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ANTIMALARIAL SPIRO-BRIDGED 1,2-DIOXOLANES VIA INTRAMOLECULAR ADDITION OF PEROXYCARBENIUM IONS TO C-C DOUBLE BONDS

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Abstract – Several 1,2-dioxolanes embedded in a rigid spiro-bridge framework fused with a built-in UV chromophore were synthesized through intramolecular [3+2] addition of *in situ* generated peroxycarbenium ions to C-C double bonds.

INTRODUCTION

Discovery of qinghaosu[1] (artemisinin), a potent naturally-occurring antimalarial agent, has brought entirely renewed interest to organic peroxides. To establish structure-activity relationships and to discover new lead compounds for antimalarial drugs, a huge number of novel organic peroxides have been designed and synthesized since the late 1970's.

An issue of central importance in the synthesis of organic peroxides is the introduction of the peroxy bond. To date, almost in all synthetic organic peroxides the peroxy bonds were taken from some inorganic species that already contain O-O bond(s), such as $^3O_2$, $^1O_2$, and O_3. Hydrogen peroxide (H_2O_2) is also a readily available source for peroxy bonds, which has received more and more attention in recent years because of the potential advantages in accessibility, handling, and cost.[2]

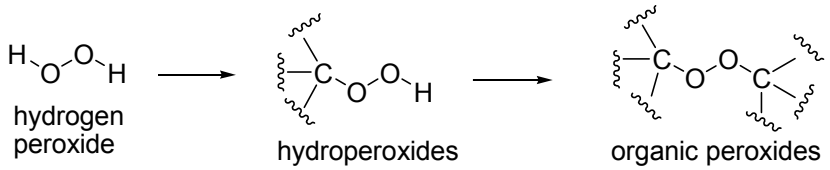


Figure 1. Incorporation of H_2O_2 into organic structures with one oxygen alkylated at a time.

This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday

Incorporation of hydrogen peroxide into an organic framework is often achieved in a stepwise manner (Figure 1), with one oxygen atom bonded to a carbon atom at a time through alkylation or ketalization. Recently, we developed[2t] a PMA (phosphomolybdic acid) catalyzed transformation of ketones and ketals into the corresponding gem-dihydroperoxyketals, which provided a facile way to complete the first step (Figure 1). In efforts to complete the second step (viz., connecting another carbon atom to the hydroperoxyl group) we noticed the Woerpel's[2p] approach to 1,2-dioxolanes (also the original work[3] of Dussault, Figure 2). Although all their products were monocyclic, it seemed that application of such reactions in an intramolecular manner would result in structurally more complex polycyclic peroxides. Prompted by this thought, we carried out the work below.

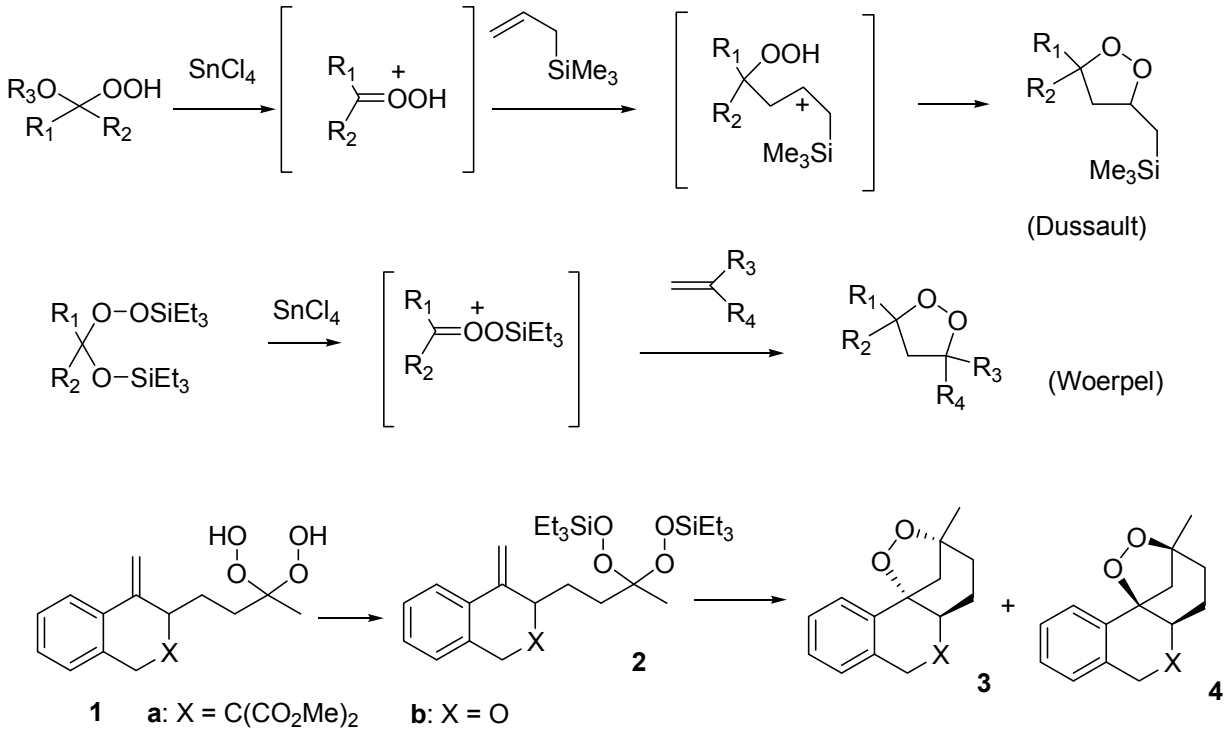
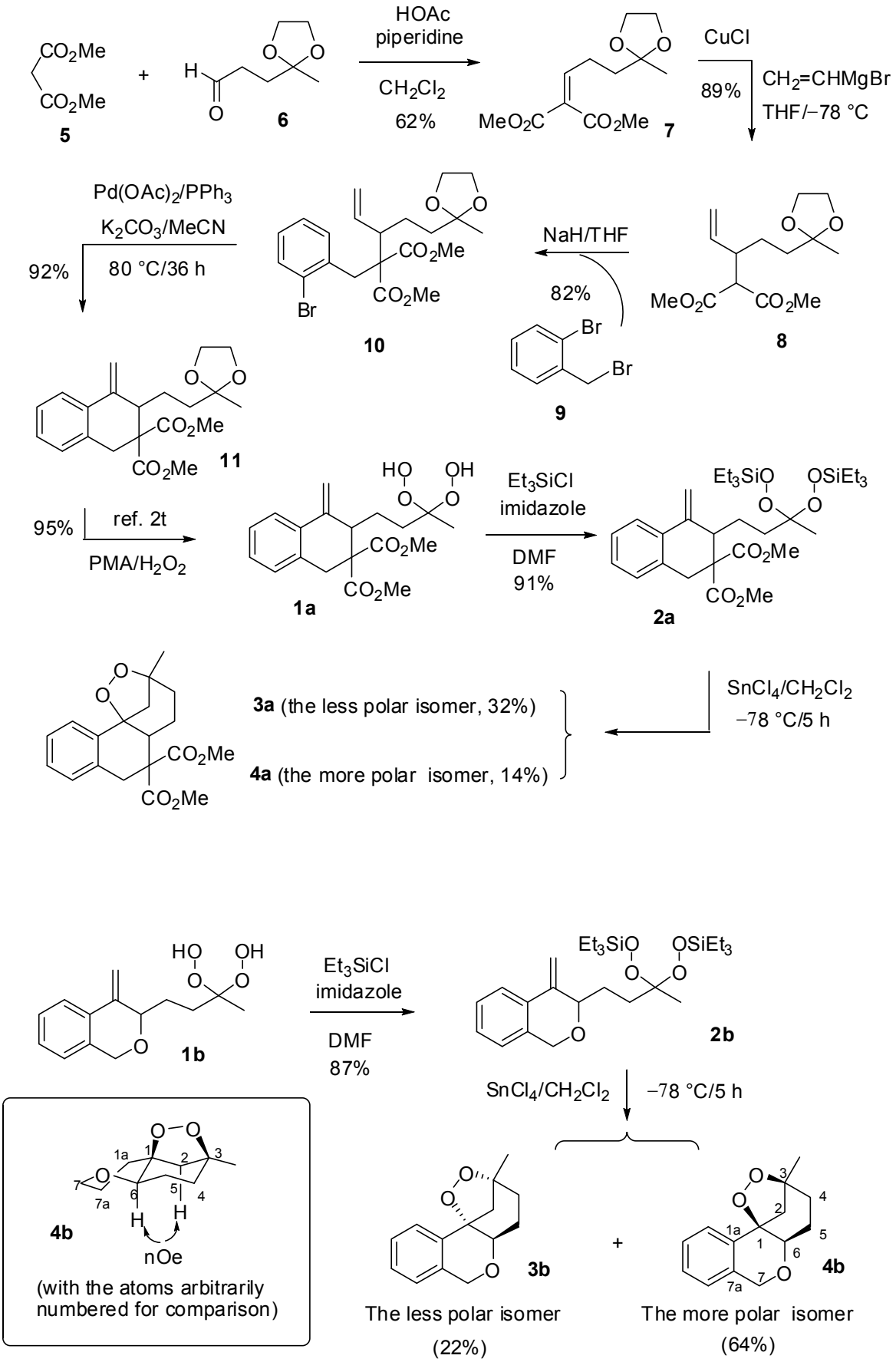


Figure 2. The intermolecular additions of peroxycarbenium ions to alkenes giving monocyclic peroxides developed by Dussault and Woerpel, and the main features of this work (conversion of **2** to **3** and **4**).

RESULTS AND DISCUSSION

The synthesis merged with the condensation[4] of dimethyl malonate (**5**) with the known[5] aldehyde **6** (Scheme 1). The resulting α,β-unsaturated species (**7**) was treated with vinyl Grignard reagent in the presence of CuCl at –78 °C gave the expected Michael addition[6] product **8** in 89% yield. The acidic malonate CH proton was then removed with NaH to afford the corresponding carbanion, which reacted with the commercially available **9** to yield **10**. A Heck reaction was then performed under the $Pd(OAc)_2/K_2CO_3/Ph_3P/MeCN$[7] conditions. The resulting **11** was then converted into the corresponding gem-dihydroperoxides **1a** via reaction with H_2O_2 as reported previously[2t] with the aid of PMA.


CO2Me
CO2Me
5
H
O
O
6
HOAc
piperidine
CH2Cl2
62%
MeO2C
CO2Me
7
CuCl
89%
CH2=CHMgBr
THF/−78 °C
Pd(OAc)2/PPh3
K2CO3/MeCN
92%
80 °C/36 h
Br
10
NaH/THF
82%
Br
Br
9
8
11
95%
ref. 2t
PMA/H2O2
HO
OH
1a
Et3SiCl
imidazole
DMF
91%
Et3SiO
OSiEt3
2a
SnCl4/CH2Cl2
−78 °C/5 h
3a (the less polar isomer, 32%)
4a (the more polar isomer, 14%)
1b
2b
4b
nOe
(with the atoms arbitrarily
numbered for comparison)
3b
The less polar isomer
(22%)
The more polar isomer
(64%)

Scheme 1

The hydroperoxide OH's in **1a** were silylated with Et_3SiCl in the presence of imidazole to deliver the bis-silylpoxyketal **2a** in 91% yield. The key [3+2] cycloaddition was then examined at –78 °C in CH_2Cl_2 in the presence of $SnCl_4$. After five hours' reaction, the desired bridged peroxides, **3a** (the less polar isomer) and **4a** (the more polar isomer), were isolated in 32% and 14% yields, respectively. The closely related bis-silylpoxyketal **2b** (derived in a similar manner by silylation of the known[2t] **1b**) also underwent facile [3+2] reaction under the same conditions, giving **3b** (the less polar isomer) and **4b** (the more polar isomer) in 22% and 64% yield, respectively.

The products of the cycloadditions (**3** and **4**) are a pair of diastereomers in each case. Although the relative configurations for **3a** and **4a** cannot be assigned with certainty, those for **3b** and **4b** are reliably established with the aid of 2D NOESY experiment; a distinct nOe (the boxed structure on the bottom left corner, Scheme 1) was observed for the polar isomer **4b**.

Table 1. The *in vitro* activity against *P. falciparum* (NF54 strain).[a,b]

Peroxide	IC_{50} (ng/mL)	IC_{50} (μM)
3a	336	0.97
4a	936	2.70
3b	502	2.16
4b	1516	6.53
Chloroquine diphosphate	6.7	0.013
Artesunate	1.2	0.0030

[a] The *in vitro* antimalarial data were obtained as described previously (ref. 8).
[b] Data shown are the values from n = 2–3 independent experiments.

The peroxides obtained were tested *in vitro* for their antimalarial activity. The results are shown in Table 1. The IC_{50}'s were in the range of 0.97-6.53 μM, with the less polar isomers somewhat more potent than the more polar ones.

In summary, several 1,2-dioxolanes with the peroxy bond installed in a rigid spiro-bridge framework were synthesized by using intramolecular [3+2] addition of *in situ* generated peroxycarbenium ions to C-C double bonds. All products contain a fused benzene ring to serve as a built-in UV chromophore, which may facilitate e.g., HPLC analysis in case of further biomedical investigations.

EXPERIMENTAL

The ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using a Varian Mercury 300 or a Bruke Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FT-IR. EIMS and EIHRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. Dry CH_2Cl_2 was obtained by distillation over CaH_2. Dry THF was distilled over Na/Ph_2CO under argon before use. Degassed MeCN was obtained by bubbling N_2 into MeCN for 20 min. All other solvents and reagents were used as received from commercial sources. PE = petroleum ether (chromatography solvent, bp 60−90 °C).

Dimethyl 2-(3-(2-methyl-1,3-dioxolan-2-yl)propylidene)malonate (7). Piperidine (0.2 mL, 2.0 mmol) and glacial acetic acid (0.12 mL, 2.0 mmol) were added in turn to a solution of dimethyl malonate (3.90 g, 30 mmol) in dry CH_2Cl_2 (5 mL) stirred in an ice-water bath. After completion of the addition, the bath was removed and the mixture was stirred at ambient temperature over night. When TLC showed completion of the reaction, sat. aq. NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O (3 × 50 mL), washed with brine (3 × 15 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel gave **7** as a colorless oil (1.6 g, 6.2 mmol, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.3 Hz, 1H), 4.00-3.87 (m, 4H), 3.84 (s, 3H), 3.78 (s, 3H), 2.42 (dt, *J* = 8.3, 7.3 Hz, 2H), 1.84 (t, *J* = 7.7 Hz, 2H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.3, 150.5, 127.5, 109.1, 64.6, 52.3, 52.2, 37.2, 24.5, 23.9; FT-IR (film) 2955, 2887, 1732, 1644, 1437, 1376, 1256, 1052, 863, 833 cm^{-1}; ESI-MS *m/z* 281.0 ([M+Na]$^+$); EI-HRMS calcd for $C_{12}H_{18}O_6$ (M^+) 258.1103, found 258.1105.

Dimethyl 2-(5-(2-methyl-1,3-dioxolan-2-yl)pent-1-en-3-yl)malonate (8). CH_2=CHMgBr (1.0 M, in Et_2O, 1.2 mL, 1.2 mmol) was added dropwise to a mixture of **7** (256 mg, 1.0 mmol) and CuCl (5.0 mg, 0.05 mmol) in dry THF (3 mL) stirred at –78 °C under N_2 (balloon). After completion of the addition, the mixture was stirred another 30 min at the same temperature, when TLC showed completion of the reaction. sat. aq. NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (3 × 30 mL), washed with brine (3 × 15 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel gave **8** as a colorless oil (236 mg, 0.89 mmol, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (dt, *J* = 17.5, 9.6 Hz, 1H), 5.12 (d, *J* = 1.9 Hz, 1H), 5.07 (d, *J* = 2.6 Hz, 1H), 4.00-3.84 (m, 4H), 3.74 (s, 3H), 3.69 (s, 3H), 3.40 (d, *J* = 9.0 Hz, 2H), 2.76 (dq, *J* = 2.8, 9.6 Hz, 1H), 1.77-1.50 (m, 2H), 1.46-1.32 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 168.4, 137.6, 117.9, 109.7, 64.6, 64.5, 56.8, 52.4, 52.3, 44.1, 36.4, 26.6, 23.8; FT-IR (film) 2955, 2883, 1739, 1642, 1435, 1377, 1255, 1151, 1039, 924, 850 cm^{-1}; ESI-MS *m/z* 309.0 ([M+Na]$^+$); Anal. Calcd for

$C_{14}H_{22}O_6$: C 58.73, H 7.74. Found: C 58.75, H 7.50.

Dimethyl 2-(2-bromobenzyl)-2-(5-(2-methyl-1,3-dioxolan-2-yl)pent-1-en-3-yl)malonate (10). A solution of the 2-bromobenzyl bromide **9** (525 mg, 2.10 mmol) in dry THF (1 mL) was added to a mixture of **8** (200 mg, 0.70 mmol) and NaH (60% in mineral oil, 84 mg, 2.10 mmol, washed thrice with petroleum ether before addition of THF) in dry THF (3 mL) stirred at ambient temperature already for 30 min. Stirring was then continued at the same temperature over night. When TLC showed completion of the reaction, sat. aq. NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (3×50 mL), washed with brine (2×15 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel gave **10** (260 mg, 0.57 mmol, 82%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.69 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.19 (d, *J* = 2.2 Hz, 1H), 5.09 (d, *J* = 1.7 Hz, 1H), 4.00-3.84 (m, 4H), 3.63 (s, 3H), 3.61 (s, 3H), 3.53 (d, *J* = 14.8 Hz, 1H), 3.38 (d, *J* = 14.8 Hz, 1H), 2.70 (t, *J* = 9.6 Hz, 1H), 1.92-1.66 (m, 2H), 1.56 (dt, *J* = 4.4, 13.1 Hz, 1H), 1.39-1.31 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.4, 137.2, 136.9, 132.5, 131.3, 128.0, 127.1, 126.2, 119.1, 109.8, 64.6, 64.5, 62.4, 52.2, 52.1, 50.4, 38.4, 37.3, 24.8, 23.8; FT-IR (film) 2981, 2880, 1732, 1474, 1435, 1377, 1248, 1045, 852, 751 cm^{-1}; ESI-MS *m/z* 477.1 ([M+Na]$^+$); MALDI-HRMS calcd for $C_{21}H_{27}O_6BrNa$ ([M+Na]$^+$) 477.08832, found 477.0893.

Dimethyl 3-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-4-methylene-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (11). A solution of **10** (190 mg, 0.42 mmol), PPh_3 (44 mg, 0.17 mmol), K_2CO_3 (300 mg, 2.52 mmol), and $Pd(OAc)_2$ (14 mg, 0.06 mmol) in degassed MeCN (8 mL) was placed in liquid N_2. The resulting solid was evacuated with an oil pump and the vaccum was released with argon. The process was repeated three time before the mixture was finally refluxed in a oil bath under argon for 36 h. The mixture was cooled to ambient temperature. Et_2O (50 mL) and water (20 mL) were added. The mixture was extracted with extracted with Et_2O (3×50 mL), washed with brine (2×20 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel gave **11** as a colorless oil (145 mg, 0.38 mmol, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.3 Hz, 1H), 7.24-7.08 (m, 3H), 5.56 (s, 1H), 5.05 (s, 1H), 4.00-3.80 (m, 4H), 3.78 (s, 3H), 3.60 (s, 3H), 3.57 (d, *J* = 17.2 Hz, 1H), 3.25 (d, *J* = 17.2 Hz, 2H), 1.49-1.82 (m, 3H), 1.38-1.22 (m, 1H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 142.3, 133.1, 132.0, 128.8, 128.1, 126.4, 124.9, 112.4, 109.7, 64.5, 64.4, 58.4, 52.9, 52.8, 46.7, 36.7, 30.7, 23.6, 23.3; FT-IR (film) 2982, 2882, 1736, 1631, 1478, 1434, 1377, 1259, 1151, 1046, 948, 778, 736 cm^{-1}; ESI-MS *m/z* 397.1 ([M+Na]$^+$); MALDI-HRMS calcd For $C_{21}H_{26}O_6Na$ ([M+Na]$^+$) 397.16216, found 397.1635.

Dimethyl 3-(3,3-bis(triethylsilylperoxy)butyl)-4-methylene-3,4-dihydronaphthalene-2,2(1*H*)-

dicarboxylate (2a). A solution of **1a** (150 mg, 0.40 mmol), Et_3SiCl (202 μL, 1.2 mmol) and imidazole (103 mg, 1.52 mmol) in dry DMF (4 mL) was stirred at ambient temperature for 10 h. Et_2O (50 mL) and water (10 mL) were added. The mixture was extracted with extracted with Et_2O (3×50 mL), washed with water (2×20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:20 EtOAc/PE) on silica gel gave **11** as a colorless oil (220 mg, 0.36 mmol, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.25-7.10 (m, 3H), 5.57 (s, 1H), 5.08 (s, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.57 (d, *J* = 16.7 Hz, 1H), 3.35-3.318 (m, 2H), 1.94-1.68 (m, 2H), 1.67-1.47 (m, 1H), 1.25-1.37 (m, 1H), 1.23 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.68 (q, *J* = 8.0 Hz, 6H), 0.59 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 142.2, 133.1, 132.0, 128.7, 128.0, 126.4, 125.0, 112.4, 110.5, 58.4, 52.9, 52.7, 46.7, 32.2, 30.8, 23.6, 18.7, 6.73, 6.66, 3.76, 3.67. FT-IR (film) 2954, 2878, 1742, 1456, 1434, 1233, 1280, 1140, 798, 733 cm^{-1}; ESI-MS *m/z* 631.4 ($[M+Na]^+$); ESI-HRMS calcd for $C_{31}H_{52}O_8Si_2Na$ ($[M+Na]^+$) 631.30929, found 631.31085.

Dimethyl 3-methyl-3,4,5,5a-tetrahydro-3,11b-methanonaphtho[1,2-*c*][1,2]dioxepine-6,6(7*H*)-dicarboxylate (3a and 4a). A solution of $SnCl_4$ in dry CH_2Cl_2 (1.0 M, 0.15 mL, 0.15 mmol) was added to a solution of **2a** (60 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) stirred at –78 °C under argon (balloon). After completion of the addition, stirring was continued at the same temperature for 5 h before the bath was allowed to warm to ambient temperature over 1 h. When TLC showed completion of the reaction, Et_2O was added, followed by sat. aq. $NaHCO_3$. The mixture was extracted with Et_2O, washed in turn with water, aq. sat. $NaHCO_3$, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel gave the less polar isomer **3a** (11 mg, 0.032 mmol, 32%) and the more polar isomer **4a** (5 mg, 0.014 mmol, 14%) as a colorless oils.

Data for **3a** (the less polar isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 1H), 7.11-7.01 (m, 2H), 6.94 (d, *J* = 7.3 Hz, 1H), 3.84 (s, 3H), 3.79 (d, *J* = 14.1 Hz, 1H), 3.76 (s, 3H), 3.68 (d, *J* = 8.5 Hz, 1H), 3.04 (d, *J* = 13.7 Hz, 1H), 2.78 (d, *J* = 7.8 Hz, 1H), 2.73 (d, *J* = 11.6 Hz, 1H), 2.59 (dt, *J* = 9.8, 2.1 Hz, 1H), 2.43-2.25 (m, 1H), 2.00 (dd, *J* = 15.0, 6.3 Hz, 1H), 1.72 (dd, *J* = 14.1, 6.7 Hz, 1H), 1.33 (s, 3H). FT-IR (film) 2953, 2929, 1729, 1488, 1450, 1257, 1237, 1180, 1112, 997, 894, 766 cm^{-1}; ESI-MS *m/z* 385.1 ($[M+K]^+$); ESI-HRMS calcd for $C_{19}H_{22}O_6Na$ ($[M+Na]^+$) 369.13086, found 369.13084.

Data for **4a** (the more polar isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.94-6.84 (m, 2H), 3.83 (dd, *J* = 5.3, 10.1 Hz, 2H), 3.75 (s, 3H), 3.39 (s, 3H), 3.23 (d, *J* = 16.2 Hz, 1H), 2.83 (dd, *J* = 11.0, 2.7 Hz, 1H), 2.61 (d, *J* = 10.9 Hz, 1H), 2.23-2.05 (m, 1H), 2.02-1.91 (m, 1H), 1.71 (dd, *J* = 12.3, 6.0 Hz, 1H), 1.52-1.41 (m, 1H), 1.35 (s, 3H). FT-IR (film) 2952, 2929, 1739, 1490, 1452, 1227, 1191, 1152, 893, 872, 759 cm^{-1}; ESI-MS *m/z* 369.1 ($[M+Na]^+$); ESI-HRMS calcd for

$C_{19}H_{22}O_6Na$ ([M+Na]$^+$) 369.13086, found 369.13086.

3,3,9,9-Tetraethyl-6-methyl-6-(2-(4-methyleneisochroman-3-yl)ethyl)-4,5,7,8-tetraoxa-3,9-disilaundecane (2b). The same procedure for conversion of **1a** into **2a** above was used (with **1b** to replace **1a**); yield (chromatography with 1:100 EtOAc/PE): 87%.

Data for **2b** (a colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.60 (m, 1H), 7.27-7.18 (m, 2H), 7.97-6.06 (m, 1H), 5.62 (s, 1H), 5.08 (s, 1H), 4.87 (d, *J* = 15.2 Hz, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H), 2.07-1.80 (m, 4H), 1.36 (s, 3H), 0.97 (t, *J* = 8.2 Hz, 18H), 0.69 (q, *J* = 8.2 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 134.4, 131.4, 127.7, 126.9, 124.3, 123.9, 110.8, 107.1, 77.3, 65.6, 30.2, 27.2, 18.8, 6.8, 3.8; FT-IR (film) 2954, 2877, 1458, 1412, 1371, 1239, 1104, 1019, 798, 730 cm^{-1}; ESI-MS *m/z* 517.2 ([M+Na]$^+$); ESI-HRMS calcd for $C_{26}H_{46}O_5Si_2Na$ ([M+Na]$^+$) 517.27760, found 517.27837.

(3*R,5a*R*,11b*S**)-3-Methyl-4,5,5a,7-tetrahydro-3*H*-3,11b-methano[1,2]dioxepino[4,3-*c*]isochromene (3b) and (3*S**,5a*R**,11b*R**)-3-methyl-4,5,5a,7-tetrahydro-3*H*-3,11b-methano[1,2]dioxepino[4,3-*c*]-isochromene (4b).** The same procedure for conversion of **2a** into **3a** and **4a** (but with **2b** to replace **2a**, chromatography with 1:20 EtOAc/PE).

Data for **3b** (the less polar isomer, a colorless oil, 22% from **2b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 3.8, 5.6 Hz, 1H), 7.29-7.20 (m, 2H), 7.00 (t, *J* = 4.2 Hz, 1H), 4.95 (d, *J* = 14.9 Hz, 1H), 4.88 (d, *J* = 14.9 Hz, 1H), 3.80 (d, *J* = 6.2 Hz, 1H), 2.93 (d, *J* = 11.7 Hz, 1H), 2.52-2.35 (m, 1H), 2.27 (d, *J* = 11.6 Hz, 1H), 1.95-1.82 (m, 1H), 1.76 (dd, *J* = 4.5, 10.4 Hz, 2H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 133.9, 127.8, 127.0, 123.8, 123.7, 84.3, 83.6, 74.8, 68.7, 54.7, 33.1, 24.7, 22.0. FT-IR (film) 2934, 2861, 1454, 1372, 1223, 1080, 1037, 855, 757 cm^{-1}; ESI-MS *m/z* 255.0 ([M+Na]$^+$); ESI-HRMS calcd for $C_{14}H_{16}O_3Na$ ([M+Na]$^+$) 255.09917, found 255.09921.

Data for **4b** (the more polar isomer, a colorless oil, 64% from **2b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.61 (m, 1H), 7.37-7.27 (m, 2H), 7.05 (t, *J* = 4.2 Hz, 1H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.76 (d, *J* = 15.9 Hz, 1H), 3.73 (dd, *J* = 5.8, 11.1 Hz, 1H), 2.93 (dd, *J* = 2.8, 11.8 Hz, 1H), 2.34 (d, *J* = 11.6 Hz, 1H), 2.23-2.33 (m, 1H), 2.05-2.16 (m, 1H), 1.94 (dd, *J* = 6.7, 14.0 Hz, 1H), 1.65-1.80 (m, 1H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.8, 128.4, 127.28, 127.27, 124.4, 83.9, 80.9, 78.8, 68.1, 53.1, 35.6, 25.6, 21.2. FT-IR (film) 2941, 2851, 1493, 1447, 1376, 1297, 1213, 1108, 1038, 866, 756 cm^{-1}; ESI-MS *m/z* 255.0 ([M+Na]$^+$); ESI-HRMS calcd for $C_{14}H_{16}O_3Na$ ([M+Na]$^+$) 255.09917, found 255.09924.

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