recrystallized from CH_3CN.

Photo-oxygenation of 1,2-bis(1-arylethenyl)benzenes **5a–d** using SET sensitizers

An oxygen-purged CH_3CN (10 mL) solution of **5** (0.20 mmol) and a catalytic amount of $TPPBF_4$ (0.02 mmol) or DCA (0.002 mmol) in the presence or absence of Bip (0.60 mmol) was irradiated ($\lambda > 360$ nm) by use of a 2-kW Xe lamp. The resulting mixture was concentrated and the residue was subjected to silica gel TLC separation (*n*-hexane–CH_2Cl_2) to afford the benzo-fused bicyclic peroxide **4** as a major product and a small amount of *o*-diaroylbenzene **6**. The structures of **4a–d** were determined by analysis of their spectroscopic data and comparison of the data with those reported for **4a** [27].

*Compound **4a***

Colorless needles; mp 192–194 °C (CH_3OH); IR (KBr, cm^{-1}) *v*: 3090, 3060, 2970, 2884, 1606, 1498, 1248, 1045; ^1H NMR (200 MHz, $CDCl_3$), *δ*: 2.27–2.52 (m, 2H), 2.71–2.96 (m, 2H), 6.68–6.78 (m, 2H), 7.18–7.28 (m, 2H), 7.35–7.70 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$), *δ*: 28.3 (t, 2C), 80.7 (s, 2C), 122.9 (d, 2C), 127.1 (d, 4C), 127.8 (d, 2C), 128.4 (d, 4C), 128.6 (d, 2C), 137.0 (s, 2C), 140.7 (s, 2C). Anal. calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.71; H, 5.84. MS (EI) *m*/*z* 314 (M^+, 2 %), 282 (100 %).

*Compound **4b***

Colorless needles; mp 222–224 °C (C_2H_5OH); IR (KBr, cm^{-1}) *v*: 3090, 2975, 2900, 1607, 1504, 1222, 1051; ^1H NMR (200 MHz, $CDCl_3$), *δ*: 2.22–2.48 (m, 2H), 2.68–2.87 (m, 2H), 6.65–6.78 (m, 2H), 7.10–7.32 (m, 6H), 7.48–7.63 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$), *δ*: 28.3 (t, 2C), 80.4 (s, 2C), 115.4 (d, 4C, $J_{C-F} = 21.8$ Hz), 122.8 (d, 2C), 128.0 (d, 2C), 129.1 (d, 4C, $J_{C-F} = 8.3$ Hz), 132.7 (d, 2C, $J_{C-F} = 3.1$ Hz), 140.5 (s, 2C), 162.8 (s, 2C, $J_{C-F} = 247$ Hz). Anal. calcd for $C_{22}H_{16}F_2O_2$: C, 75.42; H, 4.60. Found: C, 75.20; H, 4.70. MS (EI) *m*/*z* 350 (M^+, 1 %), 318 (100 %).

*Compound **4c***

Colorless prisms; mp 224–226 °C (C_2H_5OH); IR (KBr, cm^{-1}) *v*: 3010, 2945, 2905, 2830, 1607, 1508, 1238, 1038; ^1H NMR (200 MHz, $CDCl_3$), *δ*: 2.25–2.45 (m, 2H), 2.42 (s, 6H), 2.73–2.86 (m, 2H), 6.68–6.78 (m, 2H), 7.16–7.32 (m, 6H), 7.40–7.48 (m, 4H): ^{13}C NMR (50 MHz, $CDCl_3$), *δ*: 21.3 (q, 2C), 28.2 (t, 2C), 80.7 (s, 2C), 122.9 (d, 2C), 127.1 (d, 4C), 127.7 (d, 2C), 129.1 (d, 4C), 134.0 (s, 2C), 138.4 (s, 2C), 140.9 (s, 2C). Anal. calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48. Found: C, 84.04; H, 6.53. MS (EI) *m*/*z* 342 (M^+, 2 %), 310 (100 %).

*Compound **4d***

Colorless needles; mp 206–208 °C (C_2H_5OH); IR (KBr, cm^{-1}) *v*: 3040, 3010, 2897, 1596, 1513, 1259, 1034; ^1H NMR (200 MHz, $CDCl_3$), *δ*: 2.14–2.46 (m, 2H), 2.69–2.98 (m, 2H), 3.87 (s, 6H), 6.72–6.80 (m, 2H), 6.97–7.07 (m, 4H), 7.17–7.30 (m, 2H), 7.45–7.55 (m, 4H): ^{13}C NMR (50 MHz, $CDCl_3$), *δ*: 28.1 (t, 2C), 55.3 (q, 2C), 80.5 (s, 2C), 113.7 (d, 4C), 122.9 (d, 2C), 127.6 (d, 2C), 128.7 (d, 4C), 128.9 (s, 2C), 141.0 (s, 2C), 159.7 (s, 2C). Anal. calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.64; H, 5.95. MS (EI) *m*/*z* 374 (M^+, 8 %), 342 (100 %).

In vitro antimalarial activity of benzo-fused 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes **4a–d**

Plasmodium falciparum (ATCC 30932, FCR-3 strain) was used in this study. *P. falciparum* was cultivated by a modification of the method of Trager and Jensen

[53] using a 5 % hematocrit of type A human red blood cells suspended in RPMI 1640 medium (Gibco, NY, USA) supplemented with heat-inactivated 1 % type A human serum. The following procedures were used for assay of antimalarial activity. Asynchronously cultivated *P. falciparum* were used. Different concentrations of **4a**–**d** in dimethyl sulfoxide were prepared. Each solution (5 μL) was added to individual wells of a multidish, 24 wells. Erythrocytes with 0.3 % parasitemia were added to each well containing 995 μL culture medium to give a final hematocrit level of 3 %. The plates were incubated at 37 °C for 72 h in a CO_2–O_2–N_2 incubator (5 % CO_2, 5 % O_2, and 90 % N_2 atmosphere). To evaluate the antimalarial activity of a test compound, we prepared thin blood films from each culture and stained them with Giemsa (E. Merck, Germany). A total of 1×10^4 erythrocytes/1 thin blood film were examined under a microscope. All of the test compounds were assayed in duplicate at each concentration. Drug-free control cultures were run simultaneously. All data points are means from three experiments. Parasitemia in controls reached between 4 and 5 % at 72 h. The EC_{50} value is the concentration of the compound necessary to inhibit the increase in parasite density at 72 h by 50 % of control.

Toxicity against mammalian cell line

Mouse mammary tumor FM3A cells (wild-type, subclone F28-7) were supplied by the Japanese Cancer Research Resources Bank (JCRB). FM3A cells were maintained in suspension culture at 37 °C in a 5 % CO_2 atmosphere in plastic bottles containing ES medium (Nissui Pharmaceuticals, Japan) supplemented with 2 % heat-inactivated fetal bovine serum (Gibco, NY, USA). FM3A cells grew with a doubling time of approximately 12 h. Before exposure to drugs, cell density was adjusted to 5×10^4 cells/mL. A cell suspension of 995 μL was dispensed on to the test plates, and compound at different concentrations suspended in dimethyl sulfoxide (5 μL) was added to individual wells of a multidish, 24 wells. The plates were incubated at 37 °C in a 5 % CO_2 atmosphere for 48 h. All of the test compounds were assayed in duplicate at each concentration. Cell numbers were measured by use of a CC-130 microcell counter (Toa Medical Electric, Japan). All data points are means from three experiments. The EC_{50} value is the concentration of the compound necessary to inhibit the increase in cell density at 48 h by 50 % of control. Selectivity refers to the mean EC_{50} value for FM3A cells per the mean EC_{50} value for *P. falciparum*.

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