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## COMMUNICATION

Wavelength Dependent Photoextrusion and Tandem Photoextrusion Reactions of Ninhydrin *bis*-Acetals for the Synthesis of 8-Ring Lactones, Benzocyclobutenes and Orthoanhydrides.‡Received 00th January 20xx,  
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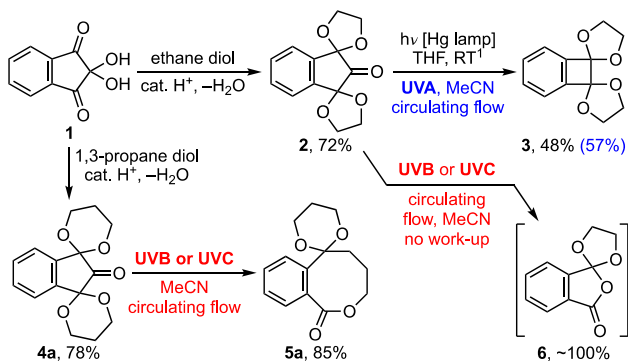
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Ninhydrin *bis*-acetals give access to 8-ring lactones, benzocyclobutenes and spirocyclic orthoanhydrides through photoextrusion and tandem photoextrusion reactions. Syntheses of fimbriallyxlactone B, isoshihuniine and numerous biologically-relevant heterocycles show the value of the methods, while TA-spectroscopy and TD-DFT studies provide mechanistic insights on their wavelength dependence.

The photodecarbonylation of ninhydrin *bis*-acetal **2** to benzocyclobutene **3** was developed by Butenschön *et al.* to provide low cost access to benzocyclobutenedione (Scheme 1).<sup>1</sup> Indeed, it remains the most convenient method for its synthesis in spite of the modest yield attained for the photoextrusion of carbon monoxide from **2**. Consequently, when a need for benzocyclobutenedione arose, we decided to develop the reaction as a flow photochemical process in order to facilitate its optimisation with respect to wavelength, residence time, solvent and acetal protecting group.<sup>2,3</sup> In the event, we uncovered conditions leading to a modest yield improvement for benzocyclobutene **3** and discovered a wavelength dependence for

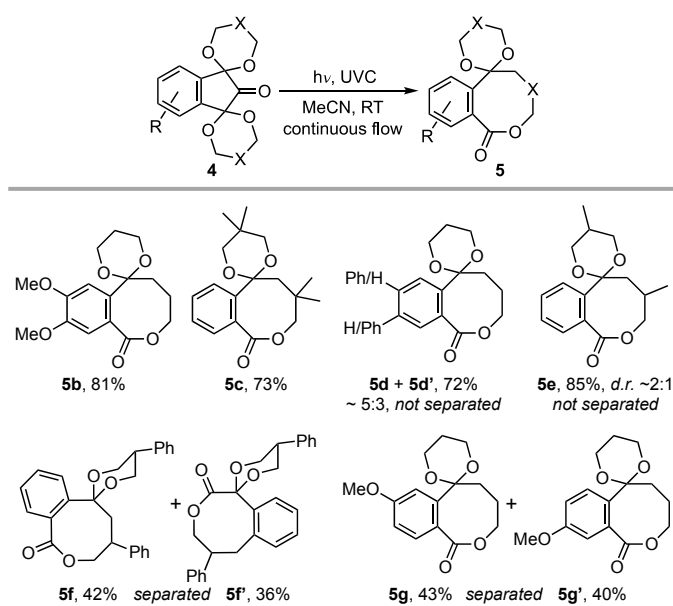
the reaction giving high-yielding access to 8-ring lactone **5a** and orthoanhydride **6**. Herein we describe our development of those methods, together with demonstrations of their usefulness in heterocyclic and natural products synthesis, and a detailed mechanistic study by transient absorption (TA) spectroscopy and TD-DFT analysis.

Our investigation began with an examination of the wavelength dependence on the photoextrusion of carbon monoxide from *bis*-acetal **2**. While all wavelengths studied led to the evolution of gas, which was vented from the system using a circulating flow technique (see ESI), only UVA irradiation gave benzocyclobutene **3** as a significant product.<sup>3,4</sup> An optimum yield of 57% was realised when a 0.05 M solution of **2** in acetonitrile was irradiated with 30 × 1.5 W UVA LEDs for residence time of 3 h. By contrast, irradiation of *bis*-acetal **2** with UVB or UVC light gave rise to a complex mixture of products on work-up that varied from experiment to experiment and contained no benzocyclobutene **3**, *vide infra*. Curiously, when the



**Scheme 1.** The discovery of wavelength and acetal dependence on the outcome of photoextrusion reactions involving ninhydrin *bis*-acetals.

**Table 1.** Extensions to other ninhydrin *bis*-acetals



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‡ Electronic Supplementary Information (ESI) available: experimental accounts with spectral details and copies of NMR spectra are available as supplementary information.

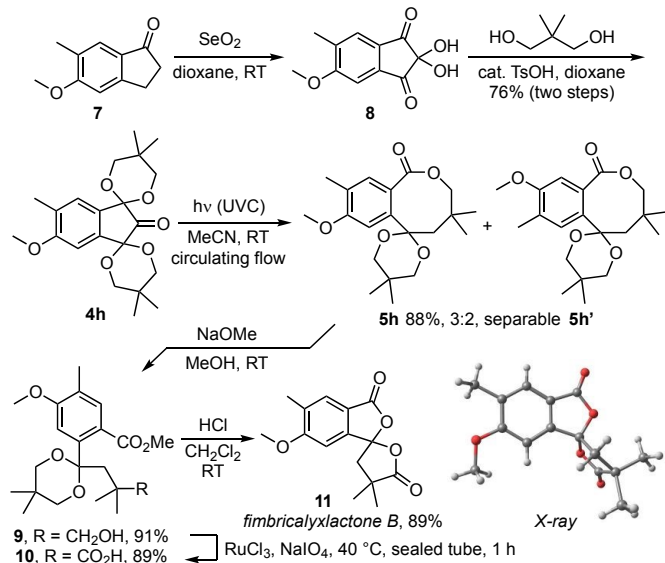


## ARTICLE

## Chemical Communications

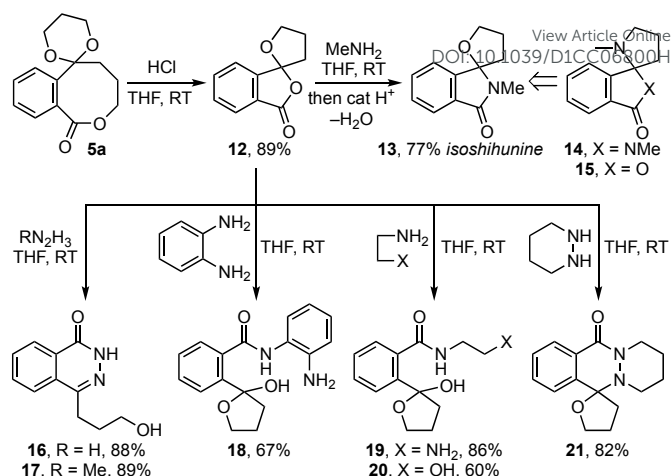
same reaction was performed on the homologous ninhydrin *bis*-acetal **4a**, 8-ring lactone **5a** was given in high yield (Scheme 1). Various analogues of **5** carrying substituents on the acetals and arene also gave the reaction in high yield (Table 1). In general, *bis*-1,3-dioxanes with a symmetrical arene and/or acetal substitution pattern gave a single product in 80–90% yield, e.g. **5a–c**. Substrates lacking those symmetry elements also gave high yields but led to isomeric mixtures, e.g. lactones **5d–g**. Though this limited the yield attained for individual products to ~40%, in the context of medium ring synthesis such an outcome remains competitive.<sup>5</sup>

To demonstrate the utility of the method, we next applied it in a total synthesis of fimbriallyxlactone **B 11**, a natural product from the roots of *Strophoblachia fimbriallyx* Boerl. (Euphorbiaceae) (Scheme 2).<sup>6</sup> Thus, *bis*-acetal **4h** was formed from the corresponding 1-indanone **7** in 76% yield through sequential SeO<sub>2</sub> oxidation and acetalisation with 2,2-dimethylpropanediol.<sup>7</sup> Exposure of an acetonitrile solution of **4h** to UVC light under circulating flow next gave a 3 : 2 mixture of lactones **5h** and **5h'** that was readily separated by column chromatography. Methanolysis of the major isomer **5h** then gave ester **9** which was advanced to fimbriallyxlactone **B 11** by ruthenium tetroxide oxidation to carboxylic acid **10** and acetal hydrolysis with HCl.<sup>8</sup> Importantly, the spectral and physical data recorded on our sample matched those reported for the natural product. Its identity was also confirmed by x-ray crystallographic analysis (Scheme 2, CCDC 1908866).<sup>6,9</sup>



Scheme 2. Total synthesis and x-ray crystal structure of fimbriallyxlactone B

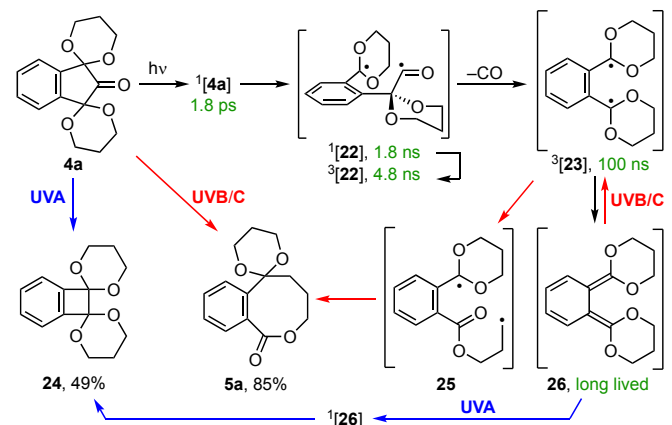
The potential of these 8-ring lactones to serve as intermediates in heterocyclic synthesis was next demonstrated with the conversion of **5a** to spiro lactone **12** on acetal hydrolysis (Scheme 3).<sup>9</sup> In turn, its treatment with methylamine gave isoshihunine **13** in 77% yield, from which the alkaloids shihunidin **14** and shihunine **15** can each be derived.<sup>10,11</sup> Furthermore, reaction with hydrazines gave high yielding access to phthalazones (e.g. **16**, **17**, **21**), which are important pharmacophores present in the chemotherapeutic agent olaparib (Lynparza<sup>®</sup>),<sup>12</sup> and azelastine (Astelin, Optivar, Allergodil), a frontline drug treatment for mild rhinitis.<sup>13</sup> By contrast, *o*-phenylenediamine, ethanolamine and ethylenediamine gave lactols **18**–**20** respectively.



Scheme 3. Heterocycles derived from 8-ring lactone **5a**

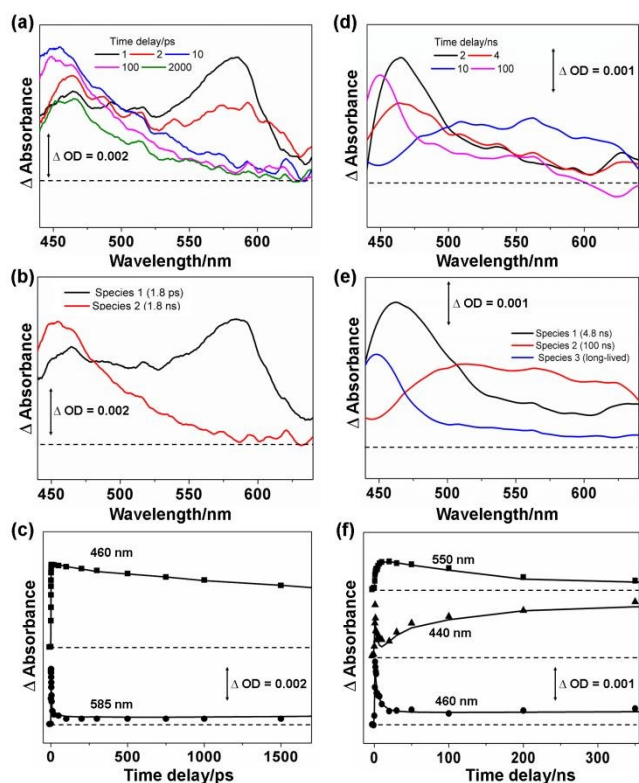
The mechanistic course of the photoextrusion reaction was next studied by transient absorption (TA) spectroscopy following excitation of *bis*-acetal **4a** in CH<sub>3</sub>CN at 266 nm using a high-pressure mercury lamp (Scheme 4 and Figure 1). Analysis of the ps-TA spectra (Figure 1a) allowed us to extract the time constants associated with spectral evolution using global kinetic analysis.<sup>14</sup> The data could be fitted using two exponential decays with time constants  $\tau_1 = 1.8 \pm 0.4$  ps and  $\tau_2 = 1.8 \pm 0.2$  ns (Figure 1b, c). The observed transient spectrum at 1 ps time delay showed an absorption band at 585 nm which was assigned to the  $n\pi^*$  ( $S_1$ ) excited state  $^1[4a]$  following comparison of the extracted spectrum with that computed for the  $S_1$  state (ESI, Figure S5). Decay of the  $S_1$  state was associated with the formation of a new transient species with an absorption band at 454 nm. This was attributed to biradical  $^1[22]$  based on comparison with results reported for the photoexcitation of 1,1,3-triphenyl-3-hydroxy-2-indanone.<sup>15</sup> Additionally, the result aligns with a recent TA study of the C–C bond cleavage of cyclopentanone in cyclohexane following 255 nm photoexcitation, which Kao *et al.* found occurred in  $\leq 1$  ps.<sup>16</sup> Likewise the  $\tau_2$  component [ $1.8 \pm 0.2$  ns] for the rate of formation of  $^3[20]$  from  $^1[20]$  is consistent with previously reported ISC timescales for acyl-alkyl diradicals.<sup>17</sup>

Spectral evolution by ns-TA spectroscopy was also monitored (Figure 1d). Three exponentials are required to describe these data, with time constants  $\tau_1 = 4.8 \pm 0.4$  ns,  $\tau_2 = 100 \pm 20$  ns, and  $\tau_3 = \text{long-lived}$



Scheme 4. Mechanistic course of the photoextrusion reactions of *bis*-acetal **4a** [UVA (broad), 355–390 nm; UVB (narrow), 310 nm; UVC (narrow), 254 nm]



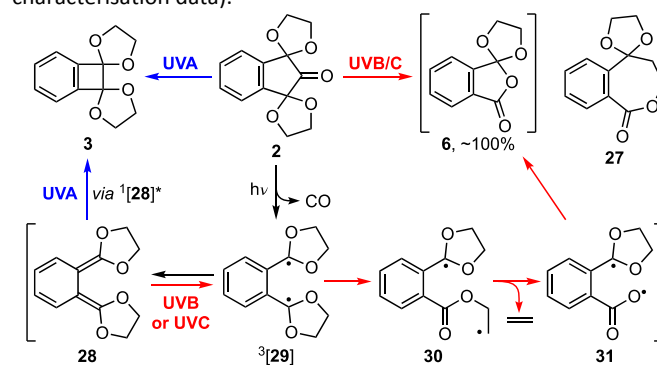


**Figure 1.** (a) ps-TA spectra at selected time delays. (b) Extracted species associated spectra from global analysis. (c) Representative kinetic traces at the selected probe wavelengths (symbols are the experimental data and the solid lines are the fits). (d) ns-TA spectra at selected time delays. (e) Extracted species associated spectra from global analysis. (f) Representative kinetic traces at the selected probe wavelengths (symbols are the experimental data and the solid lines are the fits).

(Figure 1e, f).<sup>17</sup> The  $\tau_1$  component was associated with a decay of the 460 nm band for <sup>3</sup>[22] with simultaneous formation of a new transient at 550 nm, attributed to the decarbonylation product <sup>3</sup>[23]. A similar transient spectral feature was reported for the decarbonylation of diphenylmethylacyl radical (Ph<sub>2</sub>MeCCO<sup>•</sup>) in isooctane, which had a rate constant  $k = 1.5 \times 10^8 \text{ s}^{-1}$ .<sup>15,18</sup> Decay of the 550 nm transient species <sup>3</sup>[23], with  $\tau_2 = 100 \pm 20 \text{ ns}$ , was associated with the formation of a long-lived intermediate **26** (Scheme 4). Irradiation of **26** with UVA leads to a singlet excited state <sup>1</sup>[26] that can relax to benzocyclobutene **24**. By contrast, its irradiation with UVB or UVC light gives rise to higher singlet excited states of **26** from which ISC to <sup>3</sup>[23] is allowed. Collapse of <sup>3</sup>[23] to biradical **25** then provides access to 8-ring lactone **5a**.

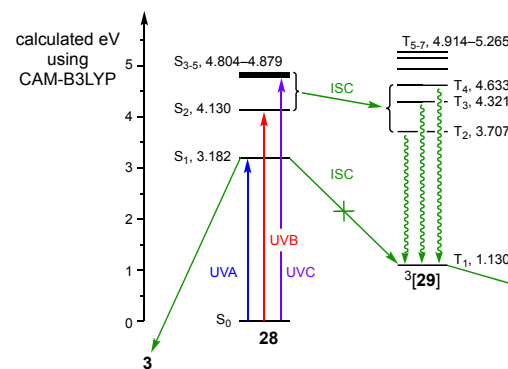
Applying this mechanistic understanding to ninhydrin *bis*-acetal **2** (Scheme 5) led us to conclude that the course of that reaction was also dictated by the nature of the excitation of quinodimethane intermediate **28**. As before, its irradiation with UVA gives a singlet excited state <sup>1</sup>[28] from which benzocyclobutene **3** is derived. Similarly, irradiation with UVB or UVC light leads to biradical <sup>3</sup>[29], which in turn collapses to biradical **30**. However, in this case, ring closure to  $\epsilon$ -lactone **27** is outpaced by the extrusion of ethene to biradical **31**, a precursor of orthoanhydride **6**. Indeed, the near quantitative formation of orthoanhydride **6** on photolysis of *bis*-

acetal **2** with UVB or UVC light was confirmed by analysis of a concentrated product mixture *before aqueous work-up* (see ESI for characterisation data).



**Scheme 5.** Proposed mechanism for the photoextrusion reactions of *bis*-acetal **2** [UVA (broad, 355–390 nm; UVB (narrow), 310 nm; UVC (narrow), 254 nm].

A TD-DFT analysis of quinodimethane **28** provided additional support for the mechanism (Figure 2).<sup>20</sup> In particular, it indicated that the energy provided by UVA irradiation ( $3.18 \text{ eV} \approx \lambda_{\text{max}} 390 \text{ nm}$ ) mirrored that required for the  $\pi \rightarrow \pi^*$  transition  $S_0 \rightarrow S_{1,2}$ , and that ISC between  $S_1$  of <sup>1</sup>[28] and  $T_1$  of <sup>3</sup>[29] was forbidden as both had  $\pi\pi^*$  character.<sup>21</sup> Consequently, irradiation of **28** with UVA induces cyclisation to benzocyclobutene **3**. By contrast, the greater energy provided by UVB and UVC irradiation facilitates ISC from <sup>1</sup>[28] to <sup>3</sup>[29] via higher excited states where both the orbital symmetry and energy requirements can each be fulfilled.<sup>21</sup> As a result, irradiation of **28** with UVB or UVC gives orthoanhydride **6**.



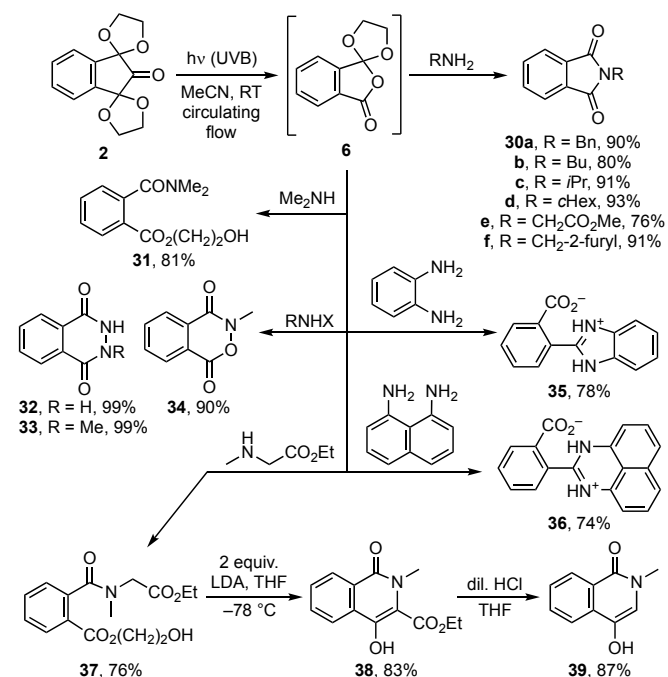
**Figure 2.** TD-DFT calculated energies for the singlet and triplet excited states of **28** and **29** respectively, and the mechanistic implications.

Finally, the use of orthoanhydride **6** as a phthalic anhydride surrogate (Scheme 6) was demonstrated with the phthalimide protection of various 1°-amines under mild conditions leading to **30a-f**.<sup>22</sup> Similarly, reactions with 2°-amines gave the expected amides, *e.g.* **31** and **37**, while *bis*-nucleophiles provided high yielding access to an array of biologically relevant nitrogen heterocycles **32–36**, **38** and **39**.

In conclusion, we have shown that the photodecarbonylation of ninhydrin *bis*-acetals is a wavelength dependent reaction that can be conducted on a gram scale to give benzocyclobutenes on UVA irradiation (60 W, ~5 h), and orthoanhydrides or 8-ring lactones on UVB or UVC irradiation (36 W, ~2 h). Notably, they formally constitute ring contraction, ring correlative, and ring expansion reactions, respectively. These versatile intermediates give access to a host of heterocycles, natural products, and pharmacophores.



Mechanistic details have been delineated using computational and spectroscopic methods, including picosecond and nanosecond transient absorption spectroscopy. We are currently exploring further applications of the chemistry in target-oriented and natural products total synthesis.



**Scheme 6.** Illustrations of the synthetic utility of orthoanhydride 1.

Author contributions: Wei Sun and William Raimbach performed the synthetic chemistry under the supervision of David Harrowven. Wei Sun and Magnus Hanson-Heine performed the DFT analyses while Mark Light conducted the X-ray analysis. Transient absorption spectroscopic analyses were by Surajit Kayal and Xue-Zhong Sun under the supervision of Michael George. We gratefully acknowledge financial support from EPSRC [EP/P013341/1, EP/L003325/1 and EP/K039466/1], the European Regional Development Fund [ERDF Interreg Va programme (Project 121)], and the University of Nottingham Green Chemicals Beacon. There are no conflicts of interest to declare.

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