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1,2,4-Trioxanes

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ABSTRACT

The photochemical behavior of several dienones was studied under aerobic conditions. 2-Allylidene-1,3-cycloalkanediones prepared *via* Knoevenagel-type condensation between simple readily available 1,3-dicarbonyl substrates and α , β -unsaturated aldehydes, afforded 1,2,4-trioxane derivatives upon UVA-irradiation in the presence of oxygen. This domino self-sensitized photooxygenation cascade of conjugated carbonyl systems proceeds stereoselectively and involves the formation of two new oxa-cycles, three new bonds (two C-O) and three stereocenters.

The 1,2,4-trioxane pharmacophore has become famous over the last decades due to the success of artemisinin (1)-based combination therapies (ACT's) against malaria's etiological agent *Plasmodium falciparum*, the most dangerous of malaria parasites (Scheme

1A).¹ Indeed, for her discoveries concerning these treatments based on the remarkable peroxidic sesquiterpene **1**, Youyou Tu was awarded the Nobel Prize in Physiology or Medicine in 2015.² Although signs of resistance have recently emerged in Southeast Asia, malaria scientists still rely on newly developed and future peroxides for the fight in the war against this long-standing problem.³

From an organic synthesis viewpoint, 1,2,4-trioxanes have been shown to be valuable as intermediates for the preparation of diverse heterocyclic scaffolds by the use of a variety of developed rearrangement and reductive processes.⁴ On the other hand and as regards their preparation, many methodologies have been made available during the last decades primarily triggered by the need of new drug candidates.⁵ One of the most conventional and reliable methods known as Type II photooxygenation, involves the reaction of singlet oxygen with olefinic compounds.⁶ Generally, singlet oxygen is generated by an energy-transfer mechanism provided a suitable dye sensitizer is excited in the presence of ground-state triplet oxygen. This reaction has been occasionally used employing 2*H*-pyrans as substrates, for example in the synthesis of bicyclic 1,2,4-trioxanes **2** and **3**, the former a natural sesquiterpenoid,⁷ the latter an intermediate in the total synthesis of phomactin A (Scheme 1B).⁸

Taking into account that malaria affects the poorest regions of the planet, the most needed protocols are those that are operationally simple and that involve readily available inexpensive reagents. In this regard, domino reactions meet these criteria since they allow the rapid assembly of complex molecules through the combination of multiple bond-forming transformations without the need to isolate and purify intermediates.⁹ Our research group previously established that natural product β -ionone **4** affords 1,2,4-trioxane derivative **6**

when toluene solutions are irradiated in the presence of oxygen without the use of an external singlet oxygen sensitizer (Scheme 1C).¹⁰ This domino process involves sequential exocyclic double bond isomerization, oxa- 6π -electrocyclic ring closure and eventual Diels-Alder type [4+2] cycloaddition between 2*H*-pyran intermediate **5** and singlet oxygen generated *in-situ*. Time-resolved laser induced experiments confirmed the formation of the excited triplet state of **4** as responsible for the generation of singlet oxygen, establishing the ability of dienones bearing a ionone-type skeleton to act as singlet oxygen sensitizers.¹¹



Scheme 1. (A) Structure of Artemisinin (1). (B) Singlet Oxygen [4+2]-Cycloaddition Leading to Bicyclic 1,2,4-Trioxanes. (C) The Self-Sensitized Photooxygenation of β -Ionone.

It is known that polyunsaturated substrates are versatile candidates for the efficient construction of polycyclic molecules *via* cycloisomerization rearrangements.¹² For

conjugated carbonyl compounds, many aspects of this chemistry have mainly been investigated with regards to electrocyclization reactions. In this context, taking into account the rapid assembly of trioxane systems *via* this unusual and underexplored cycloisomerization/oxidation sequence, and stimulated by the need and importance of endoperoxides, we decided to undertake a study aiming to establish the reaction modes of a series of substituted carbonyl-polyene systems. Herein we wish to report our findings concerning the photochemical behavior of simple structurally diverse conjugated dienones.

The first series of unsaturated precursors is depicted in Figure 1. All substrates **7a-h** were prepared *via* classical aldol and Knoevenagel condensation reactions.¹³ All of these dienones have been previously synthetized and the photochemical behavior of many have also been studied under anaerobic conditions.^{13,14} In particular, dienones **7a** and **7b**, lacking a conjugated aromatic ring at the end of the polyene chain, turned out to be quite unstable resulting in complex mixtures due to decomposition even after a few days of storage. According to our previously reported photooxidation protocol used for the oxidation of β -ionone **4**, all unsaturated carbonyl compounds **7a-h** were dissolved in toluene and their 10 mM solutions irradiated using black light fluorescent tubes ($\lambda_{max} = 350$ nm) with the bubbling of oxygen gas. Substrate **7a** structurally related to β -ionone (**4**), and also **7b** suffered thorough decomposition upon irradiation. Only *cis/trans* photoisomerization processes were found to take place for dienones **7c-g**, affording in these cases inseparable mixtures of stereoisomers.



Figure 1. Initially screened conjugated dienones 7a-h

After prolonged irradiation, cinnamylidene dimedone (**7h**), less structurally related to β -ionone (**4**) than compound **7a**, afforded the corresponding 1,2,4-trioxanes **8h** and **8'h** in 20% and 2% yield, respectively (Scheme 2). Stereochemical assignments could be drawn from NOE experiments, minor product being assigned as **8'h** particularly based on a NOE correlation between the olefinic and benzylic hydrogen atoms suggesting the *pseudo*-axial position of the latter in the bicyclic system. This stereoselective character of the reaction is not only in agreement with recently reported results on the dye-sensitized photooxygenation of 2*H*-pyrans,¹⁵ but also in line with mechanistic grounds. Photooxygenations of the [4+2]-type involving singlet oxygen are known to be highly sensitive to steric control.¹⁶ Accordingly, singlet oxygen, generated *in-situ*, would approach the pyran system **12** from the less hindered face opposite to the substituent phenyl group. Additionally, it should be noticed that the chemical shift of the benzylic proton (H^a) in the *anti*-isomer **8h** appears more downfield which could be attributed to a deshielding effect provided by the proximate peroxide linkage (Scheme 2).



Scheme 2. Self-sensitized photooxygenation of 2-cinnamylidene 1,3-dicarbonyl substrate 7h

Motivated by this finding, we then explored some adjustments to the reaction conditions in order to achieve better yields of trioxanes 8 production. In particular, the evaluation of other concentrations did not provide any improvement. In addition, replacement of actinic lamps by a mercury medium pressure lamp using an immersion well apparatus was not fruitful either. Our attention was then focused on the evaluation of other solvents in order to find suitable conditions for the preparation of trioxanes $\mathbf{8}$. Whereas no reaction was observed in methanol, in dichloromethane extensive decomposition was evidenced for substrate 7h. When acetonitrile was assayed, the yield of products 8h was slightly increased (33%) and the reaction was complete in 19 hours instead of the 40 hours required in toluene to achieve an 85% conversion of substrate 7h (Scheme 2). This improvement was particularly beneficial since, although trioxanic products 8h were shown to be stable over years of storage, they were found to be sensitive to the UV-irradiation used for their formation. In this context, under these same conditions but using hydroquinone as additive, the yield could be increased to 45%. One particular observation that caught our attention was that unlike the photooxygenation of β -ionone, 2*H*-pyran intermediate **9h** could not be observed by TLC or NMR monitoring nor found when the reaction was run with

exclusion of oxygen. We then reasoned that a short lifetime of this putative intermediate **9h** could account for this observation being the valence-equilibrium rapidly shifted towards the starting dienone open-form in the absence of oxygen. In view of this, we then contemplated the use of carbon tetrachloride as solvent as the lifetime of reactive intermediate singlet oxygen is considerably longer in this halogenated solvent being thus readily available for capturing the putative unstable intermediate **9h**. In this manner, dienone **7h** underwent successful photooxygenation towards trioxanes **8h** in 60% overall yield and taking only 8 hours for reaction completion (Scheme 3). Remarkably, both in carbon tetrachloride and acetonitrile, the same diastereoselectivity found in toluene was observed and hence the stereoselectivity of the process seems to be independent of the polarity of the solvent and mainly governed by steric factors.

Results from evaluating other dienones related to **7h** are shown in Scheme 3. All substrates **7g-7r** were readily prepared *via* Knoevenagel condensation catalyzed by Tietze base EDDA (ethylenediammonium diacetate).^{13a} As shown, in carbon tetrachloride, previously considered unreactive substrate **7g** did undergo transformation towards the corresponding trioxane derivatives **8g**. Unfortunately, low conversion was achieved even after 22 hours of irradiation. An inspection of Scheme 3 reveals the yields of trioxane formation were in general moderate and no other products could be identified in the reaction mixtures. Photoisomerization was only observed for acyclic dienones **7g** and **7o**, which underwent incomplete transformations after prolonged irradiation, the recovered material being a mixture of starting dienones **7g** and **7o** contaminated with the corresponding γ , δ -*cis* isomers. Interestingly, reactions of these two dienones along with that of trienedione substrate **7p** which does not bear an aromatic ring, were less diastereoselective giving rise to

the corresponding trioxanes as 3:1 stereoisomeric mixtures. In every case, whereas main peroxidic products were readily isolated after column chromatography purification, minor components **8'** could not be obtained in pure form. Their structures and relative abundance were determined, however, by analyses of the spectral data of crude mixtures and comparison with data gathered for isolated **8'h**. The fastest transformations were observed for those cyclic substrates not bearing the phenyl substituent or having one featuring an electronwithdrawing halogen atom on it. Among these, bromoderivative **7n** underwent complete conversion in 2 hours giving the highest yield of peroxide formation (73%), a result that we attributed to a facilitated intersystem crossing event due to the presence of the heavy atom favoring in this way the required singlet oxygen sensitization step. Curiously, whereas 2cinnamylidene-1,3-cyclohexanedione **7i** successfully afforded the corresponding trioxane derivatives **8i** in 56% yield after 4 h of irradiation, analogous cyclopentanedione derivative **7r** did not participate in the domino sequence even after prolonged irradiation (> 20 h).



^a Yields are isolated yields after chromatography purification. In cases in which minor isomer is formed, global yields along with **8/8'** ratios are informed in parentheses and only major isomer is shown.^b The corresponding regioisomers along with minor **8'j** were obtained as an inseparable mixture.^c 50% of starting material was recovered.^d 25% of starting material was recovered.

Scheme 3. Self-sensitized photooxygenation of 2-allylidene-1,3-cycloalkanediones 7

It should be noted that when β -alkyl substituted enals were used as electrophilic partners in the Knoevenagel condensation reactions carried out for the preparation of substrates **7**, no conjugated dienone **7** was obtained as product. Instead, only the 2*H*-pyran valence isomers were isolated as products of a formal [3+3]-cycloaddition, which comprises a Knoevenagel condensation followed by a spontaneous oxa-6 π -electrocyclization.¹⁷ For example, the condensation between 5,5-dimethyl-1,3-cyclohexanedione (**10**) and *trans*-2pentenal (**11**) catalyzed by EDDA yields 2*H*-pyran **9s** exclusively, albeit in low yield (Scheme 4). Curiously, when 2*H*-pyrans such as **9s** were submitted to our new photooxygenation protocol, no trioxane could be identified in the reaction mixtures. Instead thorough decomposition of the starting materials was only observed.¹⁸ It should be noted that from these species, 1,2,4-trioxanes can still be synthesized by using the conventional dye-sensitized photooxygenation. For example, irradiation of **9s** using a tungsten lamp and rose bengal as singlet-oxygen sensitizer led to the production of peroxides **8s** which were obtained as an inseparable mixture of stereoisomers in a 3.5:1 ratio. Pyran **9t**, prepared according to J. L. Renaud and co-workers,¹⁹ also underwent dye-sensitized [4+2] photooxygenation to afford polycyclic peroxide **8t** which was isolated as a single stereoisomer in low yield and proved to be very unstable.



Scheme 4. Dye-sensitized photooxygenation of 2H-pyrans 9

In summary, we have reported a stereoselective methodology for the synthesis of 1,2,4-trioxanes from simple precursors through self-sensitized photooxygenation. Undoubtedly, this one-pot approach stands as a complementary strategy for the preparation of valuable 1,2,4-trioxane derivatives which may encourage future biological studies on these remarkable peroxidic scaffolds.

EXPERIMENTAL SECTION

Materials and methods

Unsaturated precursors 7 have been previously prepared in the literature.¹³ All other chemical reagents were purchased from commercial suppliers and used without further purification. Solvents were analytical grade or were purified by standard procedures prior to use. Yields were calculated for material judged homogeneous by thin layer chromatography (TLC) and nuclear magnetic resonance (¹H NMR). All reactions were monitored by thin layer chromatography performed on silica gel 60 F₂₅₄ pre-coated aluminum sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Column flash chromatography was performed using silica gel 60 (230 – 400 mesh). Melting points (M.p.) were taken on an electrothermal melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were acquired at 300 MHz for ¹H and 75 MHz for ¹³C using CDCl₃ as solvent. Chemical shifts for proton nuclear magnetic resonance spectra are reported in parts per million relative to the signal of tetramethylsilane (TMS) at 0 ppm (internal standard) and coupling constants (J) are reported in hertz (Hz). Chemical shifts for carbon nuclear magnetic resonance (¹³C NMR) spectra are reported in parts per million relative to the center line of the CDCl₃ triplet at 77.0 ppm. The following abbreviations are used to indicate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quint = quintet, h = sextet, b = broad signal. IR spectra were obtained using an FT-IR spectrometer and only partial spectral data are listed. High resolution mass spectra (HRMS) were obtained on a Q-TOF mass spectrometer and detection of the ions was performed in electrospray ionization, positive ion mode. The structure of the products were determined by a combination of spectroscopic methods such as IR, 1D and 2D NMR (including NOE, DEPT,

COSY, HSQC and HMBC experiments) and HRMS. NMR signals assignments were based on 2D NMR experiments performed.

Representative procedure for the self-sensitized photooxidation of dienones 7

A Pyrex vessel containing a solution of dienone 7 (1 mmol) in carbon tetrachloride (100 mL, 0.01 M) was irradiated (photochemical reactor with 16 BLB lamps, $\lambda_{max} = 350$ nm, distance to the irradiation vessel = 10 cm, no added filter) with a gentle bubbling of oxygen. The reaction was monitored by TLC. After the time indicated in Scheme 3, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate = 10:1, v/v) to afford the following 1,2,4-trioxanes **8/8'**.

 $(2R^*, 3S^*, 8aR^*)$ -7,7-dimethyl-2-phenyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)one (**8h**)

Prepared according to the general procedure. Colorless solid (156 mg, $Me_{Me} = 0.545 \text{ mmol}, 54\%$). **mp** 96.0-97.0 °C. **IR** (film) (cm⁻¹): 3055, 2959, 1692, 1623, 1267, 1025. ¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.24 (m, 3H, Ar-H), 7.26 (overlapping d, J = 5.8 Hz, 1H, 4-H), 7.12-7.07 (m, 2H, Ar-H), 5.58 (d, J = 2.1 Hz, 1H, 2-H), 4.98 (dd, J = 5.7 Hz, J = 2.2 Hz, 1H, 3-H), 2.43 (bs, 2H, 6-H), 2.19 (dAB, J = 15.3 Hz, 1H, 8-H), 2.03 (dAB, J = 15.3 Hz, 1H, 8-H), 1.17 (s, 3H, 7-CH₃), 1.07 (s, 3H, 7-CH₃). ¹³C **NMR** (CDCl₃, 75 MHz): δ 193.3 (C, C-5), 139.1 (C, C-4a), 136.0 (C, Ar), 131.8 (CH, C-4), 128.6 (2 × CH, Ar), 128.4 (CH, Ar), 126.0 (2 × CH, Ar), 98.5 (C, C-8a), 75.9 (CH, C-2), 74.5 (CH, C-3), 52.1 (CH₂, C-6), 43.0 (CH₂, C-8), 31.1 (C, C-7), 29.3 (CH₃, C7-CH₃), 28.4 (CH₃, C7-CH₃). **HRMS** (ESI-TOF) m/z; [M + H]⁺ Calcd for C₁₇H₁₉O₄ 287.1278; Found 287.1281.

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(2*S**,3*S**,8a*R**)-7,7-dimethyl-2-phenyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)one (**8'h**)

Prepared according to the general procedure. Colourless solid (16 mg, $M_{B_{e}} = \frac{1}{2} + \frac$

(2*R**,3*S**,8a*R**)-2-phenyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)-one (8i)

Prepared according to the general procedure. Colourless liquid (132 mg, 0.51 ⁴⁴³ ⁴⁴¹

C-3), 38.4 (CH₂, C-6), 30.2 (CH₂, C-8), 18.2 (CH₂, C-7). **HRMS** (ESI-TOF) *m*/*z*: [M + H]⁺ Calcd for C₁₅H₁₅O₄ 259.0965; Found 259.0972.

 $(2R^*, 3S^*, 8aR^*)$ -6,6-dimethyl-2-phenyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)one (**8j**)

1-((1*S**,4*R**,6*R**)-4-methyl-6-phenyl-2,3,5-trioxabicyclo[2.2.2]oct-7-en-8-yl)ethan-1-one (**8g**)

Prepared according to the general procedure. Colourless liquid (61.5 mg, $Me \leftarrow O \to Ph$ 0.25 mmol, 25%). ¹H NMR (CDCl₃, 300 MHz): δ 7.39-7.27 (m, 3H), 7.17-7.07 (m, 2H), 7.03 (d, J = 6.1 Hz, 1H), 5,58 (d, J = 2.3 Hz, 1H), 4.92 (dd, J = 6.0 Hz, J = 2.4Hz, 1H), 2.36 (s, 3H), 1.89 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 194.0 (C), 143.9 (C), 136.4 (C), 133.9 (CH), 128.6 (2 × CH), 128.3 (CH), 125.8 (2 × CH), 98.2 (C), 74.5 (CH),

73.8 (CH), 26.7 (CH₃), 19.6 (CH₃). **HRMS** (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₄H₁₅O₄ 247.0965; Found 247.0961.

(2*R**,3*S**,8a*R**)-2-(4-methoxyphenyl)-7,7-dimethyl-2,3,7,8-tetrahydro-3,8a-

epidioxychromen-5(6H)-one (8k)



Prepared according to the general procedure. Colourless liquid (174 mg, 0.55 mmol, 55%). IR (film) (cm⁻¹): 2961, 1696, 1613, 1515, 1253, 1174, 1028. ¹**H NMR** (CDCl₃, 300 MHz): δ 7.29 (d, J = 5.7 Hz, 1H), 7.04-6.98 (m, 2H), 6.85-6.80 (m, 2H), 5.51 (d, J = 2.1 Hz, 1H), 4.93 (dd, J = 5.7Hz, J = 2.1 Hz, 1H), 3.77 (s, 3H), 2.42 (bs, 2H), 2.16 (dAB, J = 15.2 Hz, 1H), 2.02 (dAB, J = 15.2 Hz, 2H), 2.02 (AB, J = 15.2 Hz, 2H), 2.02 (AB, J = 15.2 Hz, 2H), 2.02 (AB, J = 15.2 Hz

= 15.2 Hz, 1H), 1.16 (s, 3H), 1.07 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 193.3 (C), 159.7 (C), 139.2 (C), 132.1 (CH), 128.1 (C), 127.4 (2 × CH), 114.0 (2 × CH), 98.5 (C), 75.7 (CH), 74.5 (CH), 55.2 (CH₃), 52.1 (CH₂), 43.0 (CH₂), 31.1 (C), 29.2 (CH₃), 28.4 (CH₃). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C₁₈H₂₁O₅ 317.1384; Found 317.1385.

 $(2R^*, 3S^*, 8aR^*)$ -2-(4-methoxyphenyl)-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6H)-one **(8l)**



Prepared according to the general procedure. Colourless liquid (158 mg,

0.55 mmol, 55%). IR (film) (cm⁻¹): 2956, 2937, 1694, 1623, 1515,

4-MeOPh 1252. ¹**H** NMR (CDCl₃, 300 MHz): δ 7.25 (d, J = 6.0 Hz, 1H), 7.05-6.99 (m, 2H), 6.87-6.81 (m, 2H), 5.53 (d, J = 2.4 Hz, 1H), 4.93 (dd, J = 5.7 Hz, J = 2.4 Hz, 1H), 3.78 (s, 3H), 2.60-2.51 (m, 2H), 2.28-1.92 (m, 4H). ¹³C NMR (CDCl₃, 75 MHz): δ 193.5 (C), 159.7 (C), 140.3 (C), 132.2 (CH), 127.9 (C), 127.4 (2 × CH), 114.0 (2 × CH), 98.8 (C), 75.4 (CH), 74.6 (CH), 55.3 (CH₃), 38.5 (CH₂), 30.3 (CH₂), 18.3 (CH₂). **HRMS** (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₆H₁₇O₅ 289.1071; Found 289.1068.

(2*R**,3*S**,8a*R**)-2-(4-fluorophenyl)-7,7-dimethyl-2,3,7,8-tetrahydro-3,8a-

epidioxychromen-5(6H)-one (8m)

Prepared according to the general procedure. Colourless solid (122 Me_{Me}° Me_{Be}° Me_{Be}° Me

 $(2R^*, 3S^*, 8aR^*)$ -2-(4-bromophenyl)-7,7-dimethyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)-one (**8n**)

(d, J = 6.0 Hz, 1H), 7.02-6.95 (m, 2H), 5.53 (d, J = 2.1 Hz, 1H), 4.96 (dd, J = 5.7 Hz, J = 2.4 Hz), 2.42 (bs, 2H), 2.17 (dAB, J = 15.4 Hz, 1H), 2.03 (dAB, J = 15.1 Hz, 1H), 1.16 (s, 3H), 1.07 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 193.0 (C), 139.2 (C), 135.1 (C), 131.8 (2 × CH), 131.4 (CH), 127.6 (2 × CH), 122.5 (C), 98.5 (C), 75.2 (CH), 74.1 (CH), 52.1 (CH₂), 42.9 (CH₂), 31.1 (C), 29.3 (CH₃), 28.4 (CH₃). **HRMS** (ESI-TOF) m/z: [M + H]⁺ Calcd for C₁₇H₁₈BrO₄ 365.0383; Found 365.0380.

1-((1*S**,4*R**,6*R**)-6-(4-bromophenyl)-4-methyl-2,3,5-trioxabicyclo[2.2.2]oct-7-en-8yl)ethan-1-one (**8o**)

Prepared according to the general procedure. Colourless liquid (97 mg, $Me_{Me} = 0.30 \text{ mmol}, 30\%$). ¹H NMR (CDCl₃, 300 MHz): δ 7.47-7.43 (m, 2H), 7.02-6.98 (overlapping m, 3H), 5.52 (d, J = 2.4 Hz, 1H), 4.90 (dd, J = 6.0 Hz, J = 2.4 Hz, 1H), 2.35 (s, 3H), 1.88 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 193.9 (C), 144.0 (C), 135.5 (C), 133.4 (CH), 131.7 (2 × CH), 127.4 (2 × CH), 122.3 (C), 98.2 (C), 73.9 (CH), 73.4 (CH), 26.7 (CH₃), 19.5 (CH₃). **HRMS** (ESI-TOF) m/z: [M + H]⁺ Calcd for C₁₄H₁₄BrO₄ 325.0070; Found 325.0058.

(2*R**,3*S**,8a*R**)-7,7-dimethyl-2-((*E*)-prop-1-en-1-yl)-2,3,7,8-tetrahydro-3,8aepidioxychromen-5(6*H*)-one (**8p**)



Prepared according to the general procedure. Colourless solid (75 mg, 0.30 mmol, 30%). **mp** 73.0-74.0 °C. **IR** (KBr) (cm⁻¹): 2963, 2936, 1692, 1624, 1081. ¹**H NMR** (CDCl₃, 300 MHz): δ 7.42 (d, *J* = 5.9 Hz,

1H, 4-H), 5.75 (dqd, J = 15.2 Hz, J = 6.7 Hz, J = 0.9 Hz, 1H, 2'-H), 5.04 (ddq, J = 15.3 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H, 1'-H), 4.89 (bdd, J = 7.4 Hz, J = 2.3 Hz, 1H, 2-H), 4.78 (dd, J = 6.1 Hz, J = 2.6 Hz, 1H, 3-H), 2.36 (bs, 2H, 6-H), 2.03 (dAB, J = 15.2 Hz, 1H, 8-H), 1.92 (dAB, J = 15.2 Hz, 1H, 8-H), 1.66 (ddd, J = 6.7 Hz, J = 1.5 Hz, J = 0.7 Hz, 3H, 2'-CH₃), 1.08 (s, 3H, 7-CH₃), 1.03 (s, 3H, 7-CH₃). ¹³C **NMR** (CDCl₃, 75 MHz): δ 193.5 (C, C-5), 139.1 (C, C-4a), 131.8 (CH, C-4), 131.6 (CH, C-2'), 125.9 (CH, C-1'), 97.8 (C, C-8a), 75.7 (CH, C-2), 73.3 (CH, C-3), 52.0 (CH₂, C-6), 42.9 (CH₂, C-8), 31.0 (C, C-7), 29.0 (CH₃, C7-CH₃), 28.5 (CH₃, C7-CH₃), 17.7 (CH₃, C2'-CH₃).

(2*R**,3*S**,8a*R**)-7,7-dimethyl-2-((*E*)-styryl)-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)-one (**8q**)

Prepared according to the general procedure. Colourless to pale Me_{Me} (CDCl₃, 300 MHz): δ (KBr) (cm⁻¹): 3080, 3059, 2965, 2928, 1690, 1618, 1273. ¹H NMR (CDCl₃, 300 MHz): δ 7.45 (d, J = 5.9 Hz), 7.33-7.25 (m, 5H), 6.58 (dd, J = 15.9 Hz, J = 1.2 Hz, 1H), 5.72 (dd, J = 15.9 Hz, J = 7.4 Hz, 1H), 5.12 (ddd, J = 7.3 Hz, J = 2.5 Hz, J = 1.2 Hz, 1H), 4.90 (dd, J = 5.9 Hz, J = 2.6 Hz, 1H), 2.39 (bs, 2H), 2.11 (dAB, J = 15.2 Hz, 1H), 1.96 (dAB, J = 15.2 Hz, 1H), 1.12 (s, 3H), 1.05 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 193.4 (C), 139.2 (C), 135.5

 (C), 134.4 (CH), 131.6 (CH), 128.6 (2 × CH), 128.4 (CH), 126.7 (2 × CH), 123.4 (CH), 97.9
(C), 75.7 (CH), 73.2 (CH), 52.1 (CH₂), 42.9 (CH₂), 31.1 (C), 29.1 (CH₃), 28.5 (CH₃). HRMS
(ESI-TOF) *m*/*z*: [M + Na]⁺ Calcd for C₁₉H₂₀NaO₄ 335.1254; Found 335.1242.

Preparation of 2-ethyl-7,7-dimethyl-2,6,7,8-tetrahydro-5*H*-chromen-5-one (9s)

A mixture of dimedone (**10**, 140 mg, 1 mmol), *trans*-2-pentenal (**11**, 0.1 Me_{Me}^{0} , Me_{Be}^{0} , Me_{Be}^{0} , Me_{Me}^{0} , Me_{He}^{0} , Me

Representative procedure for the dye-sensitized photooxidation of 2H-pyrans

2H-Pyran **9** (1.5 mmol) and rose bengal (30 mg) were dissolved in CH₂Cl₂ or CCl₄ (130 ml), CH₃OH (20 ml) before being irradiated with a 1000W tungsten halogen lamp (distance to the irradiation vessel = 15 cm, no filter) under bubbling of oxygen for approximately 1 hour. The solvent was then removed under reduced pressure to afford a pink

residue that was purified by column chromatography (SiO₂, hexanes/ethyl acetate = 9:1, v/v) to give the following 1,2,4-trioxanes 8/8'.

 $(2R^*, 3S^*, 8aR^*)$ -2-ethyl-7,7-dimethyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)-one (8s) and $(2S^*, 3S^*, 8aR^*)$ -2-ethyl-7,7-dimethyl-2,3,7,8-tetrahydro-3,8a-epidioxychromen-5(6*H*)-one (8's)



Prepared according to the general procedure. Pale yellow liquid (ratio = 3.5:1, 268 mg, 1.12 mmol, 75%). **IR** (film) (cm⁻¹): 2963, 2937,

1695, 1624, 1265. **8**s: ¹**H NMR** (CDCl₃, 300 MHz): δ 7.41 (d, J = 5.9 Hz, 1H, 4-H), 4.83 (dd, J = 5.9 Hz, J = 2.3 Hz, 1H, 3-H), 4.36 (td, J = 7.2 Hz, J = 2.3 Hz, 1H, 2-H), 2.42-2.28 (m, 2H, 6-H), 2.10-1.78 (m, 2H, 8-H), 1.34-1.18 (m, 2H, 1'-H), 1.06 (bs, 3H, 7-CH₃), 1.03 (bs, 3H, 7-CH₃), 0.90 (t, J = 7.4 Hz, 3H, 2'-H). ¹³**C NMR** (CDCl₃, 75 MHz): δ 193.5 (C, C-5), 138.9 (C, C-4a), 131.4 (CH, C-4), 97.6 (C, C-8a), 76.3 (CH, C-2), 72.8 (CH, C-3), 52.0 (CH₂, C-6), 42.7 (CH₂, C-8), 30.9 (C, C-7), 28.7 (CH₃, C7-CH₃), 28.6 (CH₃, C7-CH₃), 25.3 (CH₂, C-1'), 9.1 (CH₃, C-2'). **8's**: ¹**H NMR** (CDCl₃, 300 MHz): δ 7.56 (d, J = 6.1 Hz, 1H, 4-H), 4.66 (dd, J = 6.1 Hz, J = 0.8 Hz, 1H, 3-H), 3.42 (bt, J = 7.0 Hz, 1H, 2-H), 2.42-2.28 (m, 2'-H). ¹³**C NMR** (CDCl₃, 75 MHz): δ 193.8 (C, C-5), 137.5 (C, C-4a), 133.1 (CH, C-4), 97.8 (C, C-8a), 74.6 (CH, C-2), 71.2 (CH, C-3), 52.0 (CH₂, C-6), 43.1 (CH₂, C-8), 30.9 (C, C-7), 28.8 (CH₃, C7-CH₃), 28.5 (CH₃, C7-CH₃), 25.2 (CH₂, C-1'), 9.7 (CH₃, C-2'). **HRMS** (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₃H₁₈NaO₄ 261.1097; Found 261.1096.

(4a*R*,6*R*,8*R*,8a*R*,10a*R*)-7,7-dimethyl-3,4,5,7,8,10a-hexahydro-6*H*-4a,8a-epidioxy-6,8methanoxanthen-1(2*H*)-one (**8**t)

Prepared according to the general procedure. Colourless liquid (83 mg, $2 + \frac{1}{4} + \frac{1}{6} + \frac{1}{6}$

AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

NOTES

The authors declare no competing financial interest.

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ¹H and ¹³C NMR spectra of all products, 2D NMR spectra of key products (PDF).

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