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ACCESS TO SOME UV CHROMOPHORE-CONTAINING ANTIMALARIAL TRIOXANES USING HYDROGEN PEROXIDE AS SOURCE OF THE PEROXY BONDS

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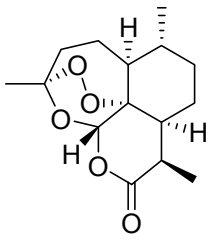
Abstract – Several trioxanes were synthesized through perhydrolysis of an allylic epoxide followed by ketal exchange with a proper dimethyl ketal.

1,2,4-Trioxane is broadly considered as the pharmacophore of qinghaosu (artemisinin, **1**), an antimalarial agent discovered by Chinese scientists in the early 1970's. This natural sesquiterpene endoperoxide was found to be highly potent against malaria parasites including the multi drug-resistant strains and thus attracted many investigators around the world.[1] Nowadays the combinations treatments with qinghaosu-derived peroxy compounds as the key ingredient have been recommended as the first-line drugs to treat malaria.



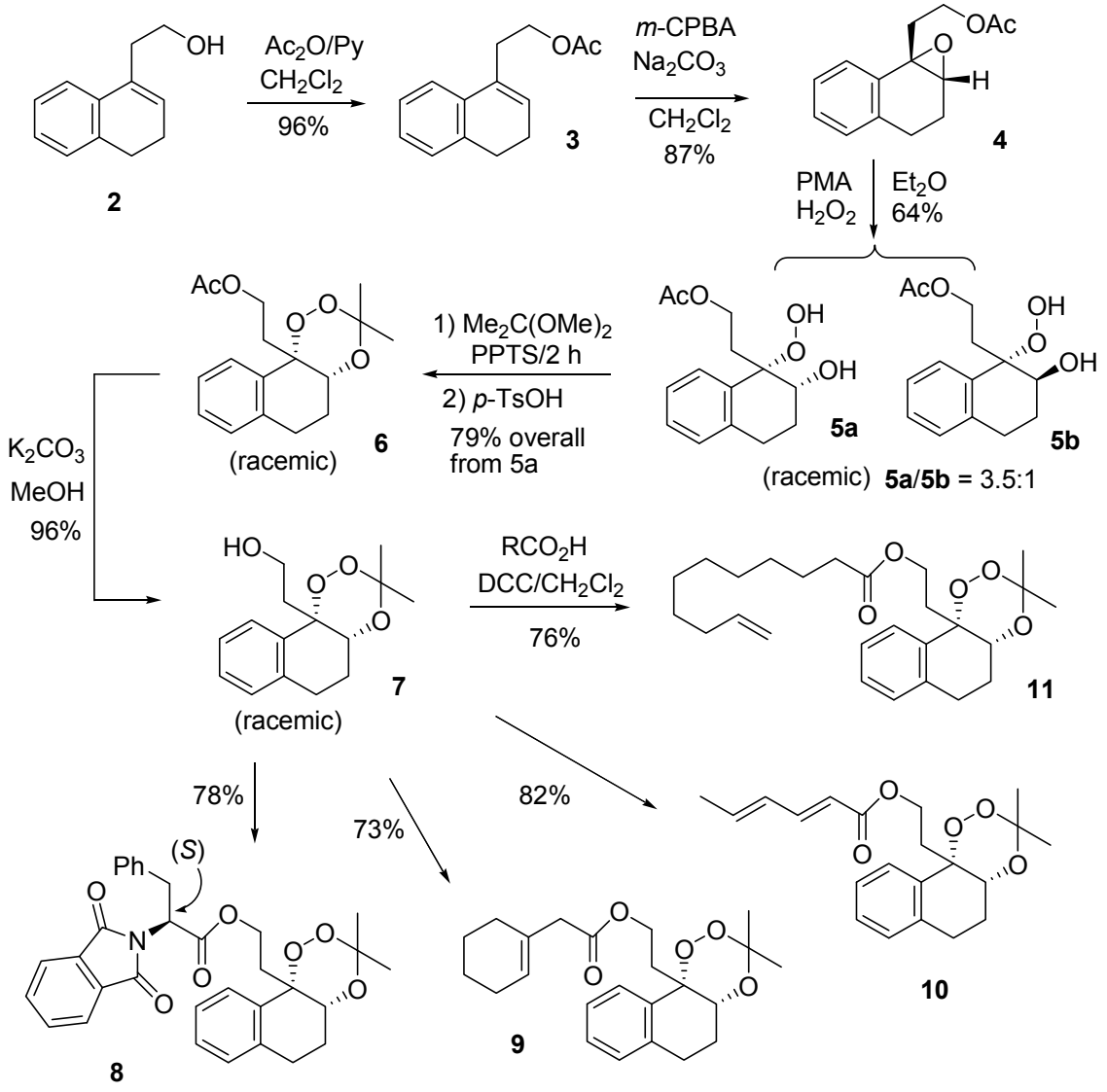
1 qinghaosu
(artemisinin)

Figure 1. The structure of natural antimalarial qinghaosu (artemisinin)

The discovery of qinghaosu has also greatly stimulated the studies on design and synthesis of simple organic peroxides,[2] because qinghaosu is still a limited natural resource and its synthesis can be achieved only on small laboratory scales to date. As part of our long-standing study, we have been working on synthesis various organic peroxides using hydrogen peroxide as the source of the peroxy bonds.[3]

This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday

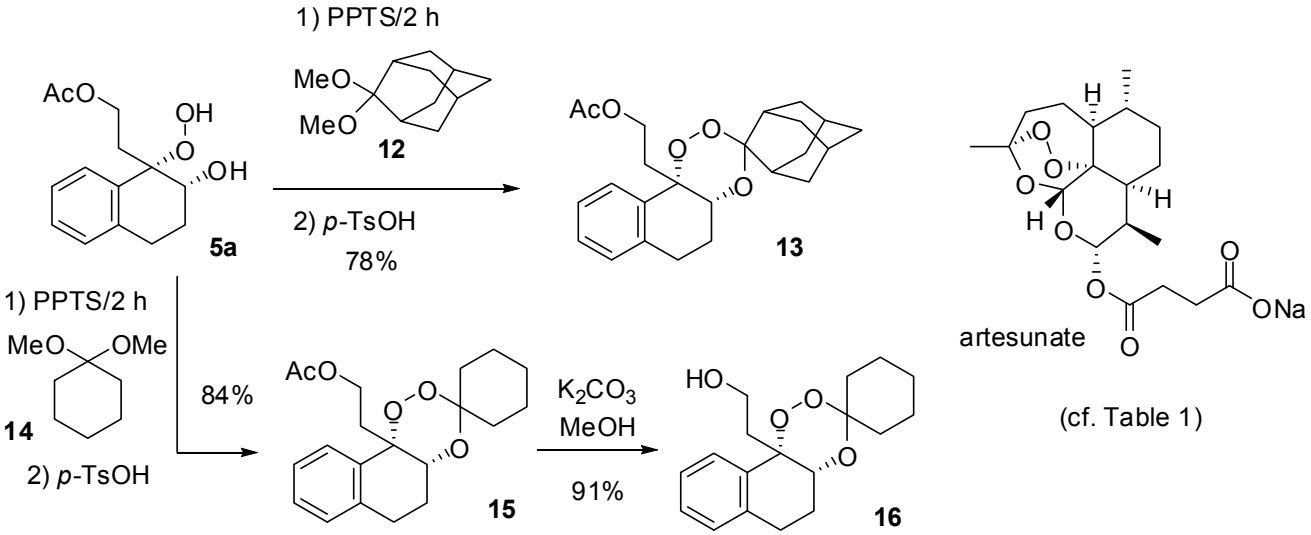
Recently, we developed[3d] a very mild yet highly efficient protocol for perhydrolysis of epoxides with PMA (phosphomolybdic acid) as the catalyst. The products of such epoxide ring opening reactions are β-hydroxyhydroperoxides, which are apparent precursors to 1,2,4-trioxanes. To exploit this potential, we designed a readily accessible UV-chromophore (which may facilitate detection in e. g. pharmacokinetic/metabolic studies) containing epoxide, from which through perhydrolysis and ketalization a range of 1,2,4-trioxanes can be obtained. The peroxides thus constructed also carry a free hydroxyl group for further derivatization. Here below are the details of this endeavor.



Scheme 1

The synthesis merged with the known[4] alcohol **2** (Scheme 1). After acetylation with Ac_2O in the presence of pyridine, the alkenic bond was oxidized with *m*-CPBA to afford epoxide **4**. It is interesting to note that use of Na_2CO_3 appears to be necessary in this epoxidation. If the more frequently employed $NaHCO_3$ was used as the buffer, the desired epoxide was isolated in only 28% yield.

The epoxide **4** was then subjected to the perhydrolysis conditions developed[3d] in our laboratories previously. Again, like observed earlier in a similar case[3d] with a benzylic epoxide, a deep blue color occurred immediately after addition of the "normal" (10 mol% with respect to the epoxide **4**) amounts of PMA. However, if reducing the added PMA to only 1 mol%, the desired ring opening products were formed in 64% isolated yield. The major (cis) isomer **5a** was converted to the corresponding acetonide by treatment with $Me_2C(OMe)_2$ first in the presence of a catalytic amount of PPTS and then a more acidic catalyst, *p*-TsOH. Lower yields were observed if the *p*-TsOH was added from the beginning.



Scheme 2

The acetyl group was then hydrolyzed with K_2CO_3/MeOH to free the hydroxyl group in the side chain, which allowed facile derivatization through simple condensation with different carboxylic acids under the standard DCC conditions to afford esters **8**, **9**, **10**, and **11**.

If the perhydrolysis product **5a** was treated with other ketals instead of $Me_2C(OMe)_2$, the corresponding 1,2,4-trioxanes could also be obtained in good yields (Scheme 2). For instance, reaction with the commercially available **12** resulted in the corresponding ketal exchange product **13**, which carries an admantyl framework similar to Vennerstrom's[5] highly potent ozonides, under otherwise the same conditions as described for the synthesis of **6**. Similarly, the reaction with **14** led to **15** in a comparable yield. The latter (**15**) could be further converted to alcohol **16** for further derivatization.

The trioxanes obtained were tested in vitro for their antimalarial activity, with the results shown in Table 1. It seems that the antimalarial activity for most of the trioxanes in this series are rather close to each other, except for **6** and **7**, which are substantially less potent.

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

Trioxane	IC_{50} (μg/mL)	IC_{50} (μM)	Trioxane	IC_{50} (μg/mL)	IC_{50} (μM)
6	5.483	17.90	**11**	1.468	3.41
7	4.401	16.65	**13**	1.074	2.70
8	2.685	4.96	**15**	1.055	3.05
9	1.624	4.20	**16**	0.805	2.64
10	2.648	7.39	artesunate	0.001	0.0030

[a] The in vitro antimalarial data were obtained as described previously (ref. 6).
[b] Data shown are the values from n = 2–3 independent experiments.

EXPERIMENTAL

Although no explosions were experienced in this work, generally speaking organic peroxides are potentially hazardous compounds and must be handled with great care: Avoid direct exposure to strong heat or light, mechanical shock, oxidizable organic materials, or transition-metal ions. A safety shield should be used for all reactions involving H_2O_2. Dry CH_2Cl_2 was obtained by distillation over CaH_2. All other solvents and reagents were used as received from commercial sources. PE = petroleum ether (chromatography solvent, bp 60−90 °C). Ethereal hydrogen peroxide was prepared using a literature procedure with slight modification as in our previous[3d] paper. The ethereal layer was then dried over anhydrous $MgSO_4$. The supernatant (ca. 1 M in H_2O_2 as titrated with 0.1 M $KMnO_4$) was used directly in the PMA catalyzed perhydrolysis.

2-(3,4-Dihydronaphthalen-1-yl)ethyl acetate (3). Ac_2O (1.6 mL, 16 mmol), pyridine (1.2 mL, 16 mmol) and DMAP (15 mg, 0.13 mmol) were added in turn to a solution of alcohol **2** (696 mg, 4.0 mmol) in dry CH_2Cl_2 (20 mL) stirred at ambient temperature. The mixture was then stirred at the same temperature for 10 h before being partitioned between Et_2O (100 mL) and water (10 mL). The phases were separated. The aqueous layer was back extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq. $CuSO_4$, water, brine (twice each), and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (50:1 PE/EtOAc) on silica gel gave the acetate **3** as a colorless oil (834 mg, 3.82 mmol, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11-7.31 (m, 4H), 5.92 (t, J = 4.6 Hz, 1H), 4.24 (t, J = 7.2 Hz, 2H), 2.69-2.85 (m, 4H), 2.21-2.32 (m, 2H), 2.05 (s, 3H); FT-IR (film) 2933, 2831, 1738, 1488, 1449, 1364, 1240, 1039, 764, 737 cm^{-1}. ESI-MS *m/z* 239.1 ([M+Na]$^+$). Anal. Calcd for $C_{14}H_{16}O_2$: C 77.75, H 7.46. Found C 77.75, H 7.44.

2-((1a*R,7b*S**)-1a,2,3,7b-Tetrahydronaphtho[2,1-*b*]oxiren-7b-yl)ethyl acetate (4).** Na_2CO_3 (18 mg, 0.17 mmol) and *m*-CPBA (75%, 74 mg, 0.32 mmol) were added to a solution of alkene **3** (63 mg, 0.29 mmol) in dry CH_2Cl_2 (2 mL) stirred in an ice-water bath. The mixture was then stirred at ambient temperature until TLC showed completion of the reaction. Sat. aq. $NaHCO_3$ (2 mL) was added. The

mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with aq. sat. Na_2SO_3 (15 mL) and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (30:1 PE/EtOAc) on silica gel gave the epoxide **4** as a colorless sticky oil (59 mg, 0.25 mmol, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.60 (m, 1H), 7.19-7.30 (m, 2H), 7.07-7.17 (m, 1H), 4.30 (t, *J* = 7.3 Hz, 2H), 3.58 (d, *J* = 2.5 Hz, 1H), 2.68-2.91 (m, 2H), 2.56 (dd, *J* = 5.2, 15.1 Hz, 1H), 2.33-2.45 (m, 1H), 2.20 (dt, *J* = 7.4, 14.6 Hz, 1H), 2.04 (s, 3H), 1.83 (dt, *J* = 5.7, 14.0 Hz, 1H); FT-IR (film) 2934, 2849, 1736, 1459, 1461, 1433, 1366, 1237, 1039, 759, 740 cm^{-1}. EI-MS *m/z* 232 (M^+). Anal. Calcd for $C_{14}H_{16}O_3$: C 72.39, H 6.94. Found C 72.41, H 6.98.

2-((1*S,2*R**)-1-Hydroperoxy-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl acetate (5a) and 2-((1*S**,2*S**)-1-hydroperoxy-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl acetate (5b).** A mixture of PMA (1.2 mg, 0.013 mmol) and epoxide **4** (300 mg, 1.27 mmol) in freshly prepared ethereal H_2O_2 solution (10 mL) was stirred at ambient temperature for 3 h, when TLC showed completion of the reaction. Et_2O (100 mL) was added, followed by water (20 mL). The phases were separated. The aqueous layer was back extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (1:1 PE/Et_2O) on silica gel gave the *cis* isomer **5a** (169 mg, 0.63 mmol, 50%) and the *trans* isomer **5b** (47 mg, 0.18 mmol, 14%) as colorless oils.

Data for **5a** (the less polar component): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.35-7.42 (m, 1H), 7.18-7.25 (m, 2H), 7.10-7.17 (m, 1H), 4.27-4.44 (m, 2H), 3.97-4.10 (m, 1H), 3.04 (dt, *J* = 8.7, 17.0 Hz, 1H), 2.66-2.87 (m, 2H), 2.12-2.40 (m, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 136.8, 133.7, 129.0, 128.1, 127.1, 126.0, 84.1, 70.0, 60.6, 34.5, 26.0, 25.0, 21.0; FT-IR (film) 3370, 2938, 1736, 1453, 1396, 1367, 1241, 1077, 1038, 761 cm^{-1}. ESI-MS *m/z* 289.1 ($[M+Na]^+$); ESI-HRMS calcd. for $C_{14}H_{18}O_5Na$ ($[M+Na]^+$) 289.1047, found 289.1050.

Data for **5b** (the more polar component): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.39-7.47 (m, 1H), 7.19-7.28 (m, 2H), 7.07-7.18 (m, 1H), 4.50 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.26-4.39 (m, 1H), 4.00-4.23 (m, 2H), 3.05 (br s, 1H), 2.89-3.01 (m, 2H), 2.34-2.48 (m, 1H), 2.08-2.26 (m, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 136.7, 135.6, 129.2, 128.1, 126.2, 125.9, 87.2, 70.2, 60.6, 31.9, 27.3, 26.7, 21.0; FT-IR (film) 3398, 2940, 1736, 1489, 1453, 1396, 1368, 1241, 1038, 975, 761 cm^{-1}. ESI-MS *m/z* 289.1 ($[M+Na]^+$); MALDI-HRMS calcd. for $C_{14}H_{18}O_5Na$ ($[M+Na]^+$) 289.1047 found 289.1055.

2-((4a*R,10b*S**)-3,3-Dimethyl-4a,5,6,10b-tetrahydronaphtho[2,1-*e*][1,2,4]trioxin-10b-yl)ethyl acetate (6).** A solution of **5a** (90 mg, 0.33 mmol), PPTS (20 mg, 0.08 mmol) and $Me_2C(OMe)_2$ (200 μL, 1.40 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 3 h. The mixture was then diluted with CH_2Cl_2 (3 mL). *p*-TsOH (monohydrate, 3 mg, 0.003 mmol) was introduced. The stirring was

continued at the same temperature for another 6 h. Sat. aq. $NaHCO_3$ (5 mL) was added. The phases were separated. The aqueous layer was back extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (20:1 PE/EtOAc) on silica gel gave acetonide **6** as a colorless oil (79 mg, 0.26 mmol, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 1H), 7.16-7.28 (m, 2H), 7.09 (d, *J* = 7.0 Hz, 1H), 4.44 (br, 1H), 4.10-4.31 (m, 2H), 3.07 (dt, *J* = 9.0, 16.5 Hz, 1H), 2.65 (dt, *J* = 17.1, 4.0 Hz, 1H), 2.03-2.15 (m, 4H), 2.00 (s, 3H), 1.85 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 136.6, 128.2, 127.3, 126.7, 126.3, 102.4, 79.7, 66.8, 59.6, 38.3, 25.6, 25.3, 23.7, 20.9, 20.6; FT-IR (film) 2936, 1743, 1451, 1366, 1234, 1097, 1039, 758 cm^{-1}. ESI-MS *m/z* 329.2 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{17}H_{23}O_5$ ([M+H]$^+$) 307.1540, found 307.1551.

2-((4a*R,10b*S**)-3,3-Dimethyl-4a,5,6,10b-tetrahydronaphtho[2,1-*e*][1,2,4]trioxin-10b-yl)ethanol (7).** A solution of **6** (82 mg, 0.27 mmol) and K_2CO_3 (110 mg, 0.81 mmol) in MeOH (8 mL) was stirred at ambient temperature for 3 h. Water (2 mL) was added. The mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (4:1 PE/EtOAc) on silica gel gave alcohol **7** as a colorless oil (68 mg, 0.26 mmol, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.1 Hz, 1H), 7.17-7.30 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 4.50 (t, *J* = 2.6 Hz, 1H), 3.80 (dt, *J* = 4.0, 6.0 Hz, 1H), 3.07 (dt, *J* = 17.0, 9.0 Hz, 1H), 2.65 (dt, *J* = 17.9, 3.8 Hz, 1H), 1.98-2.15 (m, 4H), 1.90 (br s, 1H), 1.72 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 128.3, 127.2, 126.7, 126.2, 102.5, 81.1, 66.9, 58.0, 42.3, 25.6, 25.2, 23.6, 20.6 ; FT-IR (film) 3430, 2994, 2939, 1491, 1453, 1432, 1376, 1259, 1207, 1165, 1061, 1040, 1003, 875, 758 cm^{-1}. ESI-MS *m/z* 287.2 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{15}H_{20}O_4Na$ ([M+Na]$^+$) 287.1254, found 287.1266.

General procedure for acylation of alcohol **7** leading to esters **8**-**11**. A solution of **7** (20 mg, 0.075 mmol), the carboxylic acid (0.44 mmol), DMAP (3 mg, 0.02 mmol) and DCC (45 mg, 0.22 mmol) in dry CH_2Cl_2 (1 mL) was stirred at ambient temperature for 8 h. Sat. aq. $NaHCO_3$ (5 mL) was added. The mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel gave the corresponding ester as a colorless oil.

(*R*)-2-((4a*R,10b*S**)-3,3-Dimethyl-4a,5,6,10b-tetrahydronaphtho[2,1-*e*][1,2,4]trioxin-10b-yl)ethyl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (8).** Data for **8** (yield 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.81 (m, 2H), 7.63-7.61 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.01-7.29 (m, 8H), 5.09 (dd, *J* = 4.4, 5.9 Hz, 1H), 4.23-4.48 (m, 3H), 3.40-3.59 (m, 2H), 3.01 (dt, *J* = 15.9, 9.0 Hz, 1H), 2.58 (dt, *J* = 17.0, 4.0 Hz, 1H), 1.89-2.16 (m, 4H), 1.64 (d, *J* = 11.7 Hz, 3H), 1.12 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 168.6, 167.3, 136.5, 134.1, 131.4, 128.7, 128.5, 128.2, 127.3, 126.8, 126.6, 126.2, 123.4, 102.3, 79.4, 66.5, 61.1, 53.2, 53.1, 37.9, 34.5, 34.4, 25.5, 25.1, 23.5, 20.5; FT-IR (film) 2937, 2856, 1777, 1746, 1715, 1468, 1455, 1387, 1238, 1206, 1104, 1086, 911, 720 cm^{-1}. ESI-MS *m/z* 564.2 ($[M+Na]^+$); ESI-HRMS calcd. For $C_{32}H_{31}NO_7Na$ ($[M+Na]^+$) 564.19927 found 564.19967.

2-((4a*R,10b*S**)-3,3-Dimethyl-4a,5,6,10b-tetrahydronaphtho[2,1-*e*][1,2,4]trioxin-10b-yl)ethyl-2-cyclohexenylacetate (9).** Data for **9** (yield 73%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.1 Hz, 1H), 7.16-7.29 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 5.54 (s, 1H), 4.46 (s, 1H), 4.11-4.37 (m, 2H), 3.08 (dt, *J* = 16.4, 9.2 Hz, 1H), 2.90 (s, 2H), 2.65 (dt, *J* = 17.1, 4.4 Hz, 1H), 1.92-2.20 (m, 8H), 1.70 (s, 3H), 1.49-1.67 (m, 4H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 137.0, 136.5, 130.8, 128.2, 127.3, 126.6, 126.3, 125.9, 102.3, 79.6, 66.5, 59.6, 43.6, 38.3, 28.3, 25.6, 25.2, 23.6, 22.6, 21.9, 20.6; FT-IR (film) 2932, 2857, 1737, 1453, 1435, 1374, 1255, 1207, 1166, 1065, 1002, 758 cm^{-1}. ESI-MS *m/z* 409.1 ($[M+Na]^+$); MALDI-HRMS calcd. for $C_{23}H_{30}O_5Na$ ($[M+Na]^+$) 409.1986 found 409.2003.

(2*E*,4*E*)-2-((4a*R,10b*S**)-3,3-Dimethyl-4a,5,6,10b-tetrahydronaphtho[2,1-*e*][1,2,4]trioxin-10b-yl)ethyl-hexa-2,4-dienoate (10).** Data for **10** (yield 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.14-7.29 (m, 3H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.06-6.25 (m, 2H), 5.72 (d, *J* = 15.6 Hz, 1H), 4.49 (s, 1H), 4.18-4.42 (m, 2H), 3.08 (dt, *J* = 16.8, 8.2 Hz, 1H), 2.65 (dt, *J* = 17.0, 4.2 Hz, 1H), 2.03-2.23 (m, 4H), 1.85 (d, *J* = 5.3 Hz, 3H), 1.70 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 145.4, 139.8, 137.1, 136.5, 129.7, 128.2, 127.2, 126.6, 126.2, 118.4, 102.3, 79.6, 66.5, 59.3, 38.4, 25.6, 25.2, 23.6, 20.6, 18.7; FT-IR (film) 2926, 2854, 1714, 1642, 1616, 1537, 1453, 1243, 1064, 1001 cm^{-1}. ESI-MS *m/z* 381.2 ($[M+Na]^+$); ESI-HRMS calcd. for $C_{21}H_6O_5Na$ ($[M+Na]^+$) 381.16725 found 381.16705.

2-((4a*R,10b*S**)-3,3-Dimethyl-4a,5,6,10b-tetrahydronaphtho[2,1-*e*][1,2,4]trioxin-10b-yl)ethyl-undec-10-enoate (11).** Data for **11** (yield 76%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.4 Hz, 1H), 7.16-7.30 (m, 2H), 7.09 (d, *J* = 7.1 Hz, 1H), 5.72-5.90 (m, 1H), 4.98 (d, *J* = 14.1 Hz, 1H), 4.93 (d, *J* =10.3 Hz, 1H), 4.46 (s, 1H), 4.11-4.34 (m, 2H), 3.08 (dt, *J* = 16.7, 8.1 Hz, 1H), 2.65 (dt, *J* = 17.1, 4.2 Hz, 1H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.98-2.15 (m, 6H), 1.70 (s, 3H), 1.21-1.44 (m, 12H), 1.16 (s, 3H); FT-IR (film) 2928, 2855, 1738, 1579, 1454, 1373, 1207, 1169, 1119, 993, 757 cm^{-1}. ESI-MS *m/z* 453.3 ($[M+Na]^+$); ESI-HRMS calcd. for $C_{26}H_{38}O_5Na$ ($[M+Na]^+$) 453.2603, found 453.2603.

2-((4a'*R,10b'*S**)-4a',5',6',10b'-Tetrahydrospiro[admantane-1,3'-naphtho[2,1-*e*][1,2,4]trioxine]-10b'-yl)ethyl acetate (13)**. A solution of **5a** (60 mg, 0.22 mmol), PPTS (11 mg, 0.04 mmol) and ketal **12** (86 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 3 h. The mixture was then diluted with CH_2Cl_2 (3 mL). *p*-TsOH (monohydrate, 3 mg, 0.003 mmol) was introduced. The stirring was continued at the same temperature for another 6 h. Sat. aq. $NaHCO_3$ (5 mL) was added. The phases were separated. The aqueous layer was back extracted with Et_2O (3×20 mL). The combined organic layers

were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (20:1 PE/EtOAc) on silica gel gave **13** as a colorless oil (66 mg, 0.17 mmol, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 1H), 7.14-7.31 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.41 (s, 1H), 4.11-4.29 (m, 2H), 3.04-3.25 (m, 1H), 2.90-3.04 (m, 1H), 2.55-2.69 (m, 1H), 2.02-2.26 (m, 6H), 2.00 (s, 3H), 1.17-1.95 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 136.7, 128.2, 127.2, 126.8, 126.2, 104.5, 79.3, 65.1, 59.7, 38.2, 37.2, 35.8, 33.4, 33.3, 27.2, 27.1, 25.5, 23.7, 20.9; FT-IR (film) 2934, 2856, 1743, 1489, 1469, 1451, 1366, 1235, 1085, 1001, 761, 733 cm^{-1}. ESI-MS *m/z* 421.2 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{24}H_{30}O_5Na$ ([M+Na]$^+$) 421.1986, found 421.1988.

2-((4a'*R,10b'*S**)-4a',5',6',10b'-Tetrahydrospiro[cyclohexane-1,3'-naphtho[2,1-*e*][1,2,4]trioxine]-10b'-yl)ethyl acetate (15)**. A solution of **5a** (90 mg, 0.33 mmol), PPTS (16 mg, 0.07 mmol) and ketal **14** (150 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 3 h. The mixture was then diluted with CH_2Cl_2 (3 mL). *p*-TsOH (monohydrate, 3 mg, 0.003 mmol) was introduced. The stirring was continued at the same temperature for another 6 h. Sat. aq. $NaHCO_3$ (5 mL) was added. The phases were separated. The aqueous layer was back extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (20:1 PE/EtOAc) on silica gel gave **15** as a colorless oil (96 mg, 0.27 mmol, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.15-7.29 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.46 (br s, 1H), 4.11-4.31 (m, 2H), 3.08-3.18 (m, 1H), 2.57-2.69 (m, 1H), 2.24-2.44 (m, 1H), 2.02-2.17 (m, 5H), 1.99 (s, 3H), 1.26-1.59 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 137.1, 136.6, 128.1, 127.2, 126.6, 126.2, 102.4, 79.7, 65.7, 59.6, 38.2, 34.6, 29.5, 25.5, 25.3, 23.6, 22.5, 22.1, 20.8; FT-IR (film) 2936, 2859, 1742, 1452, 1365, 1234, 1097, 1039, 757 cm^{-1}. ESI-MS *m/z* 369.2 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{20}H_{26}O_5Na$ ([M+Na]$^+$) 369.16725 found 369.16714.

2-((4a'*R,10b'*S**)-4a',5',6',10b'-Tetrahydrospiro[cyclohexane-1,3'-naphtho[2,1-*e*][1,2,4]trioxine]-10b'-yl)ethanol (16)**. A solution of **15** (50 mg, 0.15 mmol) and K_2CO_3 (59 mg, 0.43 mmol) in MeOH (4 mL) was stirred at ambient temperature for 3 h. Water (2 mL) was added. The mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (4:1 PE/EtOAc) on silica gel gave alcohol **16** as a colorless oil (42 mg, 0.14 mmol, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.16-7.32 (m, 2H), 7.10 (d, *J* = 7.1 Hz, 1H), 4.51 (br s, 1H), 3.74-3.90 (m, 2H), 3.01-3.18 (m, 1H), 2.58-2.71 (m, 1H), 2.24-2.45 (m, 1H), 1.94-2.16 (m, 5H), 1.79 (br s, 1H), 1.30-1.60 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.6, 128.2, 127.2, 126.8, 126.2, 102.4, 79.7, 65.9, 58.1, 42.23, 34.6,

29.6, 25.5, 25.2, 23.6, 22.5, 22.01; FT-IR (film) 3420, 2935, 2859, 1490, 1451, 1363, 1273, 1157, 1098, 997, 757 cm^{-1}. ESI-MS *m/z* 327.2 ($[M+Na]^+$); MALDI-HRMS calcd. for $C_{18}H_{24}O_4Na$ ($[M+Na]^+$) 327.1567, found 327.1563.

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