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Wavelength dependent photoextrusion and tandem photo-extrusion reactions of ninhydrin bis-acetals for the synthesis of 8-ring lactones, benzocyclobutenes and orthoanhydrides†

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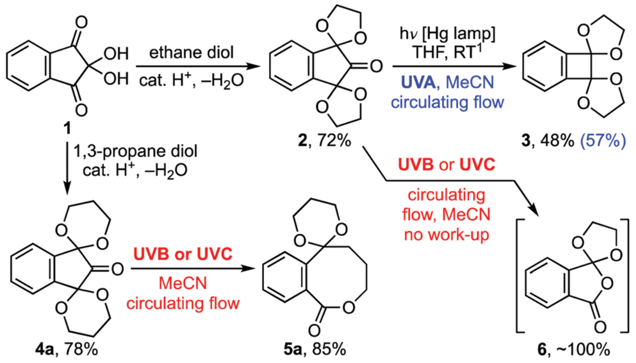
Ninhydrin bis-acetals give access to 8-ring lactones, benzocyclobutenes and spirocyclic orthoanhydrides through photoextrusion and tandem photoextrusion reactions. Syntheses of fimbricalyxlactone B, isoshihunine and numerous biologically-relevant heterocycles show the value of the methods, while TA-spectroscopy 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).[1] 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.[2,3] 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.[3,4] 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 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**. Thought this limited the yield attained for individual products to ∼40%, in the context of medium ring synthesis such an outcome remains competitive.[5]



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

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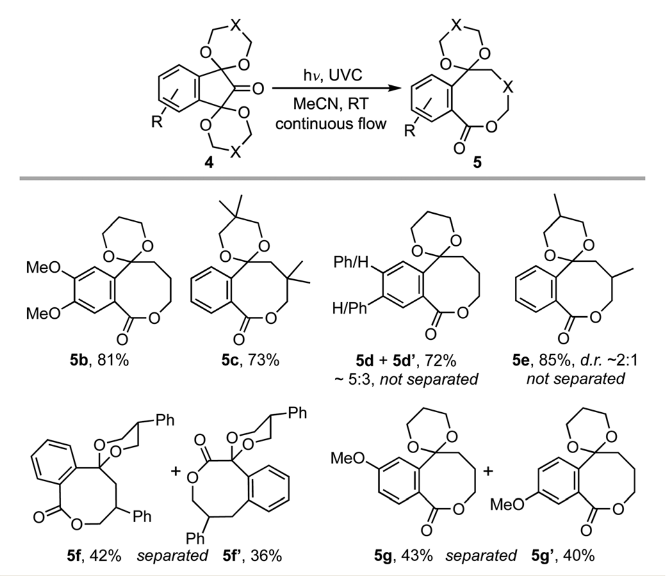
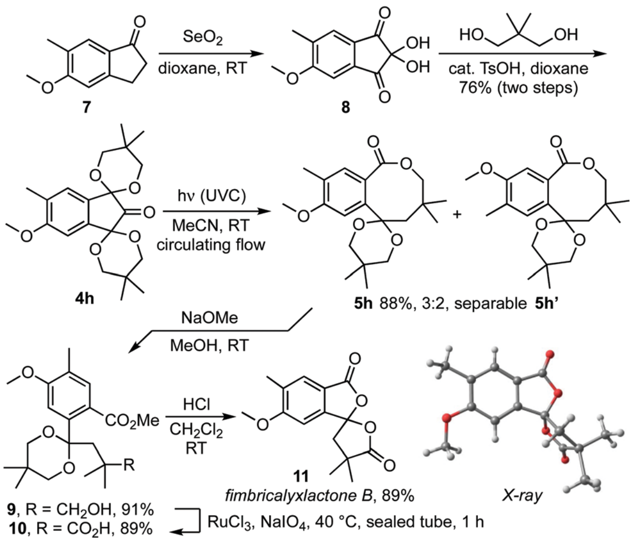
† Electronic supplementary information (ESI) available: Experimental accounts with spectral details and copies of NMR spectra are available as supplementary information. CCDC 1908866. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc06800h

Table 1 Extensions to other ninhydrin bis-acetals



To demonstrate the utility of the method, we next applied it in a total synthesis of fimbricalyxlactone B **11**, a natural product from the roots of *Strophioblachia fimbricalyx* Boerl. (Euphorbiaceae) (Scheme 2).[6] Thus, bis-acetal **4h** was formed from the corresponding 1-indanone **7** in 76% yield through sequential SeO_2 oxidation and acetalisation with 2,2-dimethylpropandiol.[7] 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 fimbricalyxlactone B **11** by ruthenium tetroxide oxidation to carboxylic acid **10** and acetal hydrolysis with HCl.[8] 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).†[6,9]

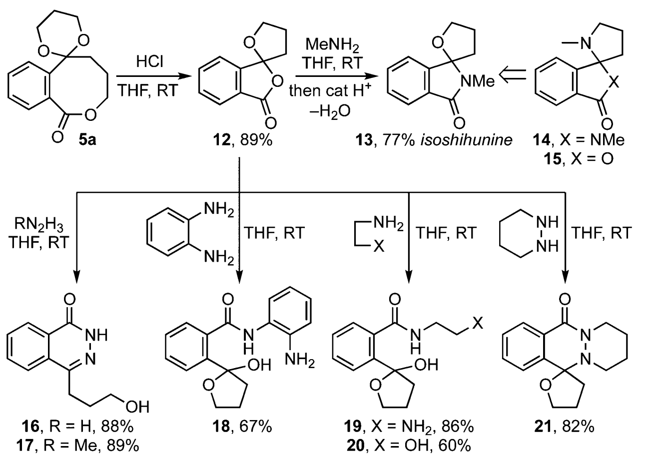


Scheme 2 Total synthesis and X-ray crystal structure of fimbricalyxlactone B.

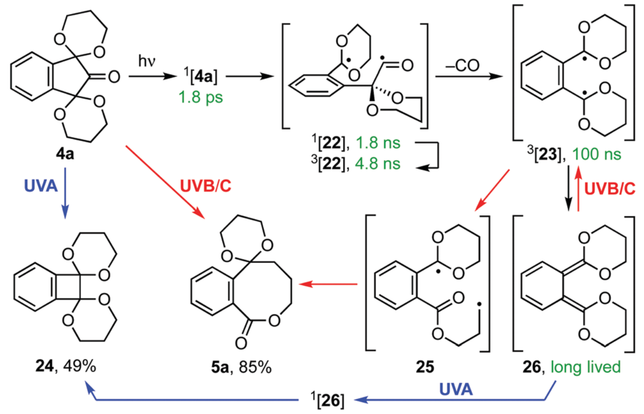
The potential of these 8-ring lactones to serve as intermediates in heterocyclic synthesis was next demonstrated with the conversion of **5a** to spirolactone **12** on acetal hydrolysis (Scheme 3).[9] In turn, its treatment with methylamine gave isoshihunine **13** in 77% yield, from which the alkaloids shihunidin **14** and shihunine **15** can each be derived.[10,11] 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®),[12] and azelastine (Astelin, Optivar, Allergodil), a frontline drug treatment for mild rhinitis.[13] By contrast, *o*-phenylenediamine, ethanolamine and ethylenediamine gave lactols **18** – **20** respectively.

The mechanistic course of the photoextrusion reaction was next studied by transient absorption (TA) spectroscopy following excitation of bis-acetal **4a** in CH_3CN at 266 nm (Scheme 4 and Fig. S1, ESI†). Analysis of the ps-TA spectra (Fig. S1a, ESI†) allowed us to extract the time constants associated with spectral evolution using global kinetic analysis.[14] The data could be fitted using two exponential decays with time constants τ_1 = 1.8 ± 0.4 ps and τ_2 = 1.8 ± 0.2 ns (Fig. S1b and c, ESI†). 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 (Fig. S7, ESI†). 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.[15] 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 ≤1 ps.[16] Likewise the τ_2 component [1.8 ± 0.2 ns] for the rate of formation of ^{3}[**22**] from ^{1}[**22**] is consistent with previously reported ISC timescales for acyl–alkyl diradicals.[17]

Spectral evolution by ns-TA spectroscopy was also monitored (Fig. S1d, ESI†). Three exponentials are required to describe these data, with time constants τ_1 = 4.8 ± 0.4 ns, τ_2 = 100 ± 20 ns, and



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

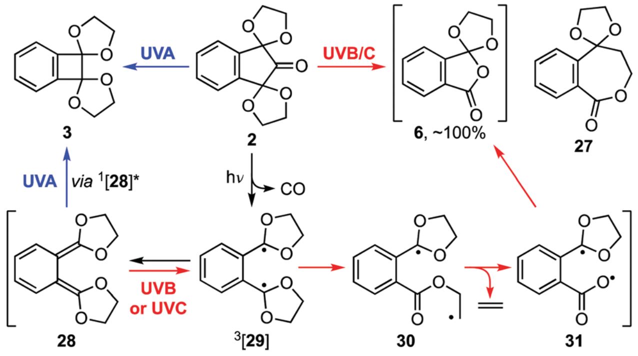


Scheme 4 Proposed mechanistic course of the photoextrusion reactions of bis-acetal **4a** [UVA (broad), 355–390 nm; UVB (narrow), 310 nm; UVC (narrow), 254 nm]

τ_3 = long-lived (Fig. S1e and f, ESI†).[17] The τ_1 component was associated with a decay of the 460 nm band for ^{3}[**22**] with simultaneous formation of a new transient at 550 nm, attributed to the decarbonylation product ^{3}[**23**]. A similar transient spectral feature was reported for the decarbonylation of diphenylmethylacyl radical ($Ph_2MeCCO^{\bullet}$) in isooctane, which had a rate constant $k = 1.5 \times 10^8$ s^{-1}.[15,18] Decay of the 550 nm transient species ^{3}[**23**], with $\tau_2 = 100 \pm 20$ ns, was associated with the formation of a long-lived transient at 440 nm assigned to quinodimethane **26**. This is in line with the rate constant measured by Fujiwara *et al.* for the formation of *o*-xylylene from 2-indanone following photoexcitation at 266 nm in cyclohexane ($k = 1.4 \pm 0.1 \times 10^7$ s^{-1}).[19] Thus, the wavelength dependence of the reaction centres on the fate of long-lived intermediate **26** (Scheme 4). Irradiation of **26** with UVA leads to a singlet excited state ^{1}[**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 ^{3}[**23**] is allowed. Collapse of ^{3}[**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 ^{1}[**28**] from which benzocyclobutene **3** is derived. Similarly, irradiation with UVB or UVC light leads to biradical ^{3}[**29**], which in turn collapses to biradical **30**. However, in this case, ring closure to ε-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).

A TD-DFT analysis of quinodimethane **28** provided additional support for the mechanism (Fig. 1).[20] In particular, it indicated that the energy provided by UVA irradiation (3.18 eV ≡ λ_{max} 390 nm) mirrored that required for the $\pi \rightarrow \pi^*$ transition $S_0 \rightarrow S_1$, and that ISC between S_1 of ^{1}[**28**] and T_1 of ^{3}[**29**] was forbidden as both had $\pi\pi^*$ character.[21] 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 ^{1}[**28**] to ^{3}[**29**] *via* higher excited states where both the orbital symmetry and energy requirements can each be fulfilled.[21] As a result, irradiation of **28** with UVB or UVC gives orthoanhydride **6**.



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].

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**.[22] 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

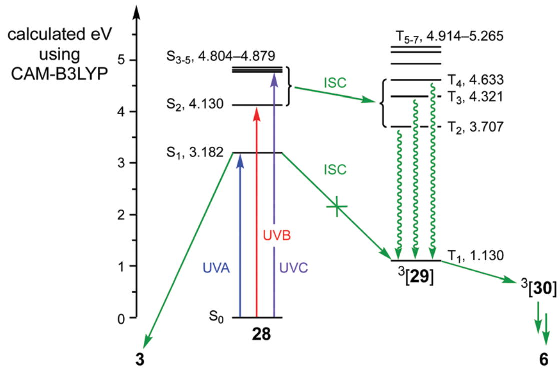
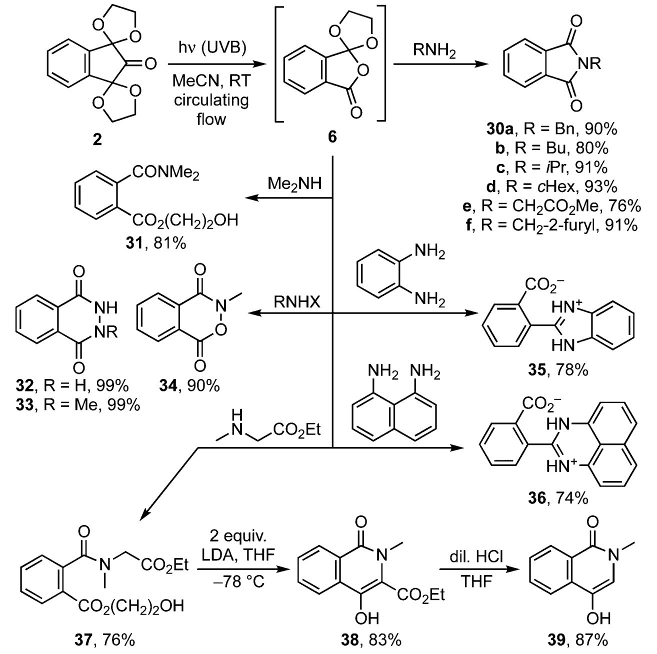


Fig. 1 TD-DFT calculated energies for the singlet and triplet excited states of **28** and **29** respectively, and the mechanistic implications.



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

transient absorption spectroscopy. We are currently exploring further applications of the chemistry in target-oriented and natural products total synthesis.

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.

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Conflicts of interest

There are no conflicts of interest to declare.

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